TDM of biologics reassures clinicians in personalized dosing

14th EBF Open Symposium

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Sanquin diagnostic services

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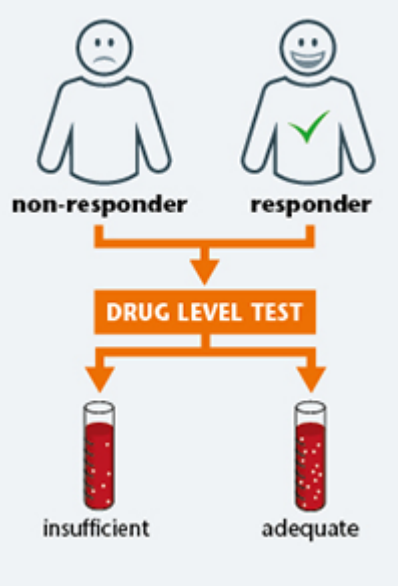
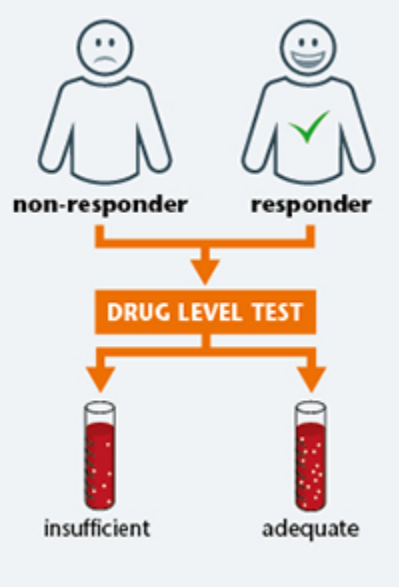
Therapeutic Drug Monitoring of biologics

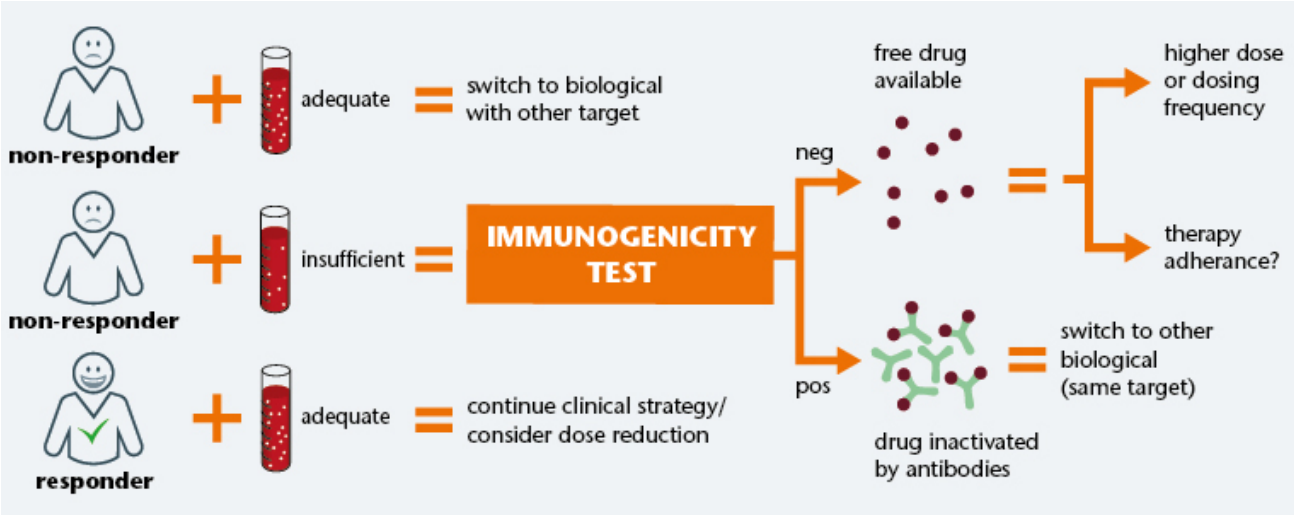
How can drug monitoring help clinicians?

- Understand drug failure
- Perform fine-tuning of drug dosage or switch to other therapeutics when necessary
- Reveal both over- and undertreatment at early stages, before recurrence of clinical symptoms
- Find the optimal dose interval by measuring drug level



Understand drug failure, how to interpret PK / ADA test results in the clinical setting?





