Evaluation of clinical impact in heterogeneous populations and additional monitoring of ADA and PK parameters using appropriately sensitive & specific bioanalytical methods

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Overview

- What is missing?
- What do we find about serum trough level in real-life compared to clinical trials?
- How well does this correlate with ADA?
- Are immune complexes a large proportion of the low drug level/ADA negative cases?
- Can we make the clinical implementation process more efficient together?

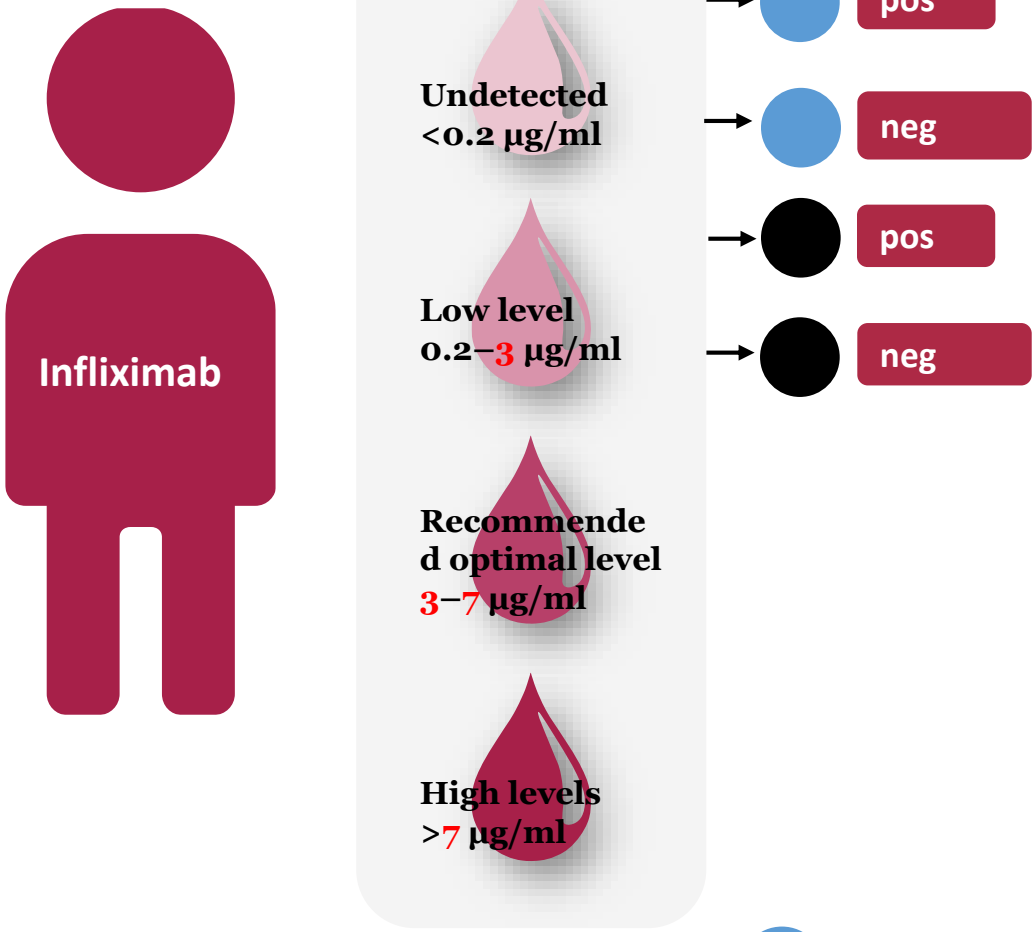
Biological treatments
given parenterally can stimulate the immune system and give rise to anti-drug antibodies

Haemophilia A (HA)	60 years of clinical testing
Multiple Sclerosis (MS)	15 years of clinical testing
Inflammatory Bowel disease (IBD)	partially implemented
Rheumatoid Arthritis (RA)	partially implemented

What is missing?

4 µg/ml?

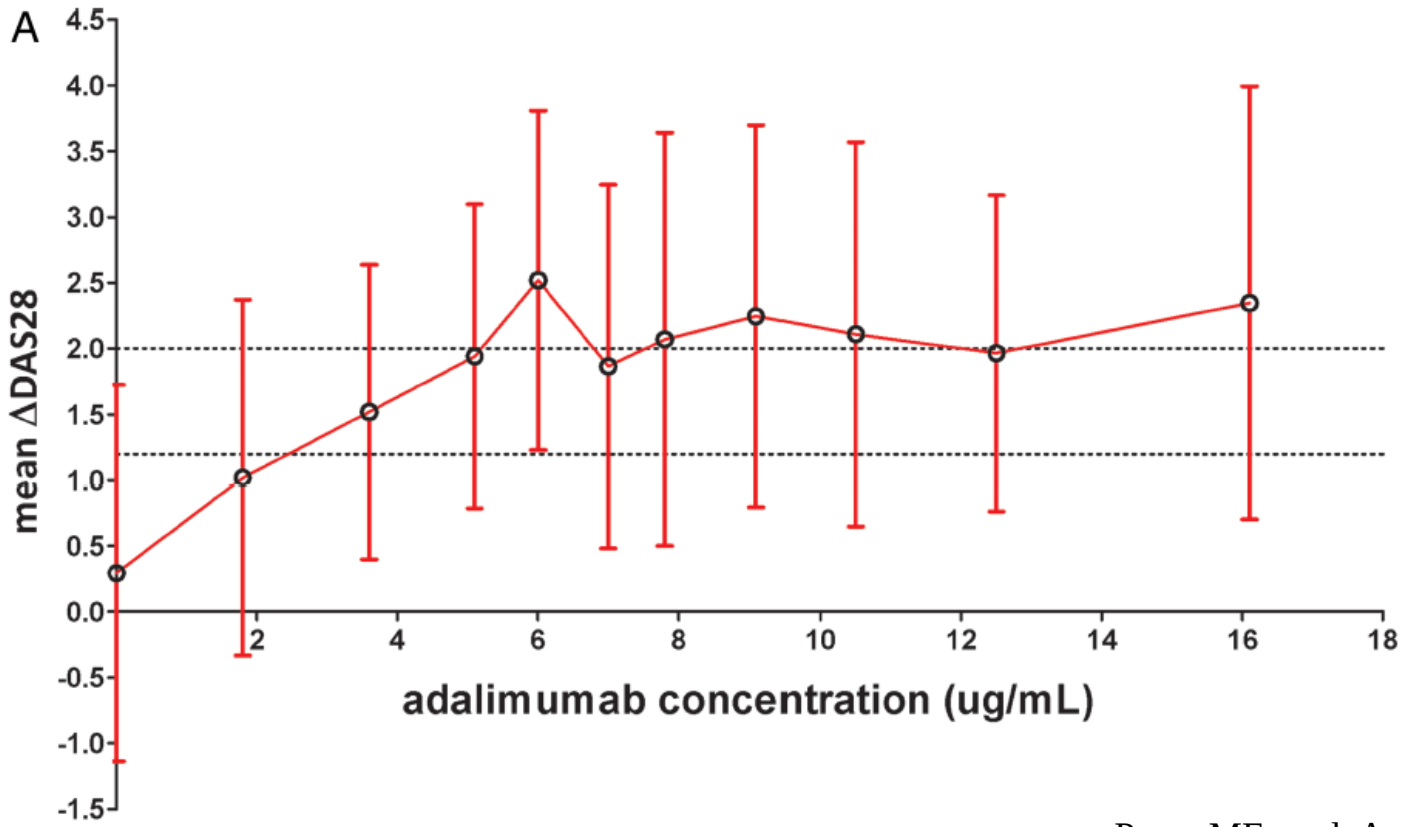
Set clinical threshold value



with ELISA

with PandA

Optimal drug level?



