Sanquin

Therapeutic drug monitoring of biologics reassures clinicians in personalised dosing

15th EBF Open Symposium

Floris Loeff, Head Biologics Laboratory

Sanquin Diagnostic Services

For Life.

Conflict of Interest Disclosure

- I have the following potential conflict(s) of interest to report

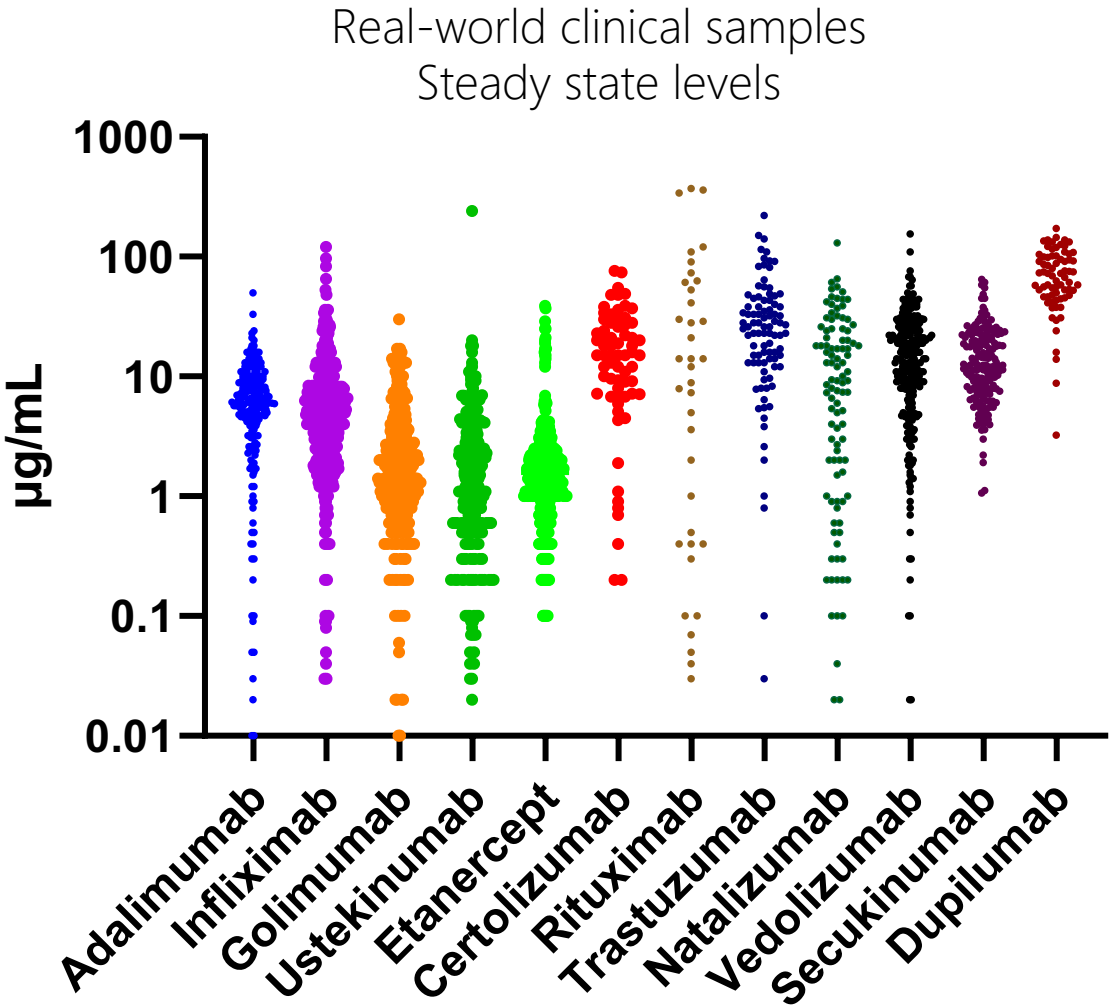
❑ Employee at Sanquin Diagnostic Services, provider of TDM of Biologics service testing