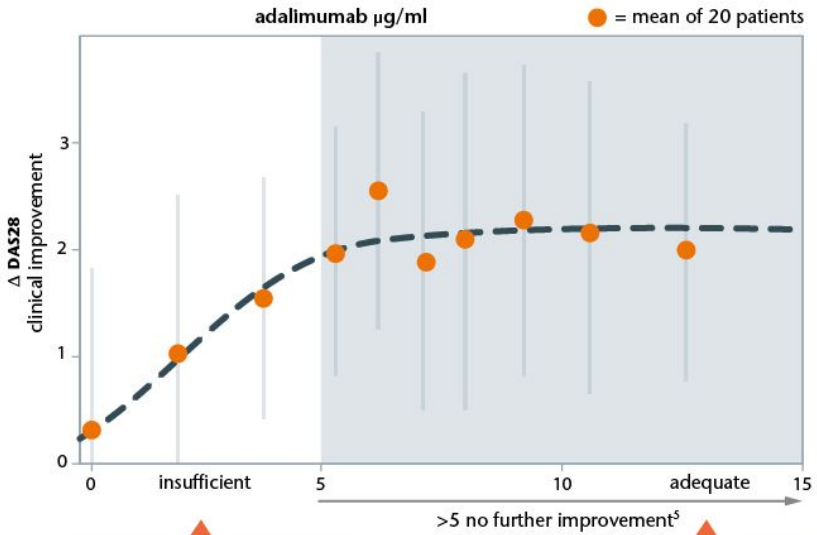
Therapy drug target concentrations not provided by clinical trial / drug label

Post-approval studies have been performed (by academia) to establish reference values

Different for biologics with same target?

Different for each disease?

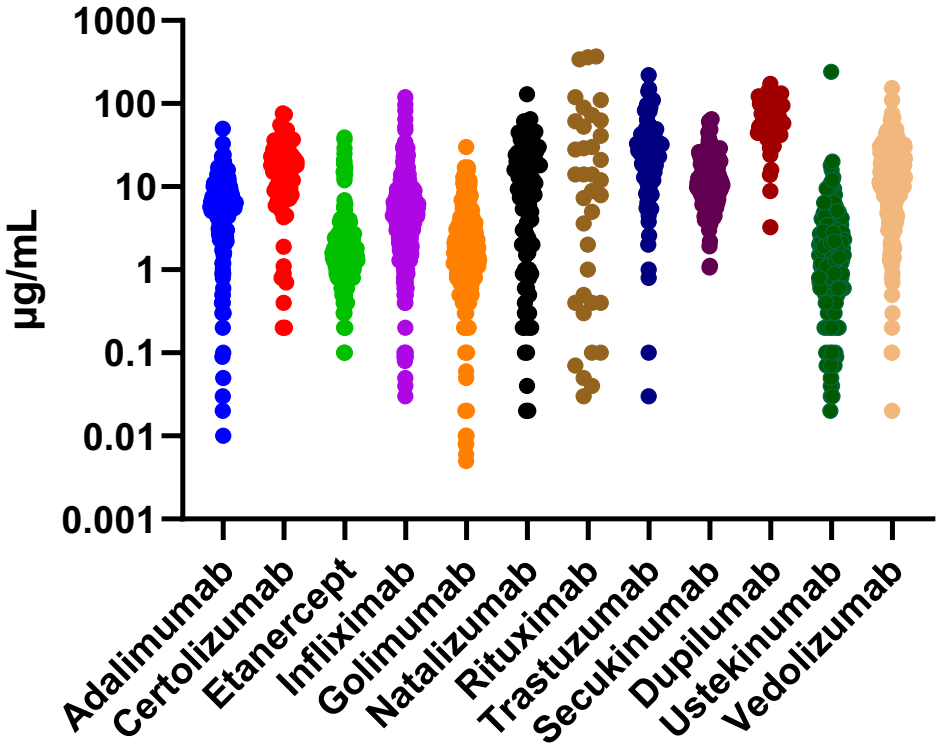
Different for individual patient?



