Therapeutic drug monitoring (TDM)
Scientific literature

Content

Highlights

What is therapeutic drug monitoring (TDM)?
TDM implies the measurement of drug and anti-drug antibodies (ADA). It improves the management of patients with inflammatory bowel diseases.

Why is TDM clinically relevant?
There is a concentration-effect relationship between the drug serum concentration and (prolonged) response to treatment.

When is TDM useful?
TDM is useful throughout the treatment of patients receiving biological drug therapy, either during induction treatment, during maintenance treatment or in patients experiencing loss of response.

How to interpret TDM results?
The drug and ADA concentrations should be interpreted in conjunction with clinical findings to optimize clinical decisions.

Can we quantify biosimilars?
Biosimilar drugs are equally well recognized as the originator drug in the RIDASCREEN® TDM assays.

Abbreviations

ADA	Anti-drug antibodies
ADM	Adalimumab
ATI	Anti-infliximab antibodies
ELISA	Enzyme-linked immunosorbent assay
IFX	Infliximab
LFA	Lateral flow assay
MA	Monoclonal antibody
MA-ADM	Monoclonal anti-adalimumab antibody
MA-IFX	Monoclonal anti-infliximab antibody
pAb	Polyclonal antibody
TDM	Therapeutic drug monitoring
TNFα	Tumor necrosis factor alpha

Definitions

Induction therapy	The first intensified series of biological drug administrations to rapidly induce remission
Maintenance therapy	Series of biological drug administrations following induction therapy to maintain remission
Reactive TDM	Application of TDM after the manifestation of disease symptoms and loss of response
Proactive TDM	Application of TDM before the manifestation of disease symptoms and loss of response
Calibrator antibody	Reference antibody with a known concentration that is used to standardize the measurement of ADA

1. Benefits of calprotectin measurement

1.1. Introduction

Inflammatory bowel diseases, Crohn's disease and ulcerative colitis, are chronic inflammatory diseases of the gastrointestinal tract that are characterized by intermittent periods of flares and remission. Typical symptoms include diarrhea, stomach cramps, urgency and fatigue, which inflict a serious burden on the patient's health and quality of life. As there is no cure available, **patients require lifelong treatment** and follow-up to avoid irreversible bowel damage. Therefore, **a durable treatment response is desired**.

Biological drugs, such as the anti-tumor necrosis factor alpha (anti-TNFα) drugs infliximab (IFX; Remicade®, Inflectra®, Remsima®, Flixabi®) and adalimumab (ADM; Humira®), and the anti-integrin drug vedolizumab (VDZ; Entyvio®), revolutionized the treatment of inflammatory bowel diseases by inducing clinical, biological and endoscopic remission in a large number of patients. Nevertheless, **many patients do not respond to treatment** (primary non-responders; ± 30 % of patients for anti-TNFα drugs) or **lose response to treatment over time** (secondary non-responders; ± 10 % of patients/patient year for anti-TNFα drugs).

It was shown that **non-responder patients typically have low or undetectable drug serum concentrations, often due to the development of anti-drug antibodies (ADA)**, an unwanted side effect inherent to all biological drugs. As a result, measurement of drug and ADA concentrations, or **therapeutic drug monitoring (TDM)**, has been introduced as an objective tool to guide clinical decision-making and personalize treatment in a cost-effective way.

Monitoring of drug and ADA serum concentrations throughout treatment helps the clinician to optimally adjust the treatment according to the individual needs of a patient. **Using TDM, the patient will benefit from a maximized and durable treatment response**. TDM has been demonstrated to be clinically useful in three different clinical situations that occur upon treatment of a patient with a biological drug:

1) In patients experiencing loss of response, TDM is useful to decipher the reason for loss of response and provide decision support to clinicians for the management of patients who lost response to biological therapy.
2) In patients on stable maintenance treatment, TDM is useful to optimize the dosing regimen to extend the time patients spend in remission.
3) In patient receiving induction treatment, TDM is useful to detect inadequate drug concentrations and to maximize treatment response.

1.2. Support clinical decisions in patients with loss of response

TDM can be applied to decipher the reason of loss of response and provide decision support to clinicians for the management of patients who lose response to biological therapy.

Why do we measure?

Patients without endoscopic remission have lower drug concentrations than patients in endoscopic remission (Figure 1).[1] Low drug concentrations may result from drug loss via the stool or ADA.[2]

A subset of patients experiences loss of response despite therapeutic drug concentrations. In these patients, the selected drug (class) doesn't work and it is likely that another inflammatory pathway is the predominant trigger of disease.[2]

Interpretation

Afif and co-authors demonstrated that in patients with subtherapeutic IFX concentrations, optimizing the dose of the drug was superior to switching to another anti-TNFα agent (86 % vs. 33 % response p<0.016).[3]

Switching to another anti-TNFα medication proved to lead to a better response than dose optimization in patients who lost response to IFX and had detectable anti-IFX antibodies (ATI; 92 % vs. 17 % response, p <0.004).[3]

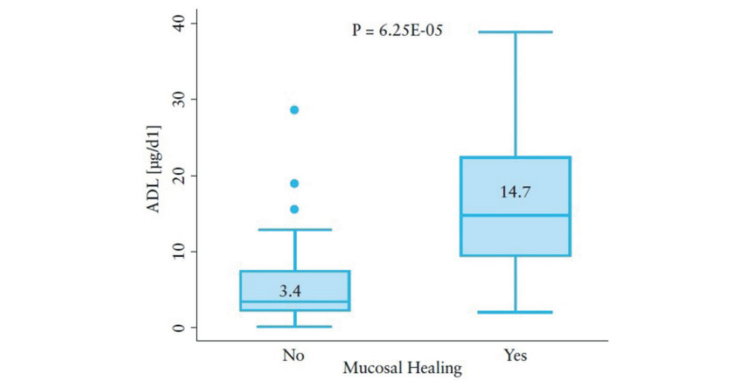

Fig. 1: ADL drug level and mucosal healing. The median ADL trough levels were significantly higher in the mucosal healing group compared to the non-mucosal healing group (14.7 vs. 3.4 µg/mL; p=6.25 x 10-5)1; ADL, adalimumab

Conclusion

Measurement of drug and ADA concentrations impacts patient management and is clinically useful.