Pouw MF, et al. Ann Rheum Dis 2015

Drug trough levels for ADA negative RA and IBD patients

Infliximab (µg/ml)	Adalimumab (µg/ml)	Etanercept (µg/ml)	Method	Reference
3.8 IQR 1.3–7.9 IBD	**8.3** IQR 5.0–11.0 IBD		fluid-phase RIA	Fredriksen et al. 2014 *Inflam Bowel Dis*
	4.25 IQR 2.03–11.20 RA	**2.3** IQR 1.4–3.3 RA	ELISA (Progenika Biopharma SA, Derio, Spain)	Chen et al 2013 *Ann Rheum Dis*
	7.4 IQR 4.6-11.4 IBD		RIA	Steenholdt 2015 *J Clin Gastroenterol*

Threshold drug levels for good EULAR response

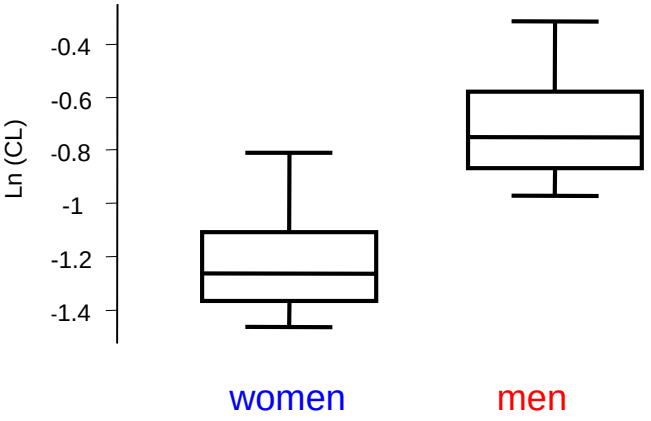
	Adalimumab (µg/ml)	Etanercept (µg/ml)	Method
At 6 months	1.274	1.242	ELISA (Progenika)
At 12 months	1.046	0.800	ELISA (Progenika)
At 12 months	0.801	0.700	ELISA (Sanquin)

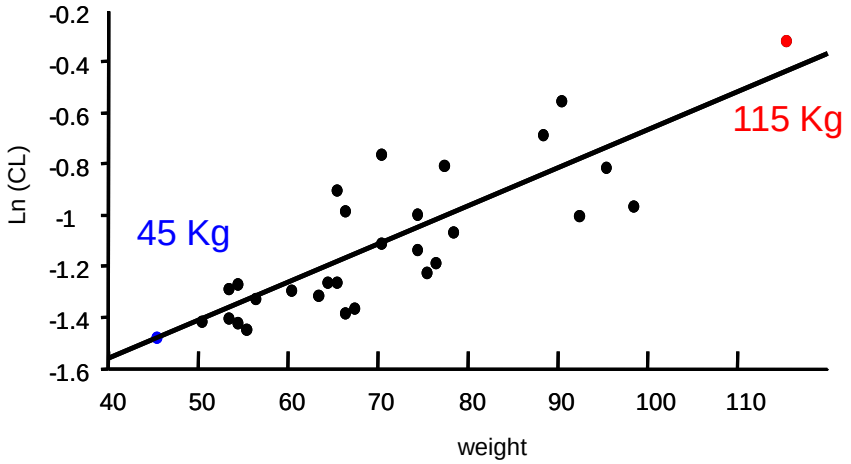
Good EULAR responders are defined as patients who have a decrease in DAS28 from baseline (ΔDAS28) >1.2 and a DAS28 $\leq$3.2

Clinical threshold of the drug level

Chen D-Y, et al. Ann Rheum Dis 2014;0:1–9

Drug clearance of adalimumab is influenced by weight and sex in RA





T ½ -β = 17 days
T ½ -β = 29 days

T ½ -β = 11 days
T ½ -β = 35 days

Clearance was higher in men than women
Clearance was proportional to weight

With courtesy to Denis Mulleman
Ternant D, et al. Br J Clin Pharm 2014

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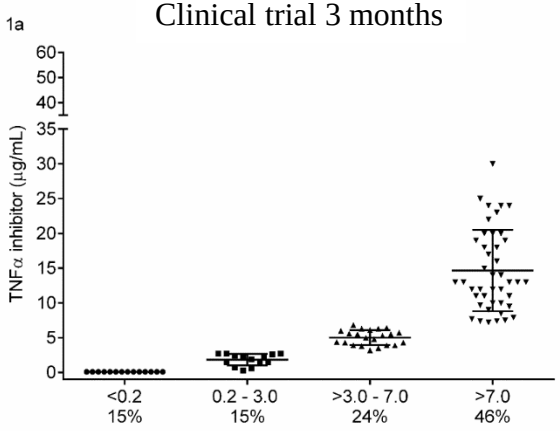
Can we translate the **results** directly from the RCT to clinical routine?

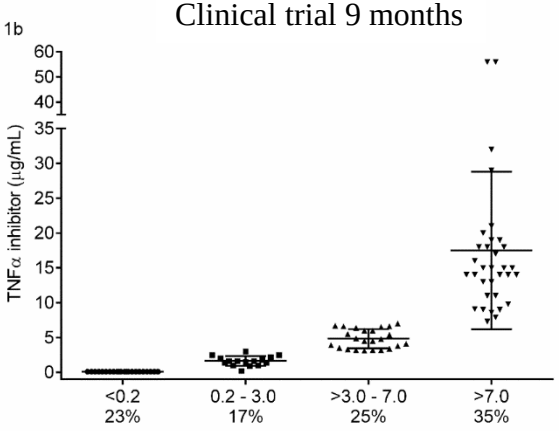
Infliximab drug level in RA comparing clinical trial with real-life