Biologics are given at a fixed dose selected for maximum clinical efficacy

Absence of toxicity means no penalty on overdosing

Large interpatient variation in serum concentration

Suggests room for personalised dosing



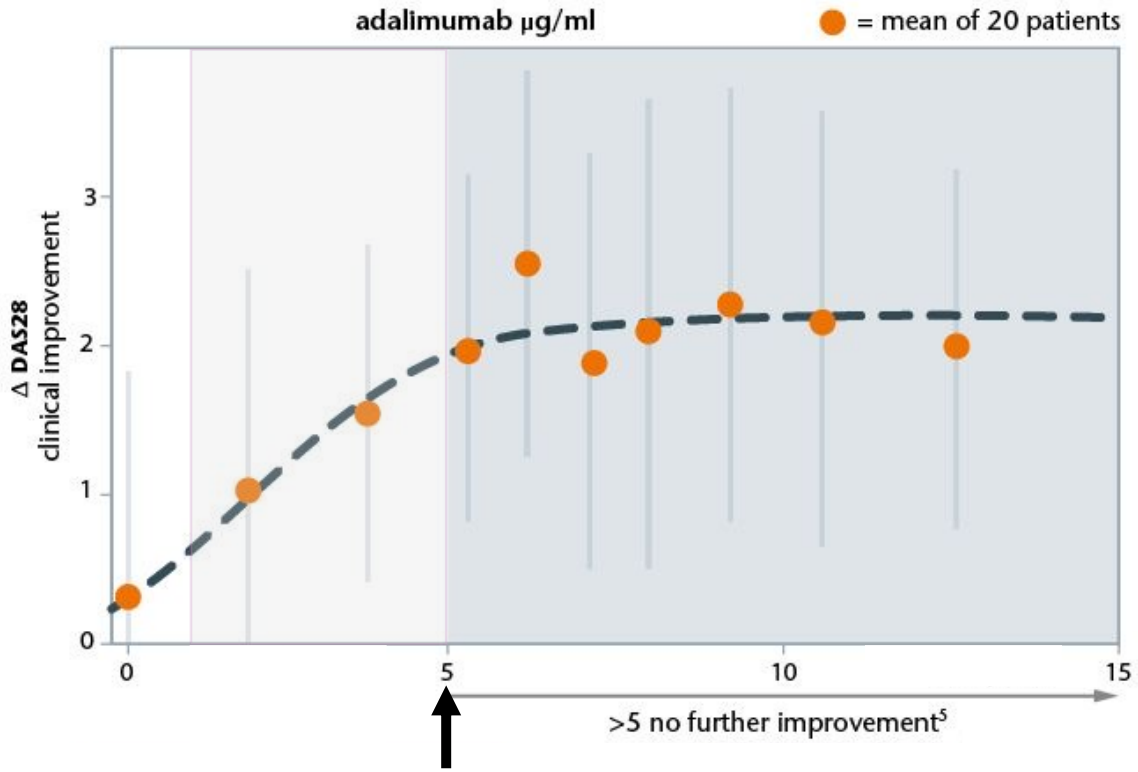
results < detection level not shown

Absence of minimal target drug level in the drug label makes physicians reluctant to implement TDM of biologics

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

Population based

Little/no insight interpatient variation in reference level



Current 'conservative' reference level

https://www.sanquin.org/products-and-services/bioanalysis-of-biologics/publications/index

Growing consensus on benefit of TDM of Biologics, implementation in clinical guidelines

American Gastroenterological Association Institute *Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease.* Gastroenterology 2017;153:827–834

A Comprehensive Literature Review and Expert Consensus Statement on Therapeutic Drug Monitoring of Biologics in Inflammatory Bowel Disease.
The American College of Gastroenterology (2021) 116:2014–25

Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases.
IBD Sydney Organisation and the Australian Inflammatory Bowel Diseases Consensus Working Group

Therapeutic Drug Monitoring to Guide Clinical Decision Making in Inflammatory Bowel Disease Patients with Loss of Response to Anti-TNF: A Delphi Technique-Based Consensus.
Swiss Society of Gastroenterology

Use of biologics for inflammatory bowel disease in Hong Kong: consensus statement.
Hong Kong IBD Society

EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases.
European Alliance of Associations for Rheumatology (EULAR) TaskForce

‘Big picture’ reference values for IBD

AGA guideline (14)	**Suggested trough level (μ g/mL)**
Reactive TDM for anti-TNF treatment in active IBD	Infliximab > 5 Adalimumab ≥ 7.5 Certolizumab ≥ 20 Golimumab unknown
No recommendation about proactive TDM for anti-TNF treatment in quiescent IBD	

ACG guideline (12)	**Suggested trough level (μ g/mL)**
Reactive TDM for all biologics (primary non response and secondary loss of response)	Infliximab: At week 2: > 20–25 Week 6: > 15–20 Week 14: 7–10 Maintenance: 5–10 Adalimumab: Week 4: 8–12 Maintenance: 8–12
Proactive TDM for anti-TNF therapy (after induction, at least once in maintenance, treatment de-escalation, drug holiday, anti-TNF monotherapy)	

AGA, american gastroenterology association; ACG, american college of gastroenterology.

