Therapeutic Drug Monitoring
*IDK*monitor® ELISAs

*IDK*monitor® Drug Level ELISAs

- For the determination of drug level
- Highly specific antibodies for drug binding

*IDK*monitor® ADA ELISAs

- For the detection of anti-drug antibodies (ADA):
  - Free ADA ELISAs
  - Total ADA (drug tolerant) ELISAs

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IDK monitor®

The Importance of Individual Therapy Monitoring Through Biologic Treatment

Biologicals can be an effective treatment option for individuals suffering from various diseases, such as inflammatory bowel disease and rheumatoid arthritis. However, some patients do not respond to treatment with a particular biologic (primary non-responders), while others lose their response over time (secondary non-responders), developing resistance to the biologic. Moreover, these treatments are expensive, and there are limited drugs available. This limited availability, combined with the potential for drug resistance, highlights the importance of therapy optimization for long-term therapeutic success.

Regular monitoring of drug levels and the formation and concentration of anti-drug antibodies (ADA) is crucial for maintaining long-term therapeutic success. This monitoring can detect and prevent secondary treatment failure at an early stage, allowing for optimal, personalized therapy and minimizing healthcare costs by avoiding unnecessary dose increases and treatments.

Both proactive and reactive monitoring are important. Regular (proactive) monitoring of drug levels and ADA measurements can help detect and counteract treatment failure early. Reactive monitoring in the event of acute treatment failure allows for informed decisions about therapeutic approaches.

Drug Level ELISAs

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

The effectiveness of biologics largely depends on the serum concentration of the drug, as bioavailability and pharmacokinetics are individual and vary during the course of disease. Monitoring the drug level, especially the trough level, is therefore essential to ensure that the drug is sufficiently available in circulation and to adjust its dose if necessary. Additionally, a reduced trough level during the course of therapy may indicate the presence of antibodies to the drug.

ADA ELISAs

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

Treatment with biologics can lead to unwanted immune reactions if the body produces antibodies to the drug. This can cause allergic reactions, decreased efficacy, and therapy failure. Although adjunctive therapy with immunosuppressants can reduce ADA production, it is not always indicated. Monitoring ADA levels allows for early intervention, resulting in personalized, 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 people with Crohn's disease treated with TNFα-blocking therapy throughout the UK.

Conclusion: Therapy failure of TNFα blockers is very common. Most of the time, the cause is a low trough level. The reasons for low trough levels range from individual pharmacokinetics to an immune response. The results of the PANTS study suggest that TNFα-blocking therapies can be optimized by therapeutic drug monitoring (TDM), which can increase the effectiveness of the treatment.

In particular, PANTS data suggest that early personalized dosing controlled by trough level monitoring, combined 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 underscores the importance of personalized therapy for those with chronic inflammatory diseases.

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

Literature:

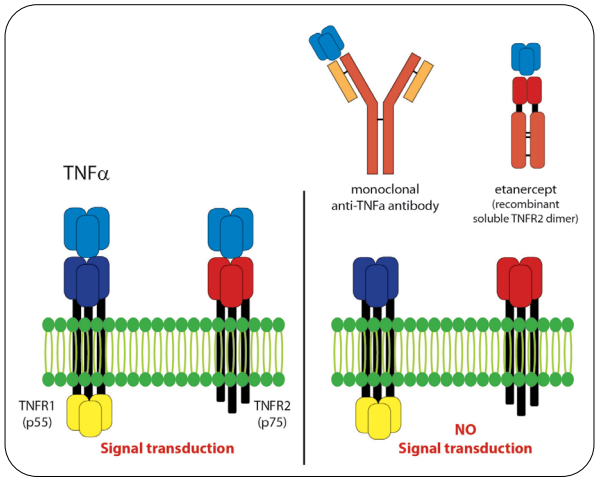
- M.A.V. Willrich et al, „Lab Testing for Therapeutic Monocolonal Antibodies: A Retrospective Analysis for Adalimumab and Vedolizumab", EuroMedLab, 2019
- N.Plevris et al., „Higher Adalimumab Drug Levels during Maintenance Therapy for Crohn's Disease Are Associated with Biologic Remission", Inflammatory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

Mechanisms of Action: Biologics in 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