With in-house direct ELISA for drug level

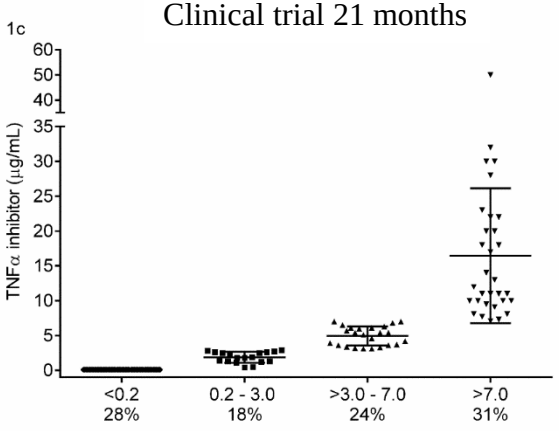
Clinical trial 3 months



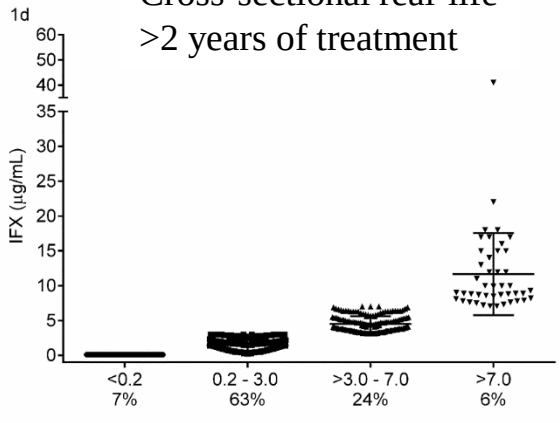
Clinical trial 9 months



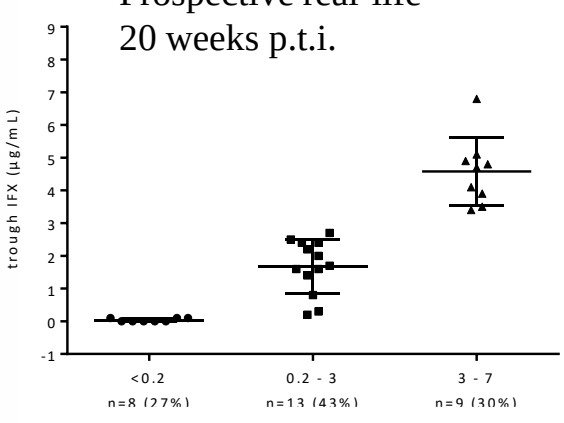
Clinical trial 21 months



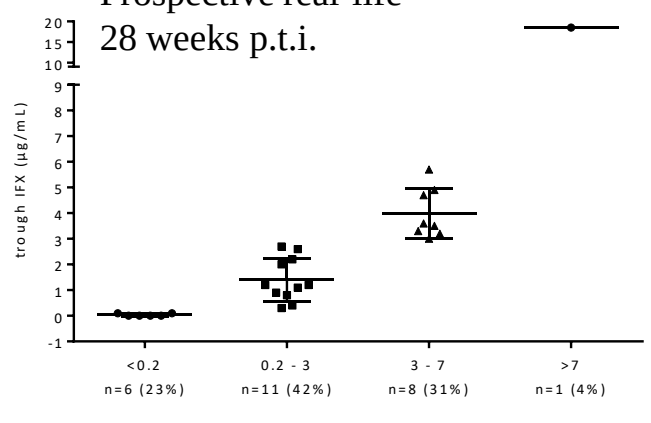
Cross-sectional real-life
>2 years of treatment



Prospective real-life
20 weeks p.t.i.



Prospective real-life
28 weeks p.t.i.



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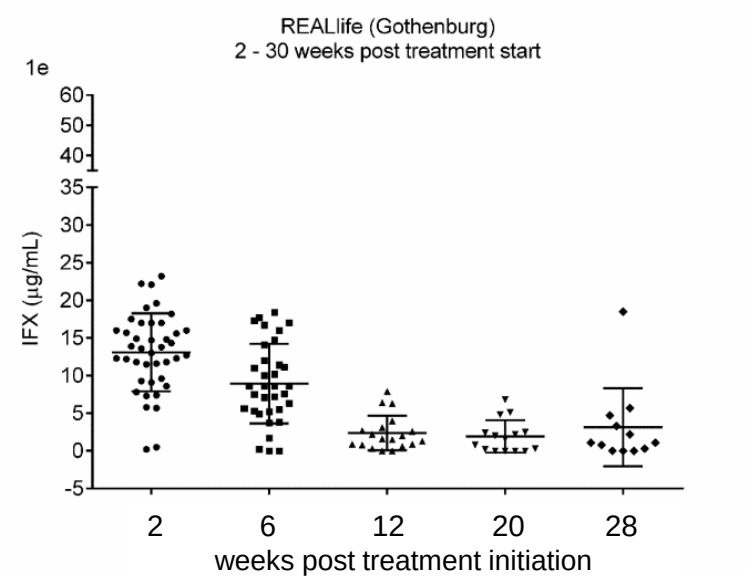
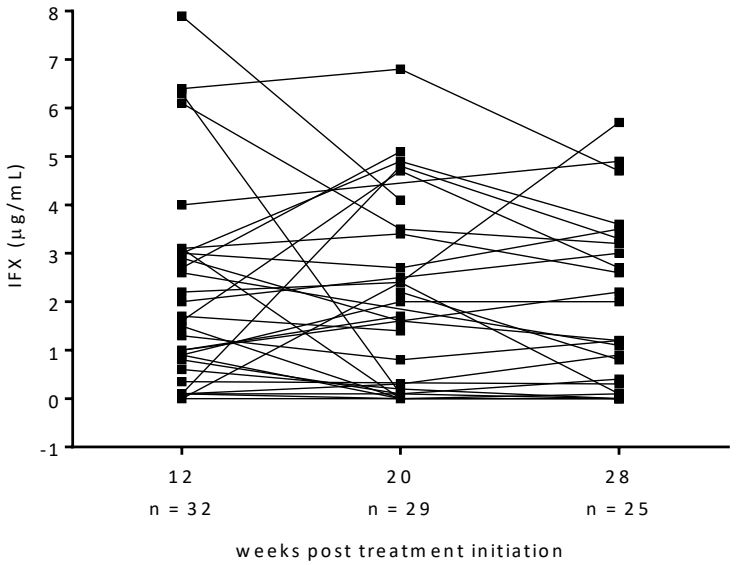
Over time
Prospective real-life