Multi-utility of therapeutic drug monitoring in inflammatory bowel diseases
Front. Med., 28 July 2022. Sec. Gastroenterology

One size does not fit all. Lower infliximab level during maintenance phase in IBD

Observational studies	IBD type; *N*	Drug	Drug level target (μ g/mL)	Time point	Therapeutic outcome
Prospective					
Clarkston et al.	CD; *N* = 72	Infliximab	≥26.7	Week 2	Clinical response at week 14
			≥15.9	Week 6	
Buhl et al.	CD and UC; *N* = 166	Infliximab	>22.9	Week 2	Clinical response at week 14
			>11.8	Week 6	
Retrospective					
Dreesen et al.	CD; *N* = 122	Infliximab	>23.1	Week 2	Endoscopic remission at week 12
			>10	Week 6	
Vande Casteele et al. (23)	UC; *N* = 484	Infliximab	≥18.6	Week 2	Endoscopic remission at week 8
			≥10.6	Week 6	
Adedokun et al.	UC; *N* = 728	Infliximab	>22	Week 6	Clinical response at week 8

Observational studies	IBD type; *N*	Drug	Drug level target (μ g/mL)	Time point	Therapeutic outcome
Prospective					
Kennedy et al. (3) (PANTS)	CD; *N* = 1610	Infliximab	≥7.0	Week 14	Clinical remission at week 14 and 54
Retrospective					
Perinbasekar et al. (31)	CD and UC; *N* = 127	Infliximab	≥3	At least once in maintenance	Clinical response at 60 days, clinical response at 1 year, endoscopic response and persistence with anti-TNF at 1 year
Bernardo et al. (32)	CD and UC; *N* = 117	Infliximab	3–7 in CD; 5–10 in UC	Every 6 months	Clinical remission at week 48
Papamichael et al. (30)	CD and UC; *N* = 264	Infliximab	5–10	Any frequency during maintenance phase	Treatment failure (IFX discontinuation due to LOR or serious adverse event or surgery)
Papamichael et al. (18)	CD and UC; *N* = 102	Infliximab	5–10	Median of 3 (range 1–7) proactive infliximab monitoring evaluations	Treatment failure and IBD-related surgery and hospitalization

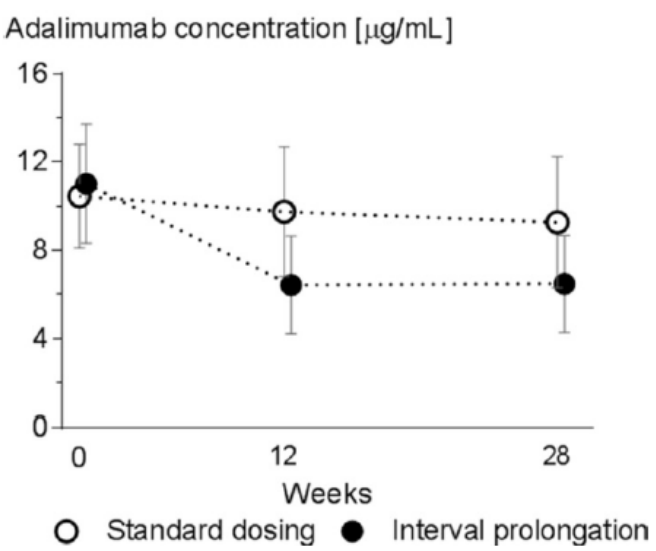
Acute phase 10 – 27 μg/mL

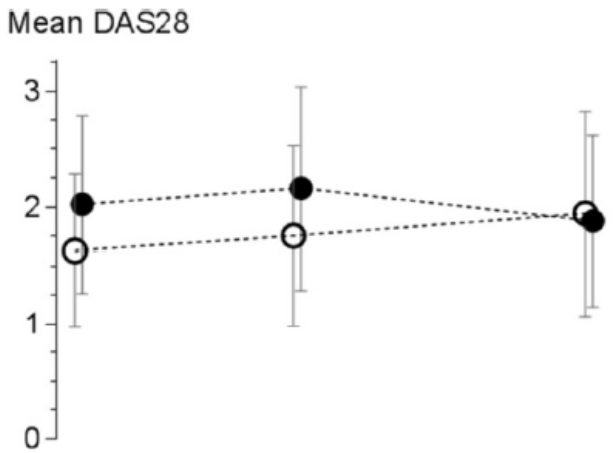
Maintenance phase 3 – 10 μg/mL

Multi-utility of therapeutic drug monitoring in inflammatory bowel diseases
Front. Med., 28 July 2022. Sec. Gastroenterology