References:

1. *Zittan E et al.* Higher adalimumab drug levels are associated with mucosal healing in patients with Crohn's disease. J Crohns Colitis 2016;10:510-515.
2. *Papamichael K, Cheifetz A.* Use of anti-TNF drug levels to optimise patient management. Frontline Gastroenterology 2016;7:289–300.
3. *Afif W et al.* Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol 2010;105:1133-1139.

1.3. Extending remission during maintenance treatment

TDM can be applied to optimize the dosing regimen and extend the time patients spend in remission during maintenance treatment.

Why do we measure?

There is a large variability in measured drug and ADA concentrations in patients who are receiving maintenance treatment.[1]

Low drug concentrations and ADA may already be present before the onset of clinical loss of response.[2]

Interpretation

In the dose optimization phase of TAXIT, dose intensification of patients with subtherapeutic trough concentrations to a therapeutic target window of 3 to 7 µg/mL led to higher clinical and biological remission rates.[1] In follow-up, patients receiving TDM-based dosing had a lower risk of relapse and were more likely to remain on IFX treatment.[1,3]

In a retrospective observational study performed by Vaughn and co-authors, tittering of patients to a therapeutic target window increased the probability of being on IFX therapy for more than 5 years (86 % in the proactive TDM group versus 52 % in the control group, Figure 2).[4]

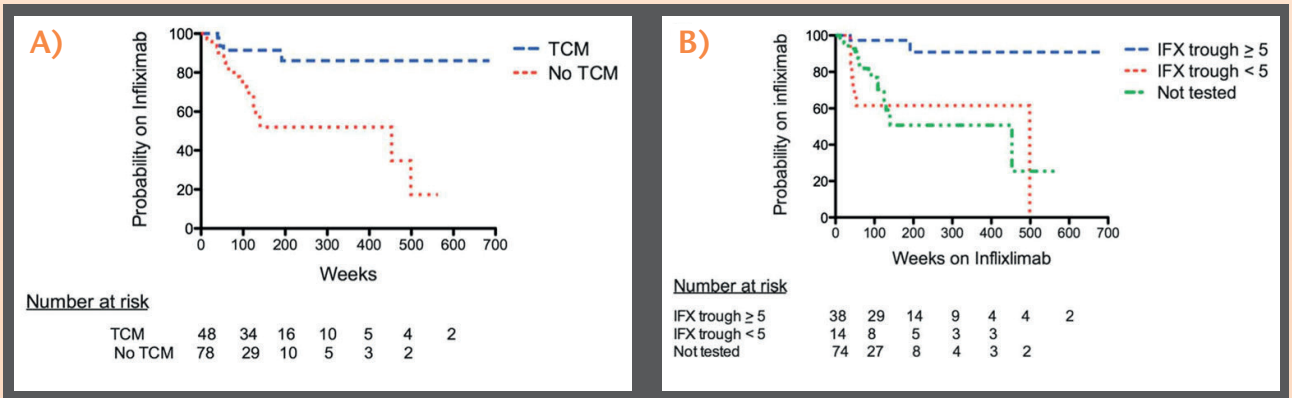

Fig. 1: Duration of IFX in weeks based on *a priori* subgroups. A) Probability of continuing on IFX in the proactive TDM vs. control groups. B) Probability of continuing IFX based on trough concentration.[4]
*TDM = Therapeutic drug monitoring ≙ TCM = Therapeutic Concentration Monitoring

Conclusion

Targeting a therapeutic concentration window during maintenance treatment is clinically useful and cost-effective.

References:

1. *Vande Casteele N et al*. Trough Concentrations of Infliximab Guide Dosing for Patients With Inflammatory Bowel Disease. Gastroenterology 2015;148:1320–1329.
2. *Ungar B et al.* The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. Gut 2014;63:1258–1264.
3. *Pouillon L et al.* Mucosal Healing and Long-term Outcomes of Patients With Inflammatory Bowel Diseases Receiving Clinic-based vs Trough Concentration-based Dosing of Infliximab. Clin Gastroenterol Hepatol 2017; Epub ahead of print.
4. *Vaughn B et al.* Proactive Therapeutic Concentration Monitoring of Infliximab May Improve Outcomes for Patients with Inflammatory Bowel Disease: Results from a Pilot Observational Study. Inflamm Bowel Dis 2014;20:1996-2003.

1.4. Maximize the response of patients to induction treatment

TDM can be applied to detect inadequate drug concentrations and to maximize treatment response in patients receiving induction treatment.

Why do we measure?

Low drug concentrations and the development of ADA during induction treatment reduce the chance of achieving response to induction treatment (Figure 3).[1-4]

Interpretation

TDM during induction treatment may help to rationalize patient management and define true primary non-response.[4] Patients without response to induction treatment may benefit from dose optimization or a switch to a drug with the same mode of action.[4] The recent availability of a rapid test for drug monitoring facilitates immediate dose optimization.[5]