Published correlation effects	RA	IBD	Psoriasis
adalimumab	5 - 8 mg/l[1]	Clinical studies ongoing	3.5 - 7.0 mg/l[4]
infliximab	≥ 3 mg/l[2]	3 - 7 mg/l[3]	Clinical studies ongoing

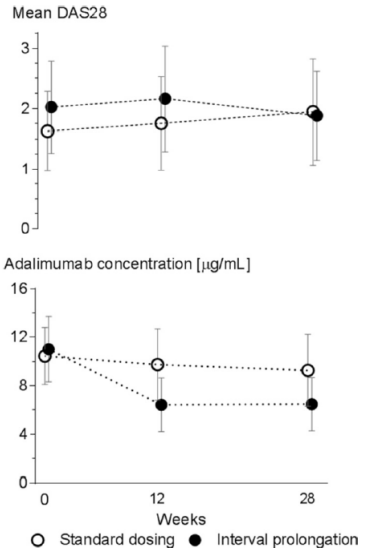
Removing overexposure by dose tapering

Patient variability at steady state trough level



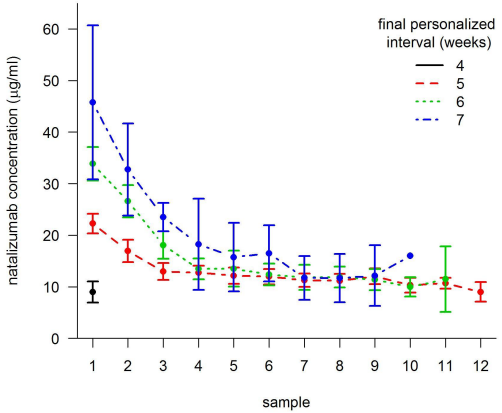
Dose interval extension can result in lower trough levels without loss of treatment efficacy

Adalimumab interval extension



Natalizumab interval extension

n 48	Baseline	12 months
Gd+ lesions	0	0
Active T2 lesions	0	0
Relapse	0	0
EDSS score	3.0 (2.0-5.0)	3.0 (2.0-5.0)
T25FW	4.3 (3.4-5.2)	4.1 (3.4-5.5)



- Less infusion related complications
- Fewer trips to the hospital for the patient
- Fewer wear-off complains
- Patients chose to stay on extended interval after study
- Lower general health care expenditure

l'Amie et al. Ann Rheum Dis 2018
Kempen et al. Multiple Sclerosis Journal 2017
Michielsens et al. Drugs 2021

Need to establish PK assay comparability between providers

Differences in assay setup may affect interpretation

- Free vs total biologic
- Intact vs fragmented biologic (e.g. ETN)
- Target, drug, ADA tolerance

Allows link between datasets generated using different assays

Initiatives by Janssen and Takeda to asses performance of commercial assays to the assays used in clinical trials

“The performance of the PK assay was determined to be within the expected range of the vedolizumab PK clinical trail assay used by Takeda, the manufacturer of Entyvio®. The clinical utility of these results is unknown.”

Essential for interpretation of individual patient result

Proactive therapeutic drug monitoring of infliximab: a comparative study of a new point-of-care quantitative test with two established ELISA assays

J. Afonso[*,†], S. Lopes[‡], R. Gonçalves[§], P. Caldeira[¶], P. Lago[**], H. Tavares de Sousa[††,‡‡], J. Ramos[§§], A. R. Gonçalves[¶¶], P. Ministro[***], I. Rosa[†††], A. I. Vieira[‡‡‡], C. C. Dias[§§§,¶¶¶] & F. Magro[*,†,‡] on behalf of Portuguese IBD Study Group (GEDII)

Comparison of Three Assays to Quantify Infliximab, Adalimumab, and Etanercept Serum Concentrations

Ji S van Bezooijen [1], Birgit C P Koch, Martijn B A van Doorn, Errol P Prens, Teun van Gelder, Marco W J Schreurs

Serum trough infliximab levels: A comparison of three different immunoassays for the monitoring of CT-P13 (infliximab) treatment in patients with inflammatory bowel disease

Karin Malíčková [a,*], Dana Ďuricová [b,c], Martin Bortlík [b,d], Miroslav Hind'oš [a], Naděžda Machková [b], Veronika Hrubá [b], Martin Lukáš [b], Tomáš Zima [a], Milan Lukáš [a,b]

Comparisons of Serum Infliximab and Antibodies-to-Infliximab Tests Used in Inflammatory Bowel Disease Clinical Trials of Remicade®