Dose interval extension studies based on TDM confirm current ‘big picture’ reference values

Adalimumab interval extension (conservative 5µg/mL target)





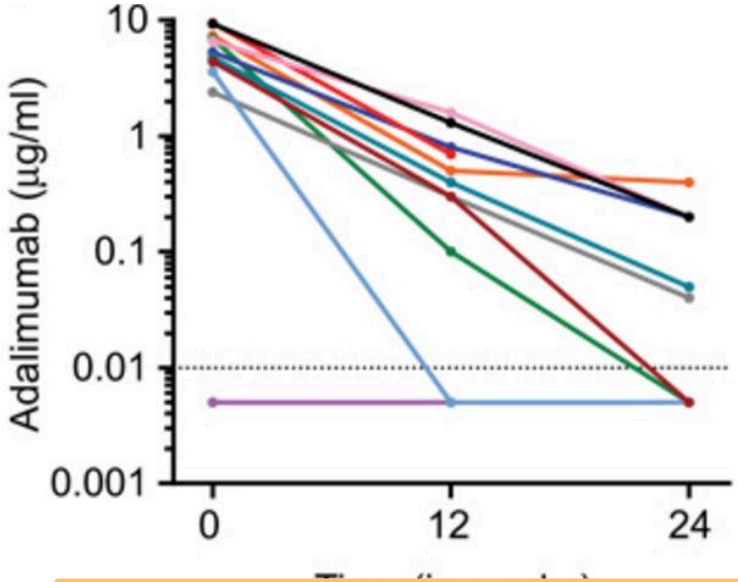
Dose interval extension results in

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

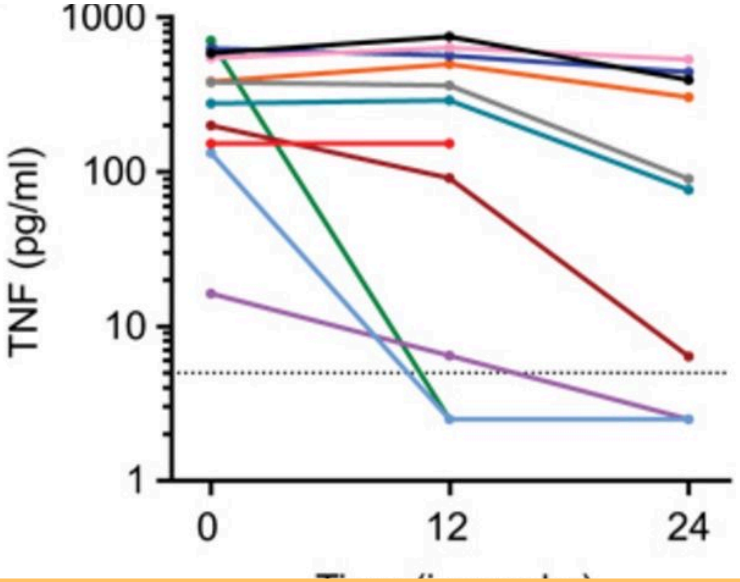
l’Amie et al. Ann Rheum Dis 2018
Kempen et al. Multiple Sclerosis Journal 2017
Michielsens et al. Drugs 2021

Continued target saturation after adalimumab discontinuation suggests an effective therapeutic drug level < 1 µg/mL for Rheumatoid Arthritis

Adalimumab



(ADL complexed) TNFa



Intervention/stopping studies

- Insight interpatient variation in required drug level

In conclusion: TDM of Biologics established the big picture of therapeutic reference levels, but may be finetuned by gaining insight in patient variation in critical concentration

Berkhout et al. Science translational medicine 2019

Pre-screening for patient inclusion of clinical trials

Natural half-life's of mAb's is ~2-3w,

Impact of prior drug on current treatment, temporary co-medication

Screening may help select drug free patients or at least interpret generated clinical data

	Half-life (days)	5 half-lives (days)
Etanercept	4.3	21.5
Infliximab	8–10	50
Golimumab	12	60
Rituximab	21	105
Tocilizumab	13	65
Abatacept	15	75

Louthrenoo et al. July 2017 International Journal of Rheumatic Diseases 20(Suppl. 10)