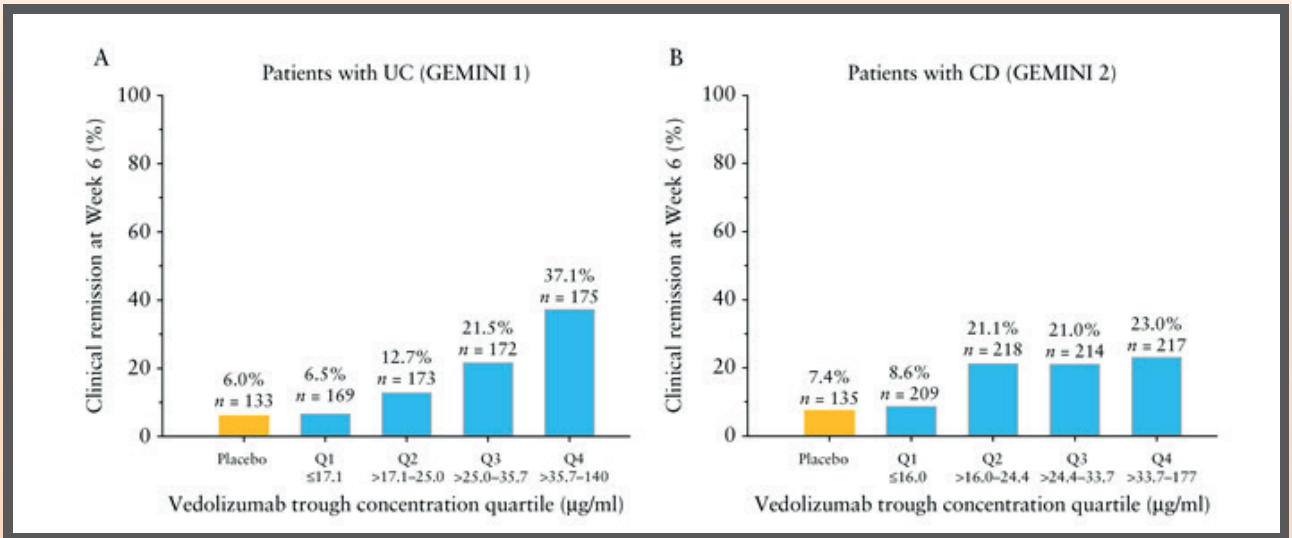

Fig. 3: Exposure – efficacy relationships for vedolizumab induction therapy in patients with Ulcerative Colitis or Crohn's Disease. Data from the GEMINI trials.[1]

References:

1. *Rosario M et al.* Exposure–efficacy Relationships for Vedolizumab Induction Therapy in Patients with Ulcerative Colitis or Crohn's Disease. J Crohns Colitis 2017;11:921-929.
2. *Yarur AJ et al.* Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. Aliment Pharmacol Ther 2017;45:933-940.
3. *Brandse JF et al.* Pharmacokinetic Features and Presence of Antidrug Antibodies Associate With Response to Infliximab Induction Therapy in Patients With Moderate to Severe Ulcerative Colitis. Clin Gastroenterol Hepatol 2016;14:251-258.
4. *Papamichael K et al.* Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: evolution in the definition and management of primary nonresponse. Inflamm Bowel Dis 2015;21:182-197.
5. *Van Stappen T et al.* Rapid Test for Infliximab Drug Concentration Allows Immediate Dose Adaptation. Clin Transl Gastroenterol 2016;7:e206.

2. Identification of a therapeutic window and threshold concentrations

The use of therapeutic windows and threshold concentrations may support clinical decisions, but do not replace the clinician's proper judgment of all patient, drug and disease-related factors – the final clinical decision on the management of the patient is solely at the discretion of the treating clinician.

Therapeutic trough concentration windows may be highly dependent on the assay used, the drug measured and the clinical outcome investigated. Generally, a therapeutic trough concentration window of 3 - 7 µg/mL for IFX and 5 - 10 µg/mL for ADM has been suggested for patients under maintenance treatment.[1]

Table 1: Recommended threshold drug concentrations from the American Gastroenterological Association (AGA) when applying reactive TDM in patients with loss of response to maintenance therapy.[2]

Drug	Suggested trough concentration, µg/mL*	Comments
Infliximab	≥5	Based on six studies, the proportion of patients not in remission decreased from 25 % when using an infliximab threshold of ≥1 µg/mL, to 15 % with an infliximab trough concentration of ≥3 µg/mL, to approximately 4 % with an infliximab trough concentration of ≥7 µg/mL or ≥10 µg/mL.
Adalimumab	≥7.5	On analysis of different thresholds from four studies, the proportion of patients not in remission progressively decreased from 17 % when using an adalimumab threshold ≥5.0 ± 1 µg/mL, to 10 % with an adalimumab trough concentration of ≥7.5 ± 1 µg/mL.

Conclusion

Optimal therapeutic (trough) concentration windows are 3 - 7 µg/mL for IFX and 5 - 10 µg/mL for ADM during maintenance treatment.

References:

1. *Papamichael K et al.* Use of anti-TNF drug levels to optimise patient management. Frontline Gastroenterology 2016;7: 289-300.
2. *Feuerstein J et al.* American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology 2017;153: 827-834.

3. Cost effectiveness of TDM

3.1 Loss of response

The use of a TDM-based treatment algorithm for the management of patients with loss of response leads to significant cost savings compared to routine dose escalation whilst maintaining similar treatment outcomes.

Steenholdt and co-authors demonstrated that treatment of patients with loss of response using an algorithm (Figure 4) based on combined drug and ADA measurements significantly reduces average treatment costs per patient compared with routine dose escalation (-34 %, € 6038 vs € 9178, p<0.001), without any apparent negative effect on clinical efficacy.[1]