Joseph C Marini [1], Jocelyn Sendecki [2], Freddy Cornillie [3,4], John W Popp Jr [5], Shawn Black [5], Marion Blank [5], Ann Gils [6], Thomas Van Stappen [6], Dörte Hamann [7], Theo Rispens [8], Lina Thérien [9], Kelly Chun [10], Gopi Shankar [11]

Need for inter-laboratory proficiency testing

Round robins for biologics

Reference standards NIBSC / WHO

https://www.skml.nl/en/home/schemes
bioanalysis@sanquin.nl
https://www.nibsc.org/products/brm_product_catalogue/who_standards.aspx
https://www.who.int/activities/providing-international-biological-reference-preparations

Interpretation of ADA results is highly assay dependent

Phase I (&II) adalimumab biosilars, single dose 40mg, 72day follow-up

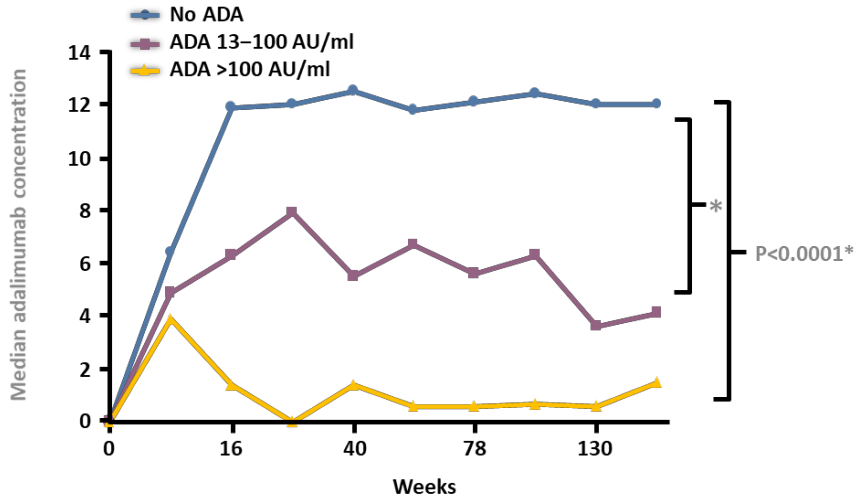
Adalimumab biosimilars	ADA (%)
Amgen	
Amgevita	46
Humira (EU)	61
Sandoz GmbH	
Hefiya	66.5
Humira (EU&US)	70.6
Kyowa Kirin Limited	
FKB327	69.5
Humira (EU)	73.3
Boehringer Ingelheim	
Cyltezo	93
Humira (EU)	84
Samsung Bioepis	
Imraldi	98.4
Humira (EU)	95.2