Real-life cross-sectional: serum infliximab concentrations over time

↑ 8% above 6 µg/mL

↕ 58% between 1-6 µg/mL

↓ 34% below 1 µg/mL

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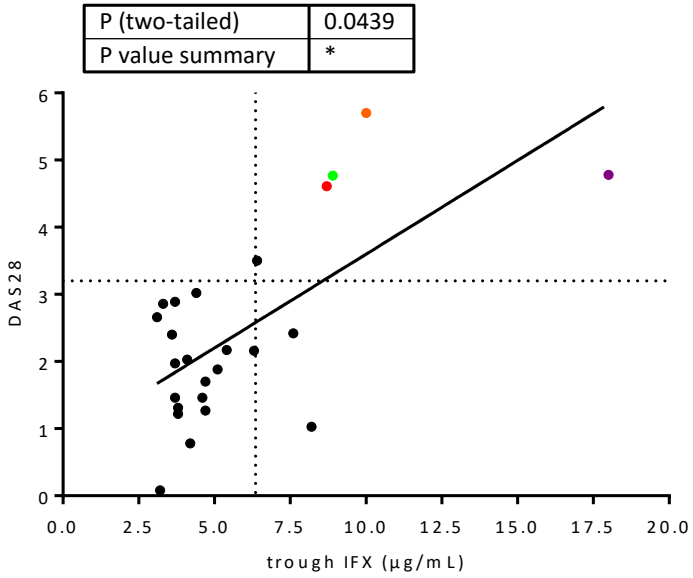
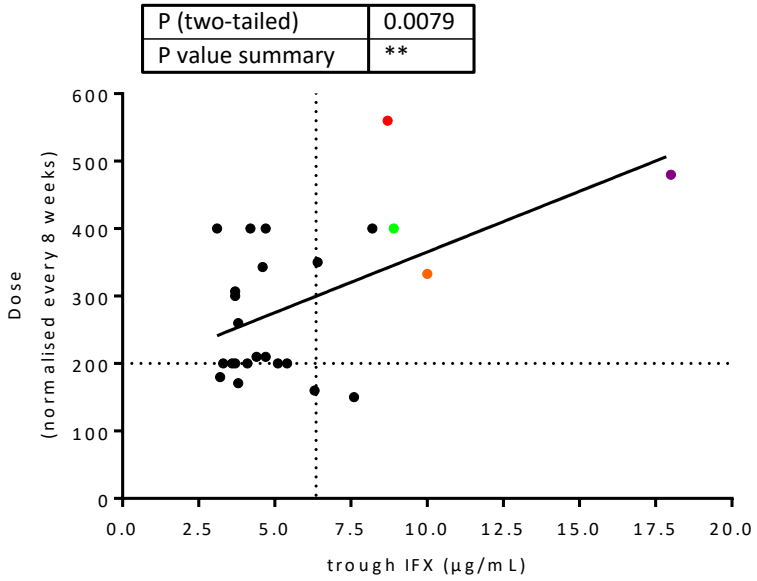
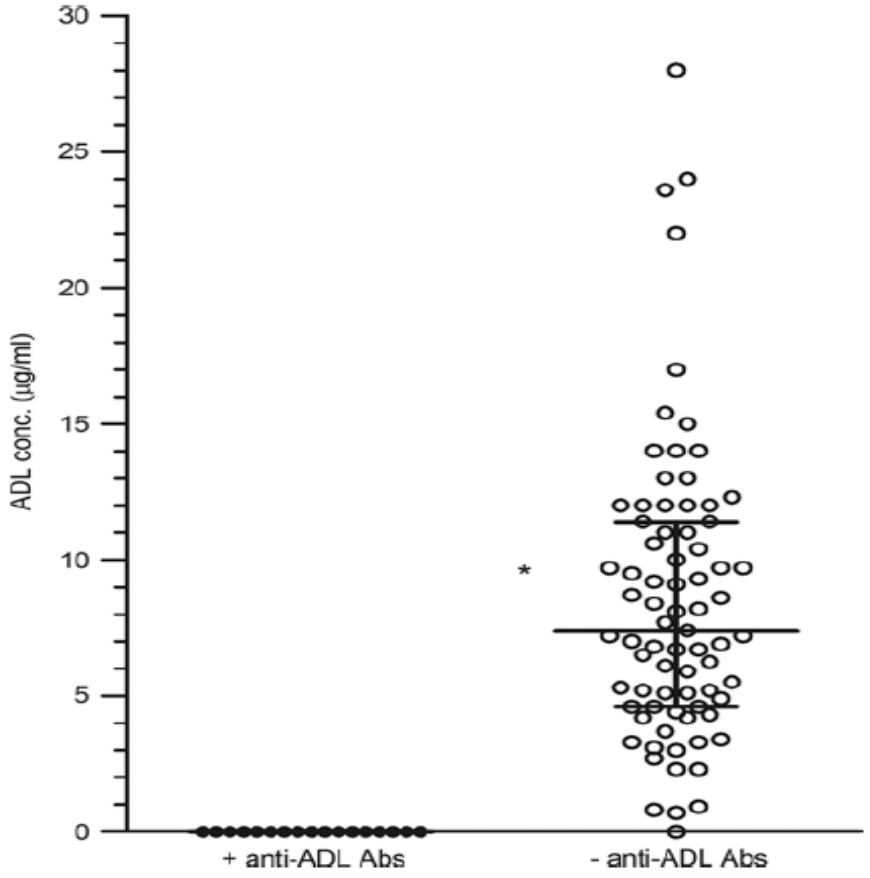
Drug level in relation to DAS28 and to dose in real-life cohort > 2 years of treatment





Over to ADA

Drug level of adalimumab in ADA positive and ADA negative IBD



Steenholdt 2015
J Clin Gastroenterol

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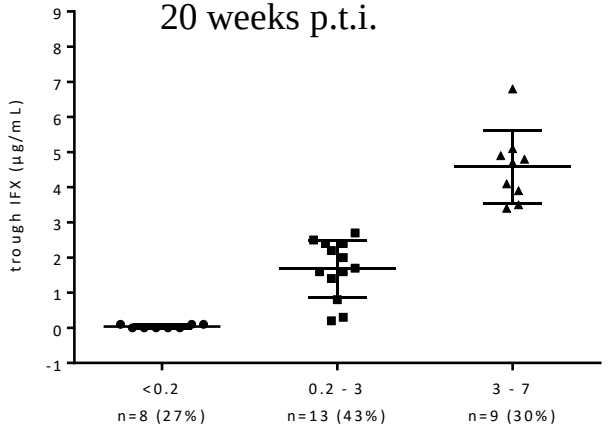
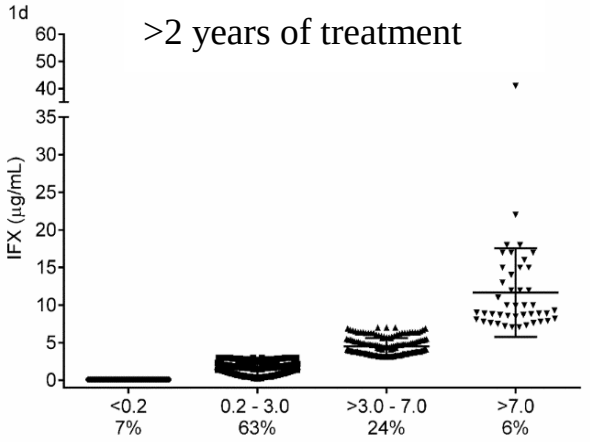
% ADA positive with ELISA

Prospective real-life
20 weeks p.t.i.