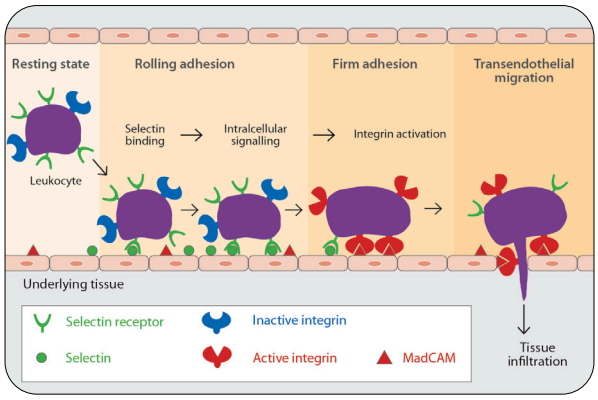


α4β7-integrin

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

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

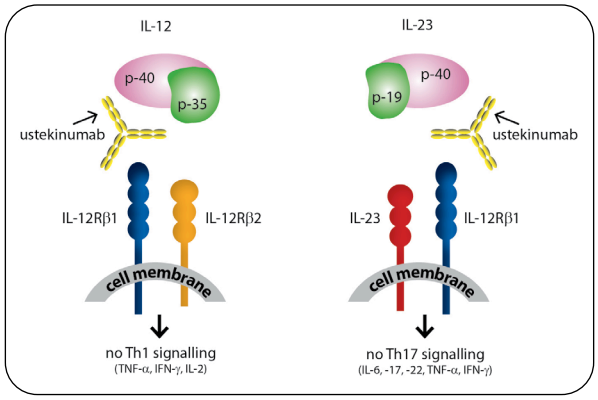
Drug: Vedolizumab



IL-12/23

Interleukin 12 and 23 are cytokines that regulate the immune system and influence inflammatory responses triggered by immune activation.
IL-12 stimulates the Th1 signaling pathway through cell membrane receptors, while IL-23 activates the Th17 signaling pathway. Both cytokines contribute to the maintenance of inflammatory reactions. IL-12/23 inhibitors target the shared subunit p40 of these cytokines, preventing their binding to their respective receptors. This inhibition blocks the inflammatory signaling cascade.

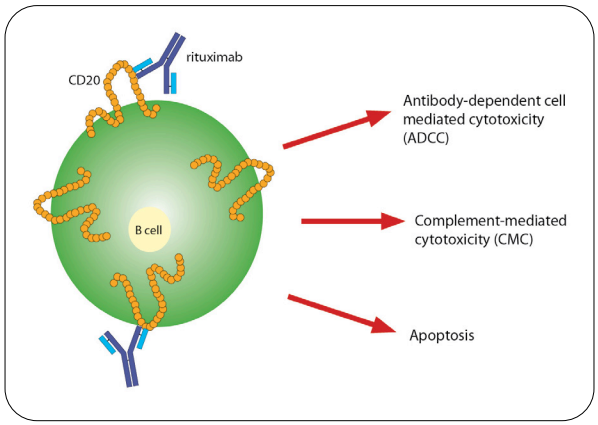
Drug: Ustekinumab



CD20

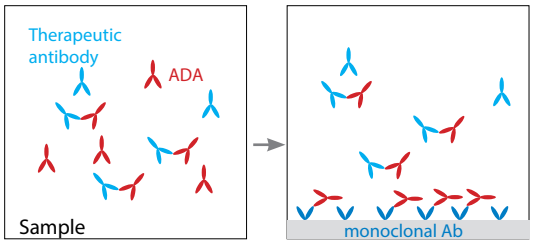
CD20 (also known as human B-lymphocyte-restricted differentiation antigen or Bp35) is a surface antigen found on normal and malignant pre-B lymphocytes as well as mature B lymphocytes. It plays a crucial role in optimizing the B cell immune response, particularly against T cell-independent antigens, and may also function as a calcium channel.
The CD20 antibody, through its binding to CD20, among other things, improves the action of natural killer (NK) cells, which cause cell death in antibody-labeled B lymphocytes. This process leads to cell death in the antibody-labeled B cells, significantly reducing their numbers. This reduction is a key goal in lymphoma therapy. In autoimmune diseases, lowering the number of B lymphocytes also decreases autoantibody production, thereby improving symptoms.

Drug: Rituximab



*IDK*monitor® free ADA ELISAs

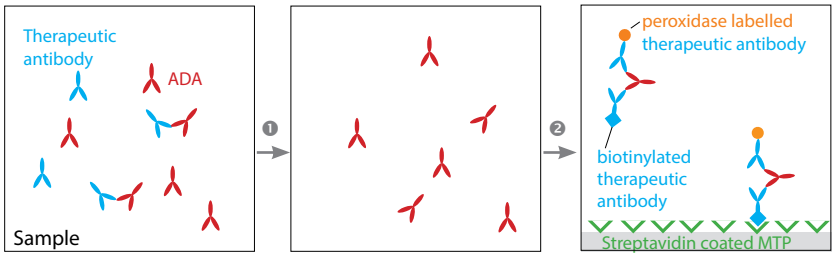
Free ADAs refer to antibodies that are not bound to the therapeutic antibody. This has technical implications; specifically, free antibodies can only be detected when the drug level is low or undetectable. Moreover, the presence of free ADAs indicates that the individual's immune response is producing more ADA molecules than there are circulating drug molecules available.



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

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

Total ADAs comprise both free antibodies and those bound in complexes with the therapeutic antibody. This allows for ADA concentration determination even when a detectable drug level is present, as the assays are drug-tolerant. Therefore, early immune responses can be detected even before drug levels decline.



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	K9655* / KR9655	K9650* / KR9650	K9654* / KR9654
	Adalimumab	K9657* / KR9657	K9652* / KR9652	K9651* / KR9651
	Golimumab	K9656* / KR9656	KR9649	–
	Etanercept	KR9646	KR9653	–
	Certolizumab	KR9662	–	–
α4β7-Integrin	Vedolizumab	KR9658	KR9648	–
IL-12/23	Ustekinumab	KR9660	KR9666	KR9667
CD20	Rituximab	KR9661	soon available	–

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

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