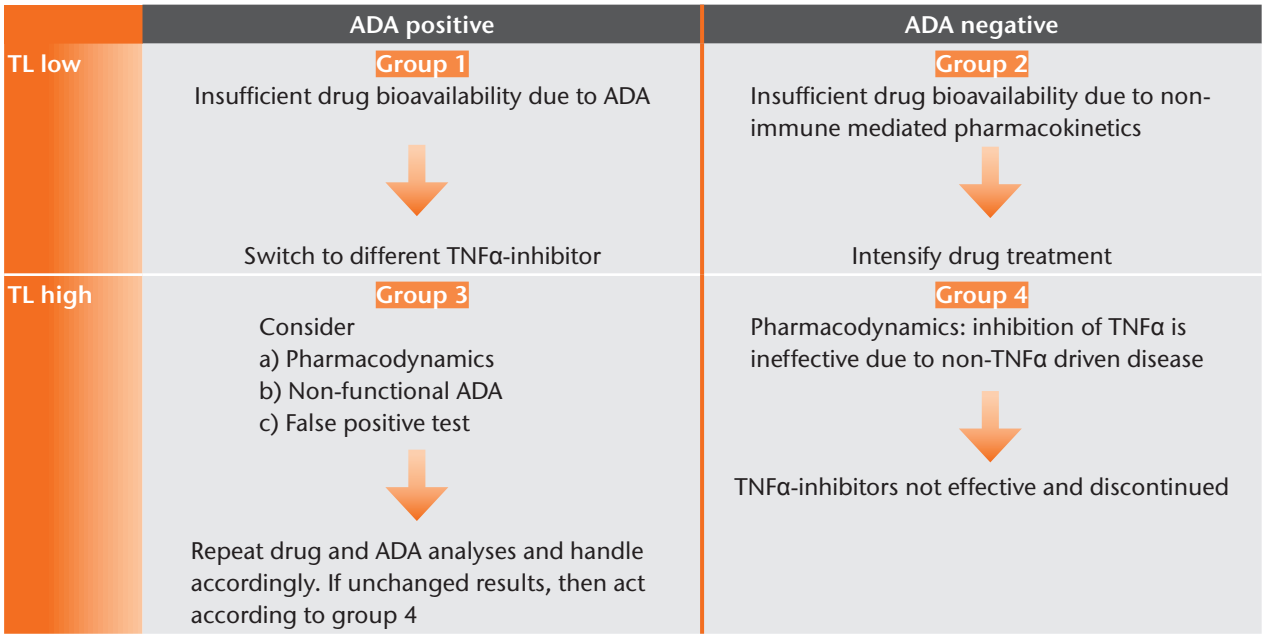

Fig. 4: Treatment algorithm for patients with Crohn's disease with secondary loss of response to infliximab (IFX). TL, trough level; ADA, anti-drug antibody. Adapted from *Steenholdt C*, Gut 2014[1]

In a simulation model, *Velayos* and colleagues demonstrated that treatment adaptations based on drug and anti-drug antibody concentrations significantly reduce treatment costs, while achieving similar outcomes, compared to empiric dose escalation for patients with Crohn's disease who lose responsiveness to IFX.[2]

References:

1. *Steenholdt C et al.* Individualized therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. Gut 2014;63:919–927.
2. *Velayos FS et al.* A test-based strategy is more cost effective than empiric dose escalation for patients with Crohn's disease who lose responsiveness to infliximab. Clin Gastroenterol Hepatol 2013;11:654–666.

3.2 Maintenance treatment

The use of a TDM-based treatment algorithm for the management of patients receiving stable IFX maintenance treatment leads to prolonged remission at a lower cost.

The TAXIT study investigated the role of continuous concentration-based dosing, representing dosing based on drug and ADA concentrations, for the management of patients receiving stable IFX maintenance treatment.[1]

After the initial dose optimization in TAXIT, patients were randomized to receive concentration-based dosing, applying the TDM-based algorithm illustrated in Figure 5, or clinically-based dosing, representing the traditional dosing based on clinical symptoms. After one year of follow-up, clinical and biological outcomes between both groups were compared.

The results of this study revealed that dosing based on drug and ADA concentrations was clearly of benefit for patients as it associated with fewer flares and lower treatment costs.

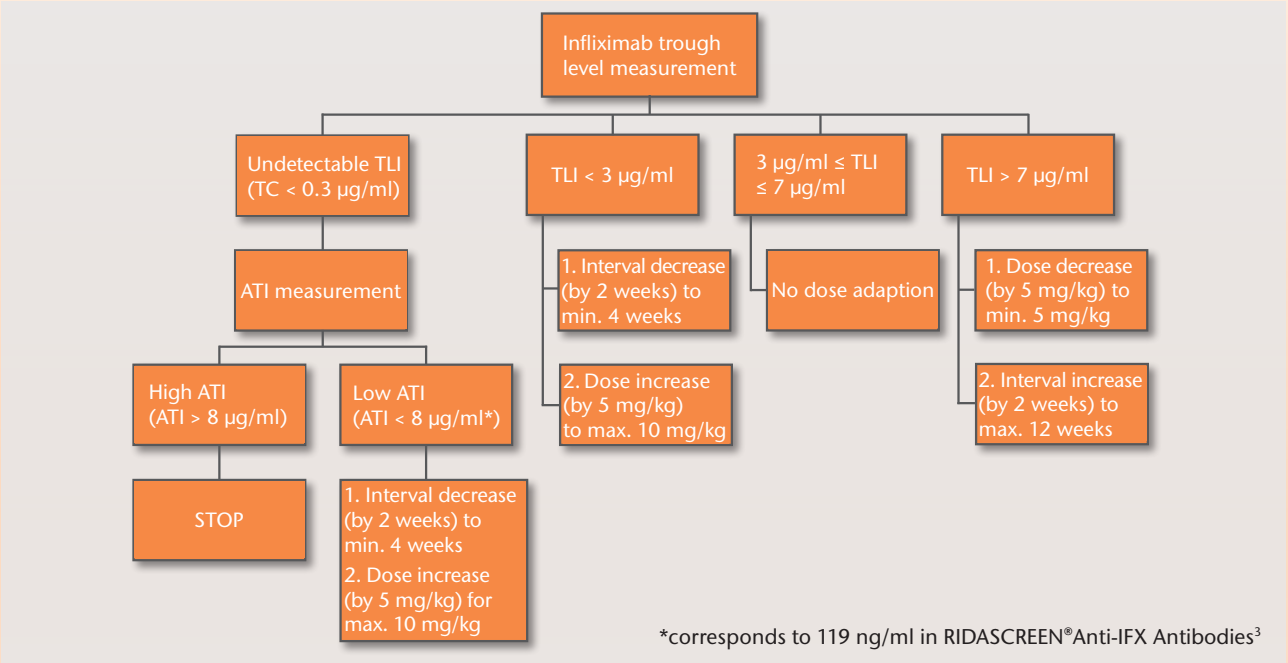

Fig. 5: TDM-based treatment algorithm used in TAXIT. TLI, trough levels of infliximab; ATI, anti-infliximab antibodies.[1] ATI were measured using a first-generation, polyclonal antibody-based assay.