100%

Cross-sectional real-life
>2 years of treatment

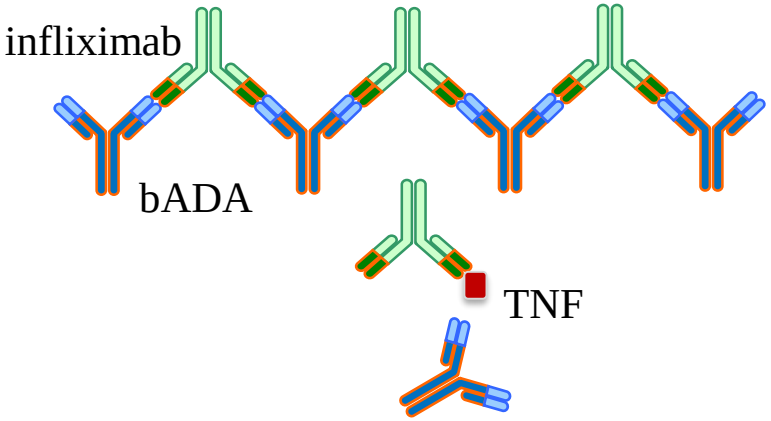


90%

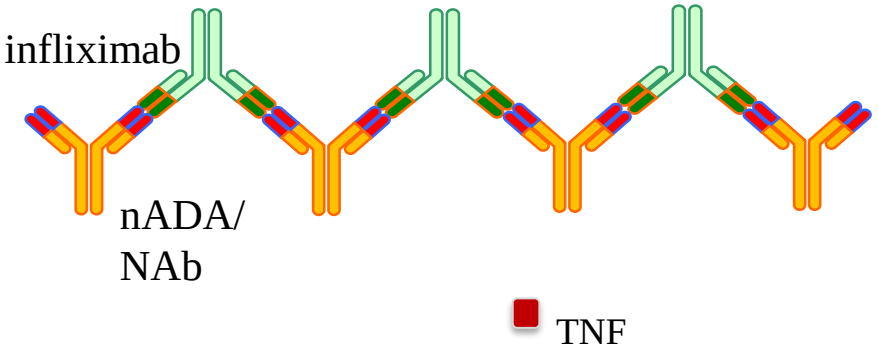
Over to immune complexes

The issue with immune complexes

In patients: Increasing clearance



Neutralizing effect

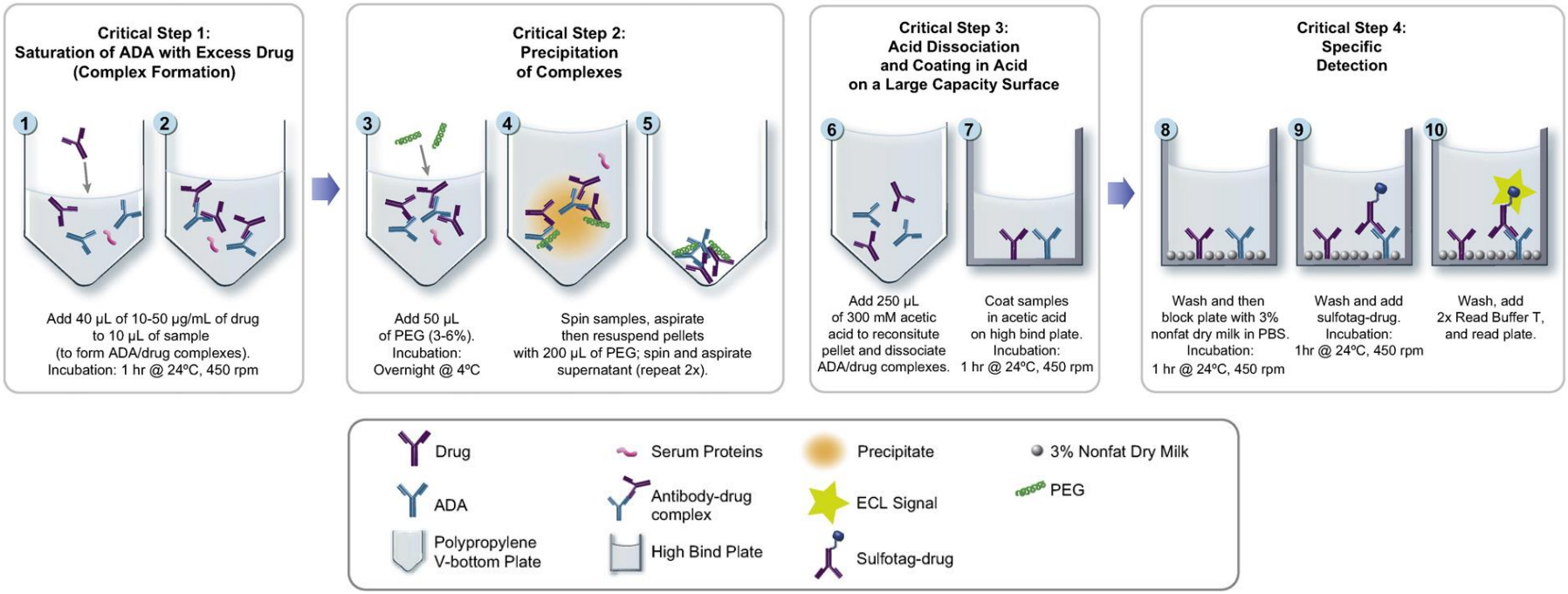


In assays: Interfering with the measurement of drug and ADA

PEG and Acid (PandA)

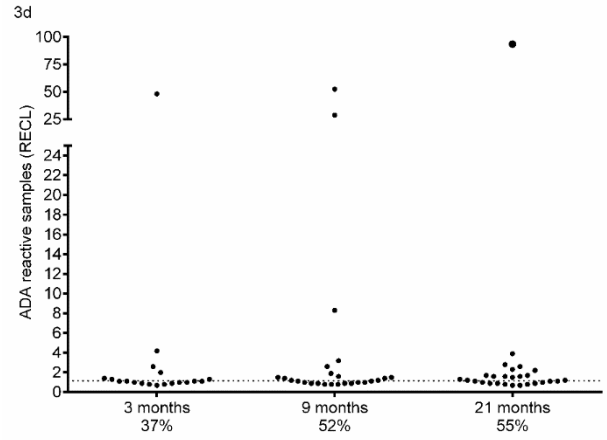
Journal of Immunological Methods 426 (2015) 62–69

Jad Zoghbi , Yuanxin Xu, Ryan Grabert, Valerie Theobald, Susan Richards
Clinical Laboratory Sciences, DSAR Sanofi, Framingham, MA, USA