- No international standards

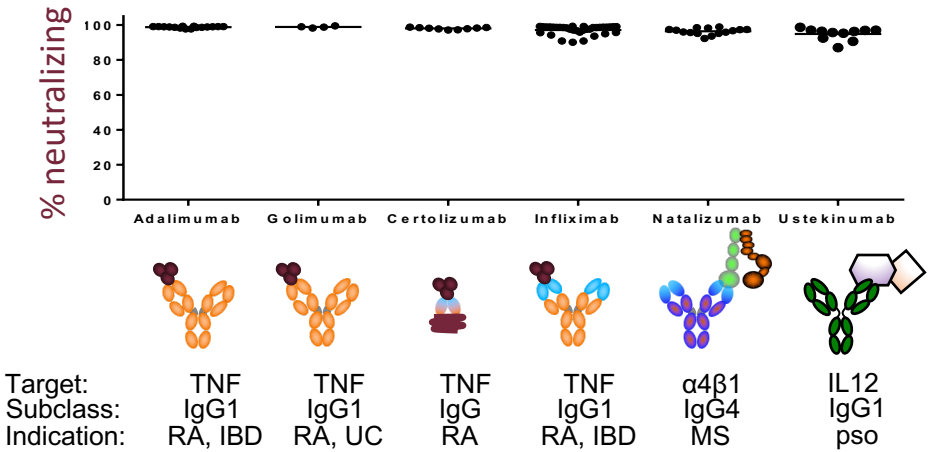
FDA EPAR documents

Pragmatic interpretation of patient specific immunogenicity

Key impact ADA on PK



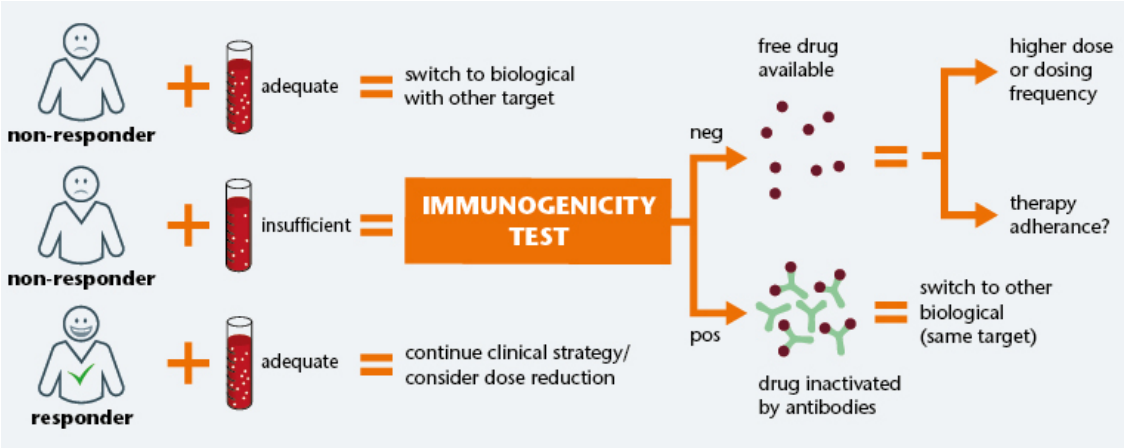
Anti-drug antibodies are largely neutralizing

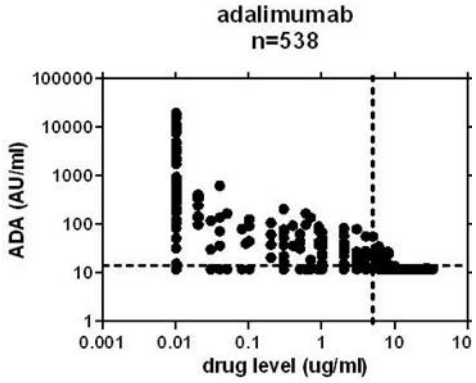


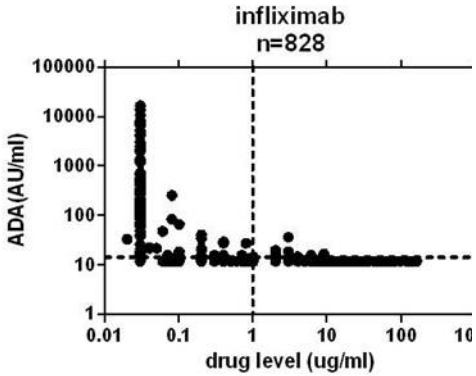
Bartelds et al. *JAMA.* 2011
van Schie et al. JACI, 2016; van Schie et al. ARD, 2015
Atiqi et al. Front Immunol. 2020

Pragmatic interpretation of patient specific immunogenicity

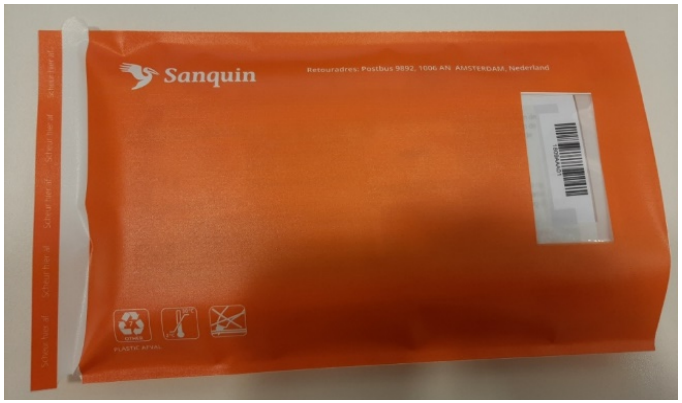
- No need for extensive drug tolerance
- No need for additional nAb testing
- Semi-quantification essential for interpretation
- Clinical decision based on known interaction between PK and ADA assay







At home sampling aides TDM



Conclusion

Therapeutic drug monitoring

- Informs clinicians in case of treatment failure
- Allows personalized dosing
- Keeps patients engaged with their treatment
- Enables cost-effective use of biologics

Acknowledgements

Patients and clinicians

(Inter)national hospitals and collaborators

Reade
revalidatie | reumatologie

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