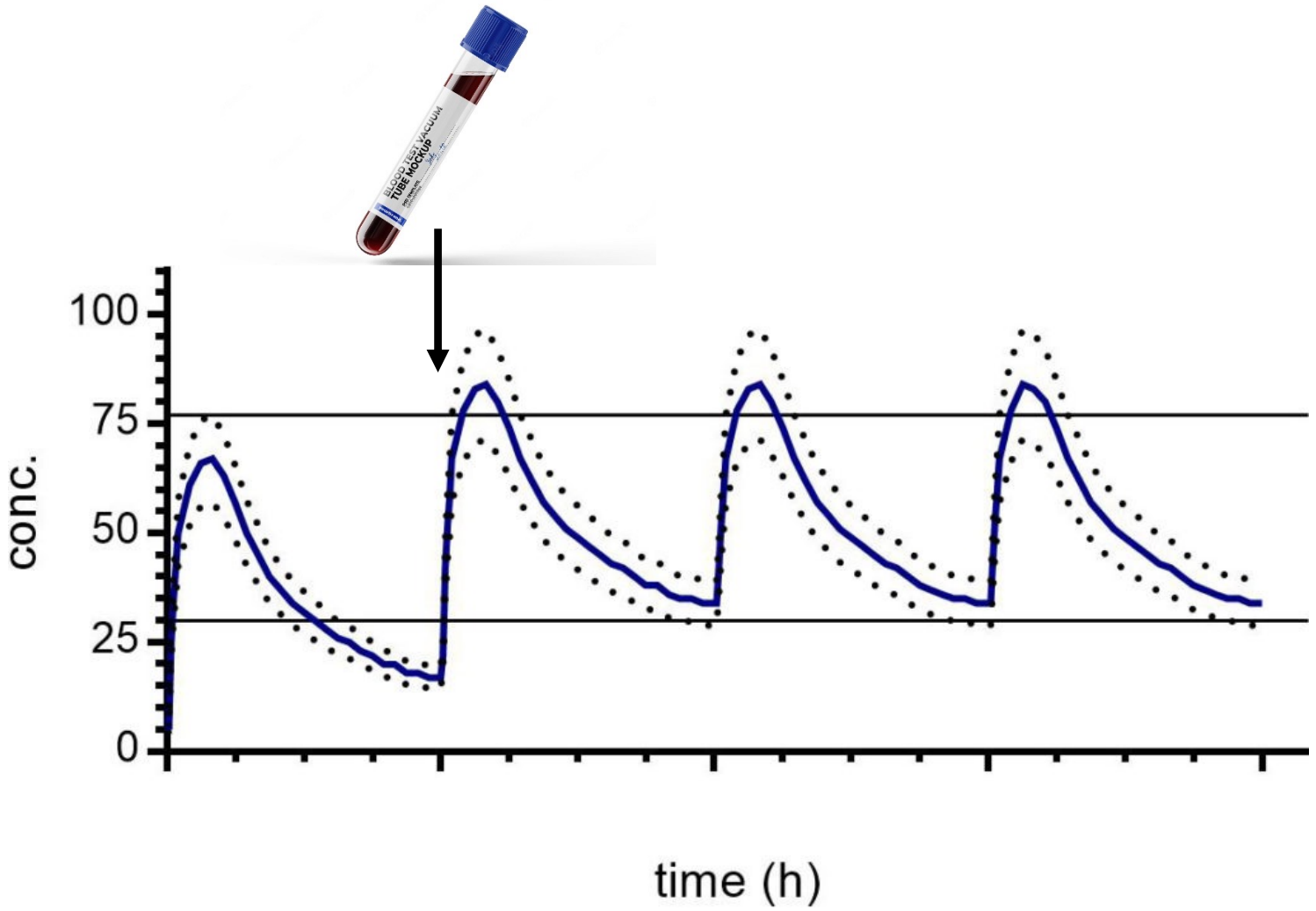
Drug exposure is a continuum, a measurement is just a single timepoint

Patient-visit is rarely at trough

Modelling would help more accurate interpretation of the result

Or

..