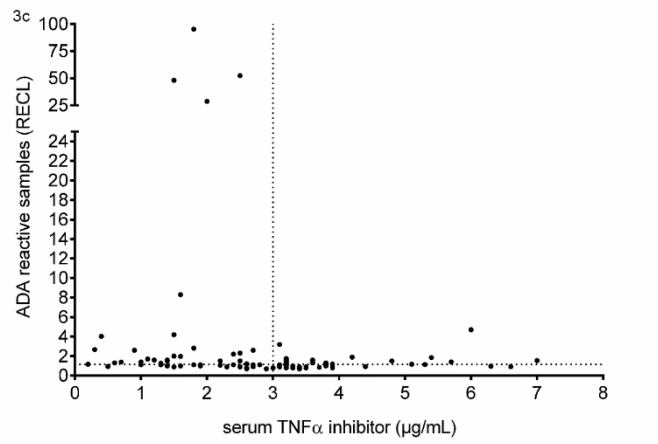


Infliximab immune complexes bound + free ADA in RA

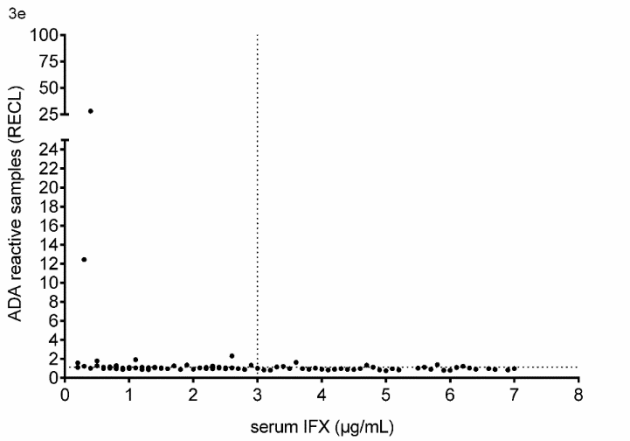
Clinical Trial



Clinical Trial

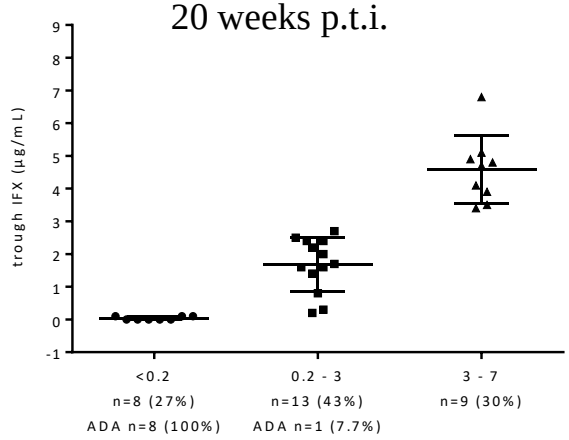


Real Life cross-sectional



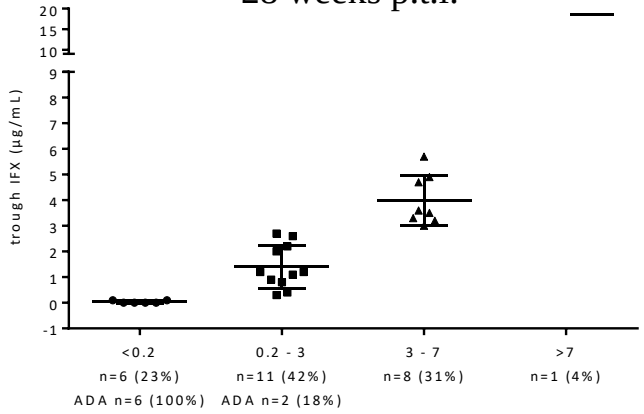
Prospective real-life ADA with PandA

Prospective real-life
20 weeks p.t.i.



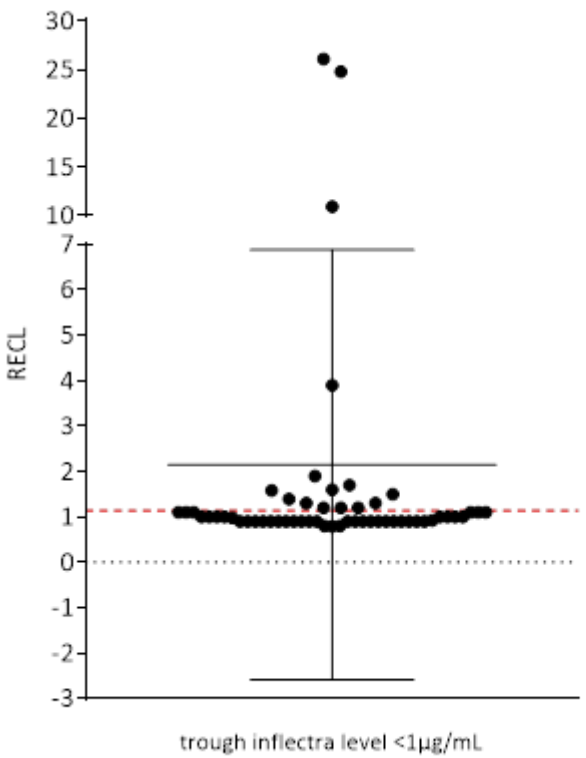
100% 8%

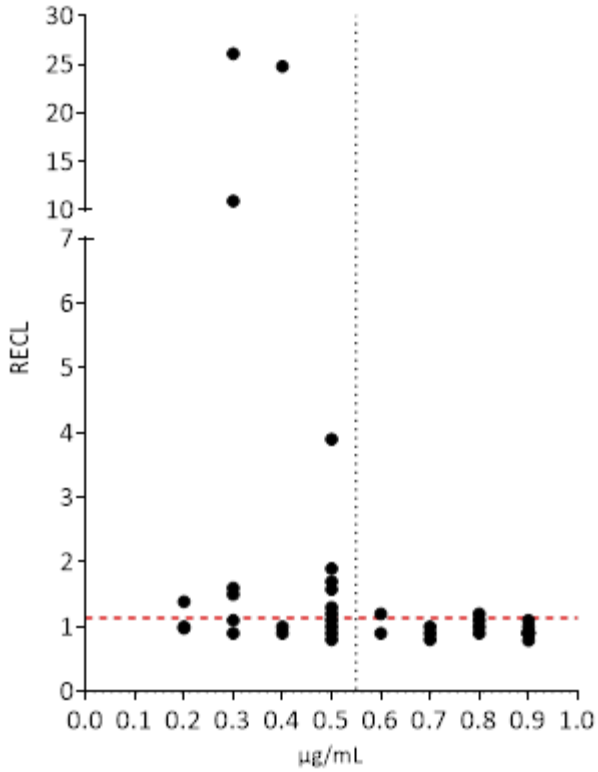
Prospective real-life
28 weeks p.t.i.