Conclusion

TDM is a cost-effective treatment strategy for the management of patients with Crohn's disease and ulcerative colitis.

References:

1. *Vande Casteele N et al.* Trough Concentrations of Infliximab Guide Dosing for Patients With Inflammatory Bowel Disease; Gastroenterology 2015;148:1320–1329.
2. *Paul S et al.* Letter: infliximab de-escalation based on trough levels in patients with inflammatory bowel disease 2015;42:939-940.
3. *Imbrechts M* et al. Anti-infliximab antibodies: How to compare old and new data? J Pharm Biomed Anal 2020;177:112842.

4. Quantification of biosimilars

Biosimilars are equally well recognized in the ELISA and rapid assays as the originator drug – ADA towards the originator drug cross-react with the biosimilar drug

Biosimilar drugs are non-identical copies of the originator biological drug that have been approved for the same indications as the originator drug. They exhibit similar characteristics, but are not an exact copy of the originator drug due to variations in manufacturing process. Consequently, subtle differences may be present, which can influence their recognition in the drug and ADA assays.

Gils and co-authors evaluated different mouse monoclonal antibodies raised against Remicade®, including MA-IFX6B7 and MA-IFX10F9, for their reactivity toward biosimilars (Remsima®, Inflectra®).[1] The authors showed that MA-IFX6B7 and MA-IFX10F9 exhibit equal reactivity towards Remicade®, Remsima® and Inflectra® (Figure 6).[1] Moreover, the RIDASCREEN® IFX Monitoring quantified the biosimilars equally well as the originator drug.[1]

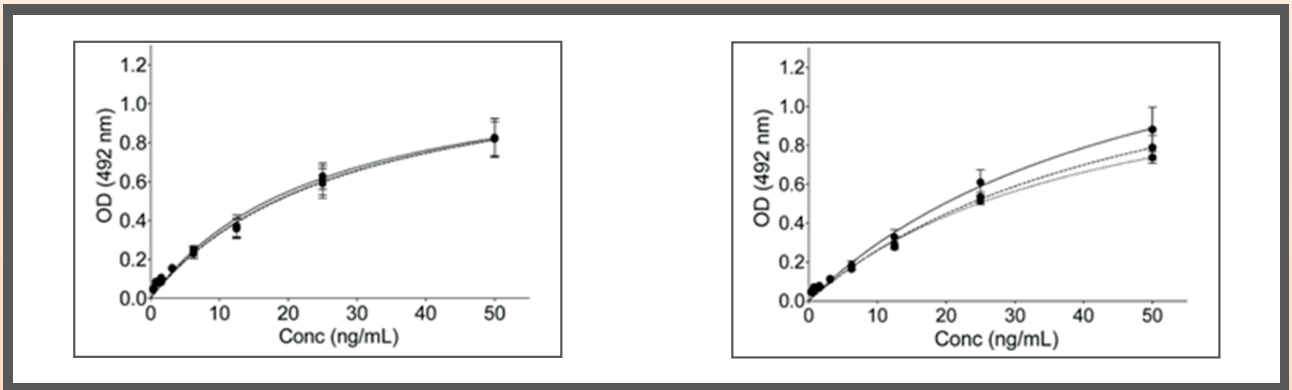

Fig. 6: Dose-response curves of the reactive of (A) MA-IFX6B7 and (B) MA-IFX10F9 towards Remicade (solid line) and Remsima (dashed line) and Inflectra (dotted line). Data are represented as mean ± SE (n= 6).

In addition, a series of ATI positive serum samples from IBD patients treated with Remicade® was found to cross-react with Remsima® and Inflectra®, revealing highly correlated ATI concentrations.

The authors concluded that the RIDASCREEN® TDM assays for Remicade® and anti-Remicade® antibodies can also be used to determine Remsima®, Inflectra® and anti-Remsima®/Inflectra® antibody concentrations.[1]

Conclusion

The RIDASCREEN® and RIDA®QUICK TDM assays can also be used to quantify biosimilar drugs and ADA towards the biosimilar drugs.

References:

1. *Gils A et al.* Harmonization of Infliximab and Anti-Infliximab Assays Facilitates the Comparison Between Originators and Biosimilars in Clinical Samples. Inflamm Bowel Dis 2016;22:969–975.

5. Publications on the antibodies used in the RIDASCREEN® TDM tests

5.1 Infliximab antibody generation and characterization

The RIDASCREEN® IFX Monitoring and RIDASCREEN® Anti-IFX Antibodies use highly specific monoclonal anti-IFX antibodies derived at KU Leuven. Both assays were clinically validated at KU Leuven.

In the RIDASCREEN® IFX Monitoring, monoclonal anti-IFX antibody (MA-IFX) clone MA-IFX6B7 is being used.[1] MA-IFX6B7 binds highly specific to the Fab fragment of IFX and, therefore, does not cross-react with other anti-TNFα drugs (ADM, etanercept, golimumab) or a human IgG-mixture.