At home sampling aides TDM of biologics

Better timing of sampling

Less effort, more frequent sampling

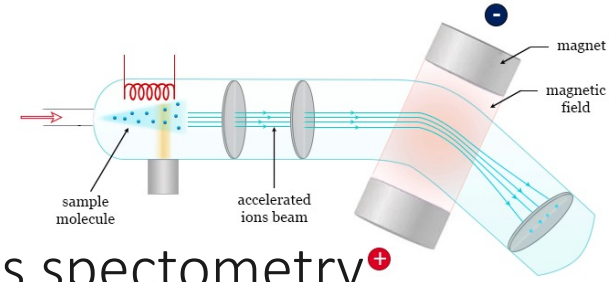
16:20	**18:20**	**Microsamping / Clinical & Patient Centric Considerations (Parallel) - Auditorium**
		Session chair: Matthew Barfield, F. Hoffmann La Roche
17:40	18:00	***Maurice Steenhuis, Sanquin Diagnostic services***
		Towards the use of fingerprick blood sampling for therapeutic drug monitoring

Different techniques to establish concentration

ELISA / ECL

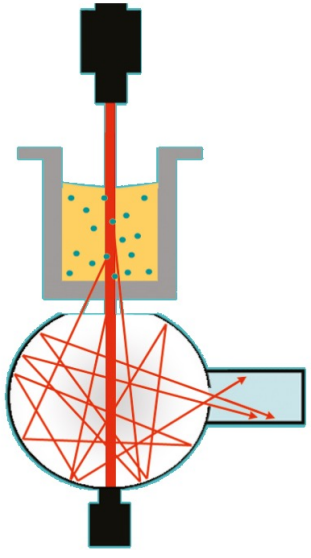
+ Clinical trial data, golden standard
+ Sensitivity (low ng vs ~µg)
- Batched analysis
- Biologic specific reagents

Central lab



Mass spectometry

+ Generic reagents
- Batched analysis
~ One workflow for multiple biologics



Nephelometry

+ Optimised for single ad hoc test
+ Minimally trained personnel
+ Fast
- Portfolio (no antidrug antibody testing)

POC

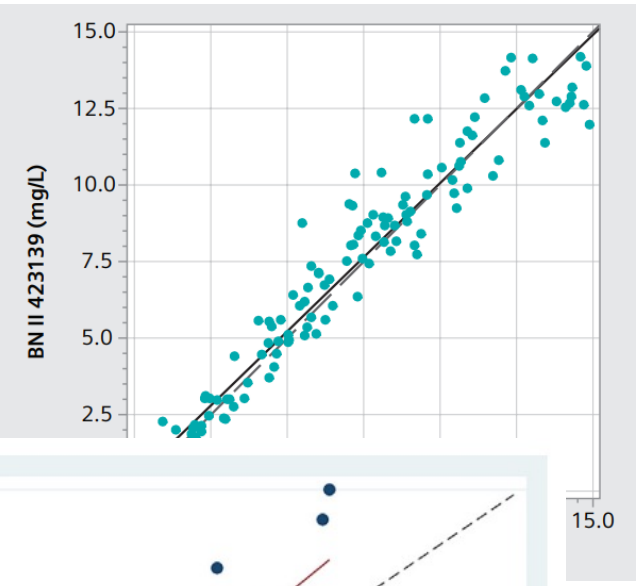
+ Single ad hoc test
+ Minimally trained personnel
+ Fast
- Specific machine and cartridges

Important to know what you measure and how to relate to published values

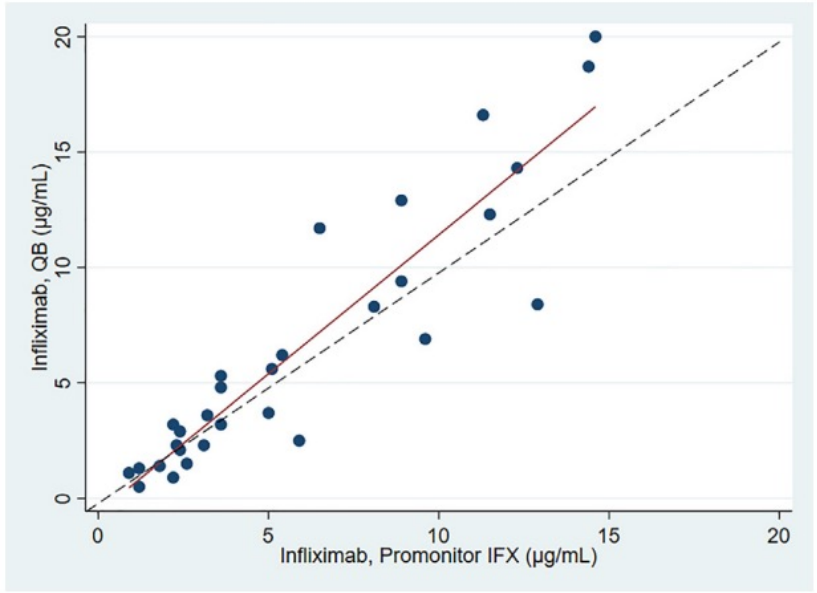
In general, good correlation between methods (after correction factor)