100% 18%

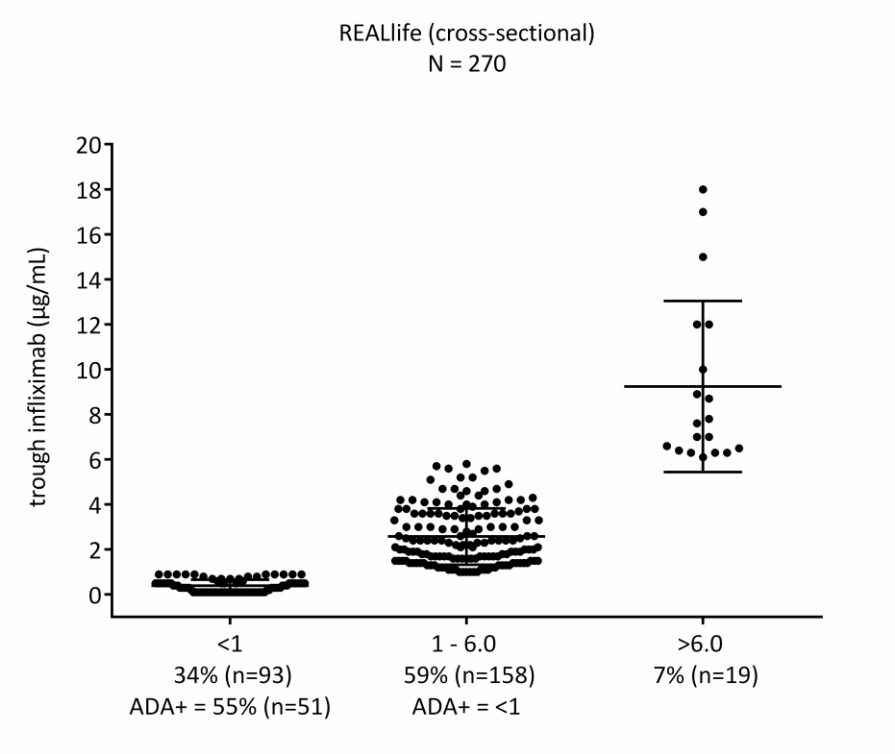
Cross-sectional drug level 0.2-1 µg/ml





27% ADA reactive (n=56)

ADA with PandA in real-life cross sectional >2 years treatment



Infliximab in RA
Resolving the pattern

Table I. Patterns of ADA positivity measured with ELISA over time.

Pattern	3 mpi	9 mpi	21 mpi	Total number of patients (%)
#1	+	+	+	n = 2 (2.2)
#2	+	+	nd	n = 1 (1.1)
#3	+	nd	+	n = 3 (3.2)
#4	+	nd	nd	n = 4 (4.3)
#5	nd	+	nd	n = 10 (10.8)
#6	nd	nd	+	n = 9 (9.7)
#7	nd	+	+	n = 5 (5.4)

ADA = anti-drug antibodies; mpi = months post treatment initiation; + = ADA positive; nd = not determined since the drug level was above 0.2 µg/mL

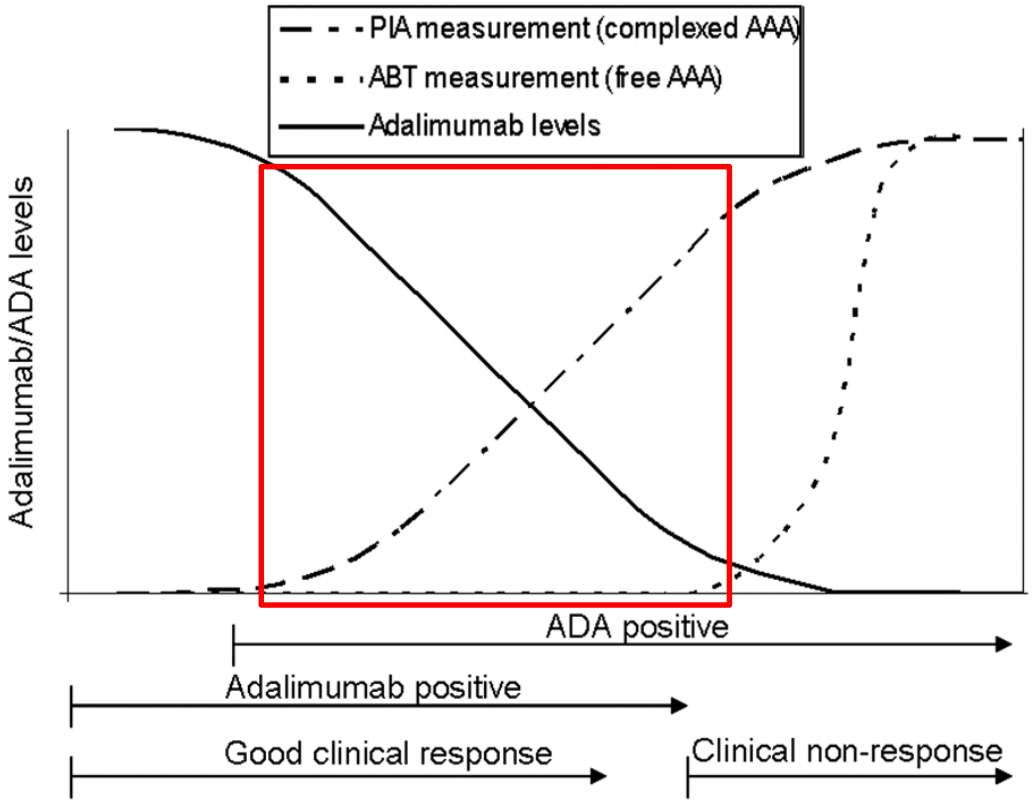
Table II. Patterns of ADA positivity measured with PandA over time.