The selected monoclonal antibody-based (MA-based) IFX ELISA was in perfect agreement with the clinically validated, reference polyclonal antibody-based (pAb-based) ELISA (Figure 7).[1]

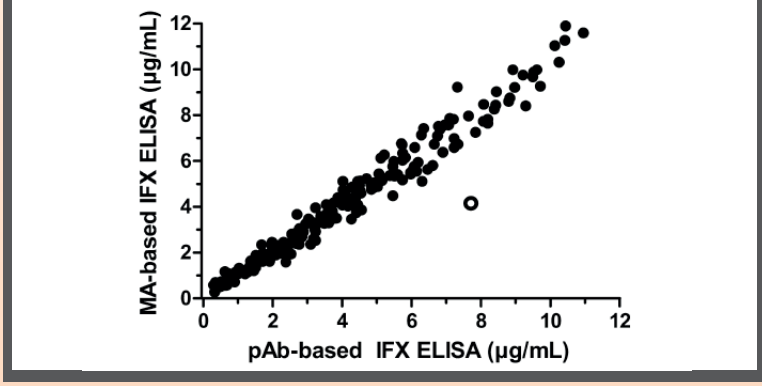

Fig. 7: Comparison of IFX values determined with the MA-based and pAb-based IFX ELISA. The MA-based IFX ELISA correlated well with the pAb-based IFX ELISA (R= 0.986). One sample (open dot) contained ADM from previous ADM treatment.[1]

In the RIDASCREEN® Anti-IFX Antibodies, MA-IFX10F9 is being used as calibrator antibody. It was selected by KU Leuven to replace the polyclonal antibody calibrator in their home-brew anti-IFX antibody ELISA.[2] MA-IFX10F9 binds highly specifically to the Fab fragment of IFX and, therefore, does not cross-react with other anti-TNFα drugs or a human IgG-mixture. Selection of MA-IFX10F9 led to a higher reproducibility and improved sensitivity and specificity of the anti-IFX antibody ELISA.[2] MA-IFX10F9 can be used as a universal calibrator to compare and harmonize anti-IFX antibody assays.

References:

1. *Van Stappen T et al.* Generation of a Highly Specific Monoclonal Anti-Infliximab Antibody for Harmonization of TNF-Coated Infliximab Assays. Ther Drug Monit 2015;37:479–485.

2. *Van Stappen T et al.* An Optimized Anti-infliximab Bridging Enzyme-linked Immunosorbent Assay for Harmonization of Anti-infliximab Antibody Titers in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2015;21:2172–2177.

5.2 Adalimumab antibody generation and characterization

The RIDASCREEN® ADM Monitoring and RIDASCREEN® Anti-ADM Antibodies use highly specific monoclonal anti-ADM antibodies derived at KU Leuven. Both assays were clinically validated at KU Leuven.

In the RIDASCREEN® ADM Monitoring, monoclonal anti-ADM antibody (MA-ADM) clone MA-ADM40D8 is being used.[1] MA-ADM40D8 binds specifically to the Fab fragment of ADM and, therefore, does not cross-react with other anti-TNFα drugs or a human IgG-mixture. As shown in Figure 8, TNFα only interferes with the quantification of ADM at supra-physiological concentrations.[1]

The RIDASCREEN® ADM Monitoring was externally validated with the ELISA assay from Sanquin, showing excellent agreement. The excellent agreement of the two commercially available ELISAs allows harmonization of treatment algorithms in and between different hospitals/infusion centers.[1]

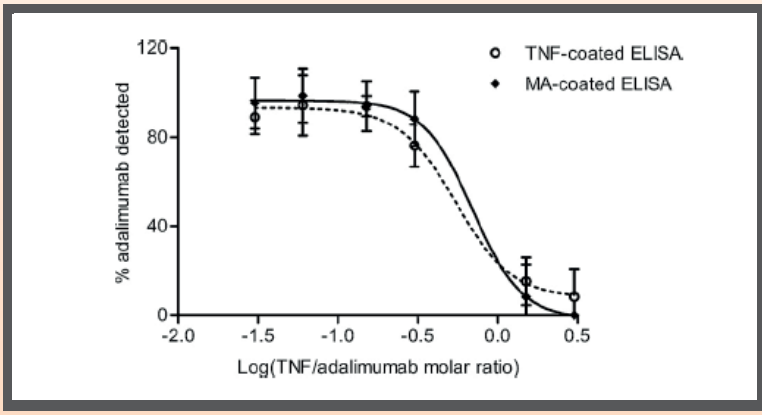

Fig. 8: Effect of TNF on ADM determination in the TNF-coated ELISA and the MA-coated ELISA, both developed at KU Leuven. Each point represents mean value plus standard deviation (n=3).[1] The RIDASCREEN® ADM Monitoring was based on the TNF-coated ELISA.[1]

In the RIDASCREEN® Anti-ADM Antibodies, monoclonal anti-ADM antibody (MA-ADM) clone MA-ADM6A10 is being used as calibrator antibody, upon selection at KU Leuven.[2] MA-ADM6A10 binds specifically to the Fab fragment of ADM and, therefore, does not cross-react with other anti-TNFα drugs or a humanized IgG-mixture.[2] MA-ADM6A10 can be used as a universal calibrator to compare and harmonize anti-ADM antibody assays.

References:

1. *Bian S et al.* Generation and characterization of a unique panel of anti-adalimumab specific antibodies and their application in therapeutic drug monitoring assays. Journal of Pharmaceutical and Biomedical Analysis 2016;125:62–67.
2. *Gils A et al.* Development of a Universal Anti-Adalimumab Antibody Standard for Interlaboratory Harmonization. Ther Drug Monit 2014;36:669-673.

6. Publications on the R-Biopharm TDM-ELISAs

6.1 RIDASCREEN® IFX Monitoring

The RIDASCREEN® IFX Monitoring shows excellent assay performance – as indicated by two independent assay comparison studies.