- Total vs free antibody concentration
- Non-functional complexed drug (target or anti-drug antibodies)
- Non-functional drug fragments (LC-MS/MS)

Nephelometry vs ELISA



POC vs ELISA



Novakovic et al. Clinical Biochemistry 2019

Interpretation of immunogenicity results is highly assay dependent

Phase I/II adalimumab biosimilars, single dose 40mg, 72d 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

FDA EPAR documents

Difference in anti-drug antibody ratio despite

- Same technique (MSD ECL)
- Same assay design (homogeneous bridging with acid dissociation)
- Same capture/detection reagents (labeled biologic)

➢ Small difference is reagent concentrations, and the properties of surrogate positive control determines cut-off for positivity

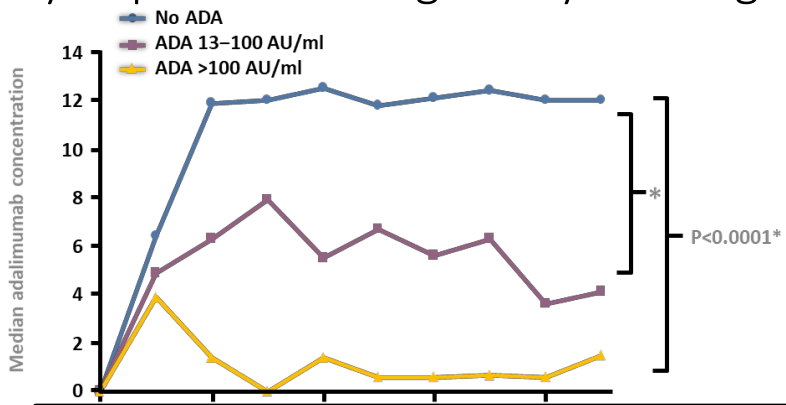
No international anti-drug Ab standard available

➢ Infliximab soon to come (NIBSC)

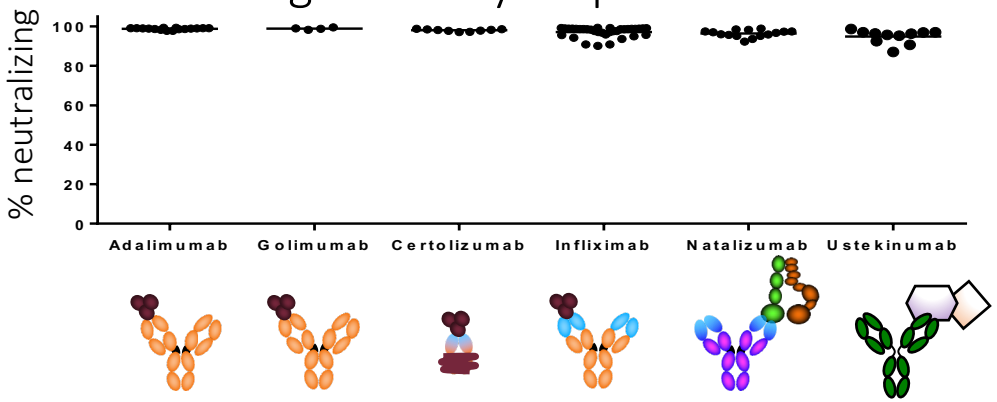
One standard is not enough to reflect the variation in affinity and avidity of a polyclonal ADA response

Opposed to immunogenicity testing according the FDA/EMA guidelines, for detection of clinically relevant anti-drug antibody levels; keep it simple!

Key impact immunogenicity on drug concentration



Mature anti-drug antibody responses are neutralizing

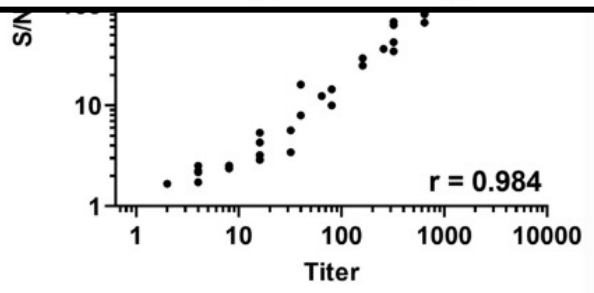


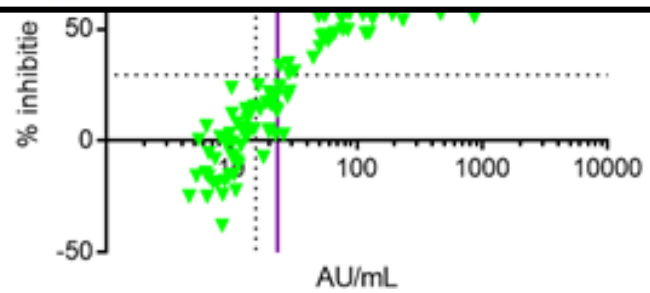
16:20 18:00 Immunogenicity Technology - Interference Focus (Parallel) - Jupiter

Session chair: Jo Goodman, AstraZeneca

17:20 17:40 ***Karien Bloem, Sanquin Diagnostic Services***

Anti-drug antibody testing of therapeutic monoclonal antibodies, have we gone too far?





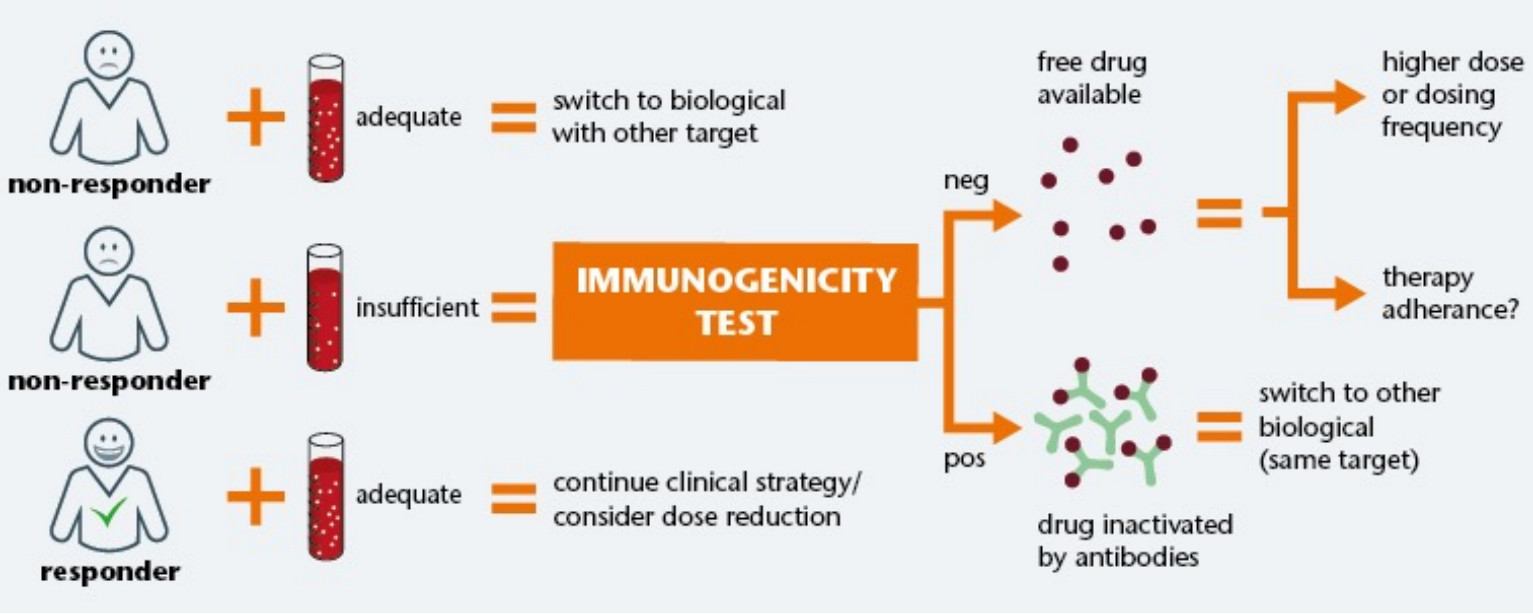
Mature immune response will at least contain IgG

Bartelds et al. *JAMA*. 2011
van Schie et al. JACI, 2016; van Schie et al. ARD, 2015
Atiqi et al. Front Immunol. 2020
Manning et al. The AAPS Journal 2022

Simple assay design for anti-drug antibody detection

- No need for drug tolerance
- No need for additional nAb testing, isotyping, characterization or sample titration
- Semi-quantitative screening setup is sufficient for interpretation

- PK is leading for clinical decision, ADA provides some additional information



Acknowledgements

f.loeff@sanquin.nl

Patients and clinicians

(Inter)national hospitals and collaborators

Colleagues at