In a study from *Schmitz* and co-authors, the RIDASCREEN® IFX Monitoring, distritbuted by apDia (Turnhout, Belgium) as apDia Infliximab ELISA kit, and two other commercially available assays (LISA-TRACKER Infliximab, Theradiag, France and Promonitor®-IFX assay, Progenika, Spain) were compared to the in-house method of Sanquin Diagnostics (Amsterdam, The Netherlands).[1] The RIDASCREEN® IFX Monitoring has the lowest and most consistent imprecision of the three kits and the best agreement to the target value (96 % -108 %) as compared to the other assays (Table 2).[1]

Spiked	Sanquin	Lisa Tracker	Promonitor	apDia
10.0	8.5 (85 %)	>8 (n.d.)	9.7 (97 %)	10.8 (108 %)
5.0	5.9 (118 %)	5.9 (118 %)	4.6 (92 %)	5.1 (102 %)
2.5	1.7 (68 %)	1.7 (68 %)	1.3 (52 %)	2.4 (96 %)
0.5	0.4 (80 %)	0.4 (80 %)	0.3 (60 %)	0.5 (100 %)
Agreement to the target values is given between brackets.				

Tabele 2: Concentration of IFX-spiked plasma samples (µg/mL), as measured by Sanquin Diagnostics and three commercially available ELISA kits.[1] apDia = RIDASCREEN®

In an international study from *Marini* and co-workers, the reliability of Janssen's IFX and ATI assays was compared with commercial assays from KU Leuven (RIDASCREEN® IFX Monitoring), Sanquin, Dynacare, and LabCorp.[2] The RIDASCREEN® IFX Monitoring was found highly specific, accurate and reproducible and was in strong agreement with the Janssen's IFX assay.[2]

Conclusion

Comparative studies revealed a top-notch assay performance of the RIDASCREEN® IFX Monitoring, which was clinically validated at KU Leuven.

References:

1. *Schmitz E et al.* Therapeutic drug monitoring of infliximab: performance evaluation of three commercial ELISA kits. Clin Chem Lab Med 2016;54:1211-1219.
2. *Marini J et al*. Comparisons of Serum Infliximab and Antibodies-to-Infliximab Tests Used in Inflammatory Bowel Disease Clinical Trials of Remicade® The AAPS Journal 2017;19:161-170.

6.2 RIDASCREEN® Anti-IFX Antibodies

The RIDASCREEN® Anti-IFX Antibodies shows a very high sensitivity for the quantification of ATI. MA-IFX10F9 can be used as a universal calibrator for assay harmonization.

In an international study from *Marini* and co-workers, the reliability of Janssen's IFX and ATI assays was compared with commercial assays from KU Leuven, Sanquin, Dynacare, and LabCorp.[1]

All ATI assays specifically and reproducibly detected ATI.[1] The commercial assays were at least as sensitive as Janssen's "original" ATI method, but only two (KU Leuven and LabCorp) were as sensitive as Janssen's newer "drug tolerant" ATI method.[1] Interestingly, KU Leuven and the Janssen "original" ATI method demonstrated outstanding agreement, as analyzed through a ROC curve plotting the true positive rate against the false positive rate.[1]

Importantly, the authors highlighted that all ATI assays reported different ATI titer/concentration values.[1]
Consequently, **reported ATI of different ATI assays are not interchangeable**. As previously pointed out, the highly specific and reproducible calibrator antibody used in the RIDASCREEN® Anti-IFX Antibodies, MA-IFX10F9, can be used as a universal calibrator to facilitate assay comparison and harmonization.[2]

Conclusion

The RIDASCREEN® Anti-IFX Antibodies uses a highly specific and reproducible calibrator antibody, MA-IFX10F9, which can be used as a universal calibrator for assay harmonization.

References:

1. *Marini J et al.* Comparisons of Serum Infliximab and Antibodies-to-Infliximab Tests Used in Inflammatory Bowel Disease Clinical Trials of Remicade® The AAPS Journal 2017;19:161-170.
2. *Van Stappen T et al.* An Optimized Anti-infliximab Bridging Enzyme-linked Immunosorbent Assay for Harmonization of Anti-infliximab Antibody Titers in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2015;21:2172–2177

6.3 RIDASCREEN® vs. RIDA®QUICK IFX Monitoring

With a time-to-result of 20 minutes, individual sample analysis and user-friendliness, the RIDA®QUICK IFX Monitoring outplays conventional ELISA as a rapid, accurate tool to monitor IFX concentrations

In this study, a novel lateral flow-based assay (LFA; RIDA®QUICK IFX Monitoring) for rapid IFX quantification was benchmarked to a reference IFX ELISA (RIDASCREEN® IFX Monitoring) using 190 serum samples, prospectively collected from a cohort of 29 patients with ulcerative colitis starting IFX.[1]

In total, 190 unique patient samples were analyzed in parallel by the LFA and ELISA. A very good correlation and intra-class correlation coefficient was observed for samples withdrawn during induction and maintenance of IFX treatment (Figure 9). The positive and negative percent agreement between LFA and the reference ELISA are 99.7 % and 98.6 %, respectively.[1]

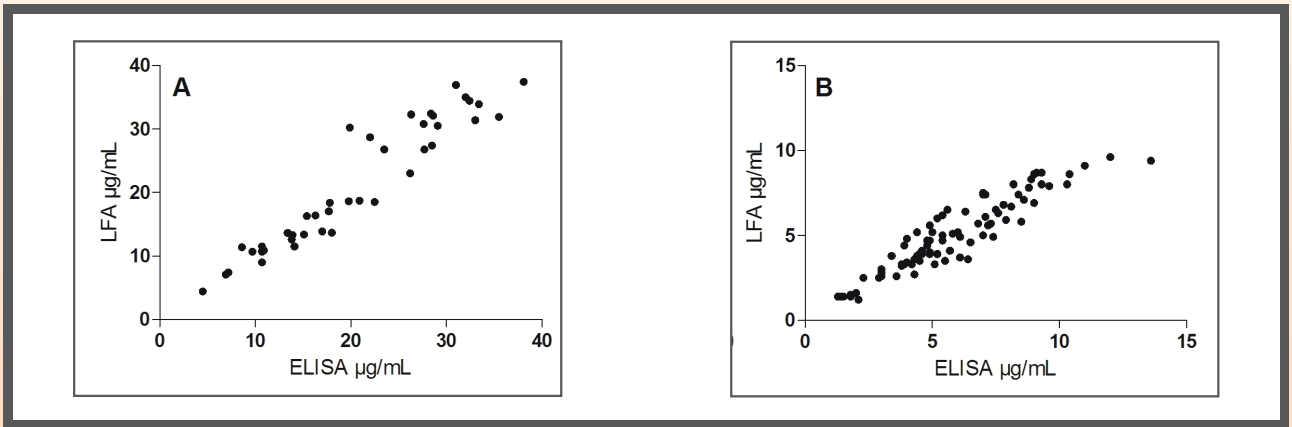

Fig. 9: Correlation analysis of week 2 and 6 serum samples (A, n=41) and maintenance treatment serum samples (B, n=84) between ELISA and the lateral flow assay (LFA).[1]

Conclusion

The availability of a rapid test for IFX quantification introduces a new era of TDM, comprising rapid and on-site drug concentration monitoring, which allows immediate dose adaptation.

References:

1. *Van Stappen T et al.* Rapid Test for Infliximab Drug Concentration Allows Immediate Dose Adaptation. Clin Transl Gastroenterol 2016;7:e206.

6.4 Branding of drug and anti-drug antibody ELISAs

The drug and anti-drug antibody ELISAs are distributed by R-Biopharm (Darmstadt, Germany) and apDia (Turnhout, Belgium) under a different brand name. R-Biopharm distributes the TDM products worldwide with the exception of Belgium, the Netherlands, Luxemburg and Slovenia. ApDia distributes the TDM products in Belgium, the Netherlands, Luxemburg and Slovenia.

R-Biopharm product name	Art. No.	apDia product name
RIDASCREEN® IFX Monitoring	G09041	apDia Infliximab ELISA kit
RIDASCREEN® Anti-IFX Antibodies	G09042	apDia Anti-Infliximab ELISA kit
RIDASCREEN® ADM Monitoring	G09043	apDia Adalimumab ELISA kit
RIDASCREEN® Anti-ADM Antibodies	G09044	apDia Anti-Adalimumab ELISA kit
RIDASCREEN® VDZ Monitoring	G09045	apDia Vedolizumab ELISA kit
RIDASCREEN® GLM Monitoring	G09047	apDia Golimumab ELISA kit
RIDA®QUICK IFX Monitoring	GN3041	
RIDA®QUICK ADM Monitoring	GN3043	

7. Drug tolerant vs. drug sensitive assays

A drug-tolerant assay markedly increases the quantification of ADA – nevertheless its clinical relevance remains unclear.

The RIDASCREEN® Anti-IFX Antibodies and the RIDASCREEN® Anti-ADM Antibodies only detect the "free" ADA fraction or, in other words, the ADA fraction that is not bound to drug. This "free" ADA fraction is associated with loss of response, infusion reactions and/or hypersensitivity. Assays that only detect "free" ADA are known as **drug-sensitive assays**.

Recently, researchers developed assays that not only detect the "free" ADA fraction, but also the "bound" ADA fraction, referring to the ADA fraction that is bound to the drug. Such assays are also known as **drug-tolerant assays**. Drug-tolerant assays typically use a sample pretreatment step involving acid, as illustrated in Figure 10, allowing them to detect drug-bound ADA.[1]

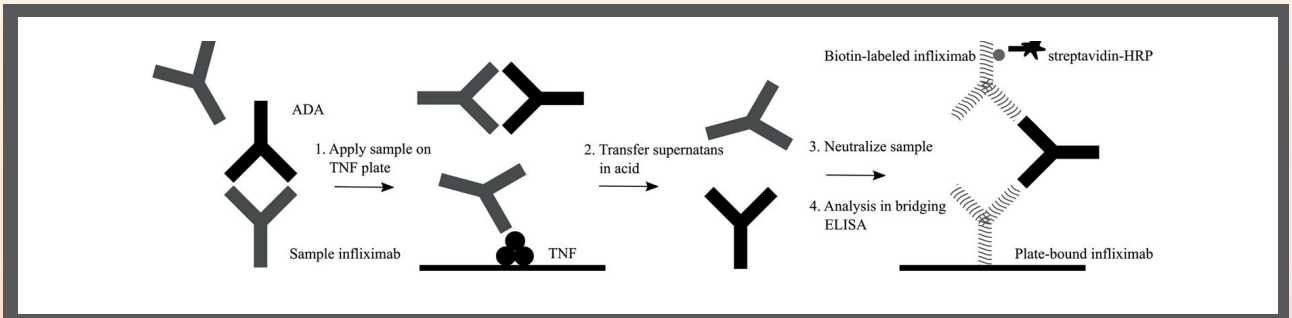

Fig. 10: Example of a drug-tolerant assay for the measurement of ATI. Patient samples containing complexes of ADA and infliximab are applied to a TNFα-coated plate for the removal of excess infliximab. Then, supernatant is transferred into a new tube and acidified to dissociate remaining drug-ADA complexes. After neutralization, the sample is applied on the conventional bridging ELISA. (adopted from *Van Stappen T* et al. Drug Test Anal 2017)

To date, the clinical utility of drug-tolerant assays remains subject of debate, as indicated by Van Stappen and colleagues, who concluded that a drug-tolerant assay is not superior to a drug-sensitive assay for the management of patients with inflammatory bowel disease under stable maintenance treatment.[2]

Conclusion

The RIDASCREEN® Anti-IFX Antibodies and the RIDASCREEN® Anti-ADM Antibodies are drug-sensitive assays that detect the clinically relevant – "free" – fraction of ADA.

References:

1. *Van Stappen T et al.* Validation of a sample pretreatment protocol to convert a drug-sensitive into a drug-tolerant anti-infliximab antibody immunoassay. Drug Test Anal 2017;9: 243-247.
2. *Van Stappen T et al.* Clinical relevance of detecting anti-infliximab antibodies with a drug-tolerant assay: post hoc analysis of the TAXIT trial. Gut 2017;Epub Ahead of Print.

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