Pattern	3 mpi	9 mpi	21 mpi	Total number of patients (%)
#1	+	+	+	n = 11 (12.8)
#2	+	+	neg	n = 3 (3.5)
#3	+	neg	+	n = 1 (1.2)
#4	+	neg	neg	n = 1 (1.2)
#5	neg	+	neg	n = 2 (2.3)
#6				not determined
#7	neg	+	+	n = 9 (10.5)

ADA = anti-drug antibodies; mpi = months post treatment initiation; + = ADA positive

Only those with drug level < 0.2 µg/ml tested

Immune complexes can be detected earlier than free ADA?



van Schouwenburg Ann Rheum Dis 2013;72:1680–1686

Cases from prospective study showing that ADA could be detected **earlier** with PandA

- Of **17** RA patients positive for ADA against infliximab by ELISA, **5** patients were PandA postive and ELISA negative (n.d.) in a earlier sample
- **Of these 5 postive according to the PandA:**
  - 2 were **high** ADA positive
  - 2 were **low** ADA positive
  - 1 **transient**
- **ADA could have been detected**
  - 4 weeks (high pat 1)
  - 4 months (high pat 2)
  - 8 weeks (low pat 1)
  - 4 months (low pat 2)
  - 10 weeks (transient)

Leaving some grey zones, but resolved some issues

Drug	Undetected <0.2 µg/ml	Low level 0.2–1 µg/ml	Medium level 1–3 µg/ml	Recommended optimal level 3–6 µg/ml	High levels >6 µg/ml
ADA	99%	25%	<1%	0%	0%
Proportion of patient estimation	10%	20%	20%	40%	10%

Set clinical threshold value

DRUG LEVEL		WHAT TO DO. IF ...	THEN ...
Undetected <0.2 µg/ml	ADA+	If in **remission**	Stop treatment and wait
		If **active** disease	Change treatment
	ADAneg	Measure ADA with PandA method	
Low level 0.2–1 µg/ml	ADA+	If in **remission**	Stop treatment and wait
		If **active** disease	Change treatment
	ADAneg	If in **remission**/ low active disease	→ Continue treatment but take a new sample within 2 months
		If **active** disease	Change treatment
Recommended optimal level 1–6 µg/ml		If in **remission**	→ Continue treatment
		If **not in remission**	Change treatment to other mode of action (not TNF-mediated disease)
High levels >6 µg/ml		If in **remission**	→ Continue but consider lowering the dose
		If **active** disease	Change treatment to other mode of action (not TNF-mediated disease)

with ELISA with ELISA

with PandA with PandA

Clinical judgment or algorithm – does it matter?

- A large proportion of those patients in the clinic having over 2 years of treatment did still have suboptimal level of drug

- Would we treat them different if we knew the drug level and ADA status?
  - Way out of treatment is ADA pos high titer
  - Dose adjustment more controlled
  - Other mode of action identified
  - Long-term safety issues

- Potential risk factors for treatment failure can be factors regulating drug level or ADA

Risk factors for ADA

For examples for interferon beta treatment in MS

- Age
- Smoking
- HLA
- Notch-2

Additional questions to resolve

- Is drug level at trough the most informative time point?
  - Infliximab cases with ADA have infusion reactions
  - Cases with serum sickness 10 days after infusion with rituximab – all ADA positive (submitted)

Advantages of introducing drug level and ADA measurements in clinical routine

For the industry:

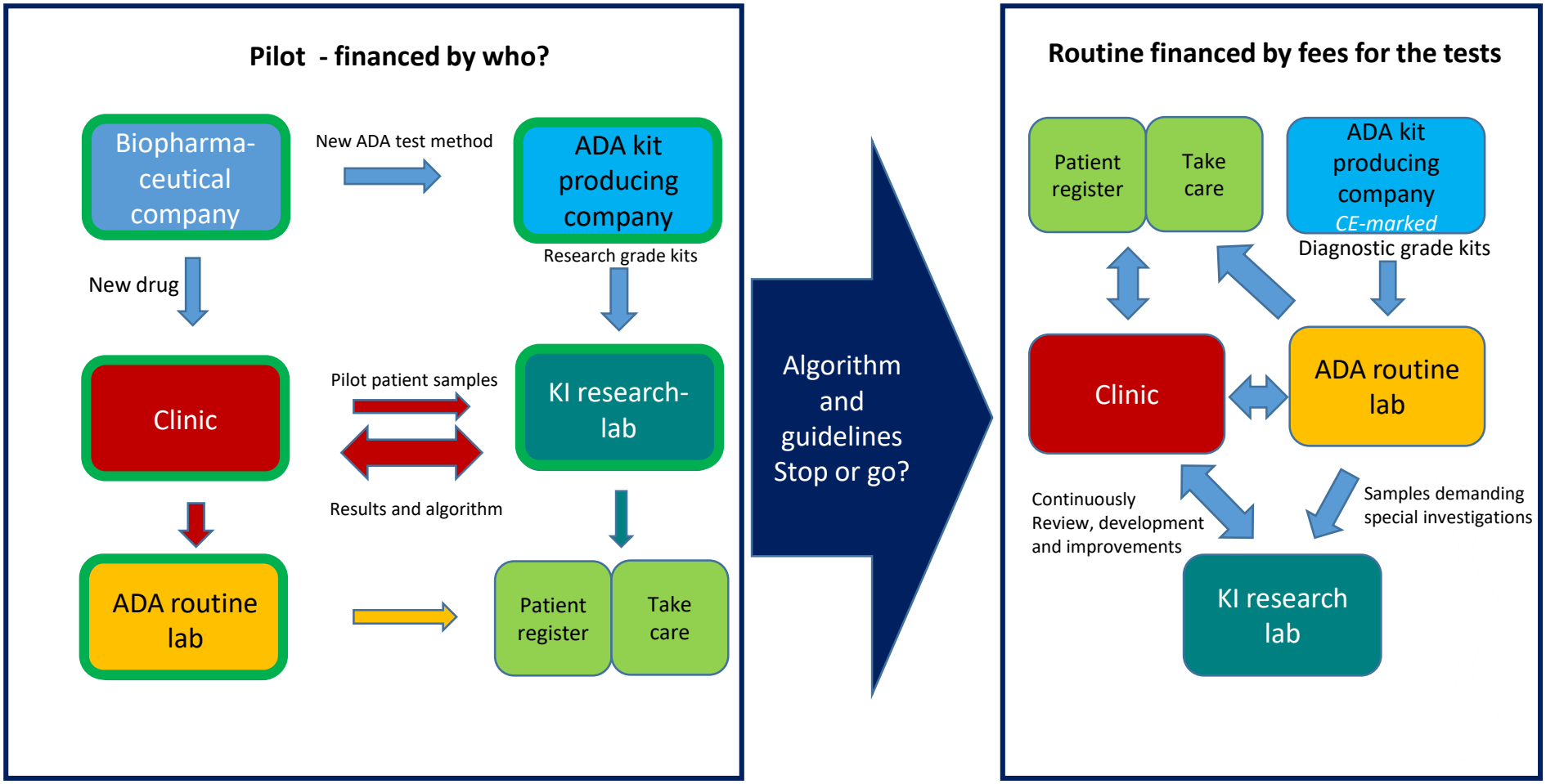
- For those who been working hard to reduce immunogenicity an earlier appreciation in the clinic would be achieved
- Risk mitigation strategy: if you have a routine to identify the ADA positive, then they can switch in time and the rest can have a benefit of the treatment

For the clinic:

- Patients developing ADA could be shifted to a another drug
  - Less infusion reactions
  - Resolving issue with serum sickness
- Patients with too low or too high drug level might have their dose regulated in a more structured way
- Detecting patients with other mode of action

Can we translate the **methods** directly from the RCT to clinical routine?

Translating methods from pharma to clinical routine: a model



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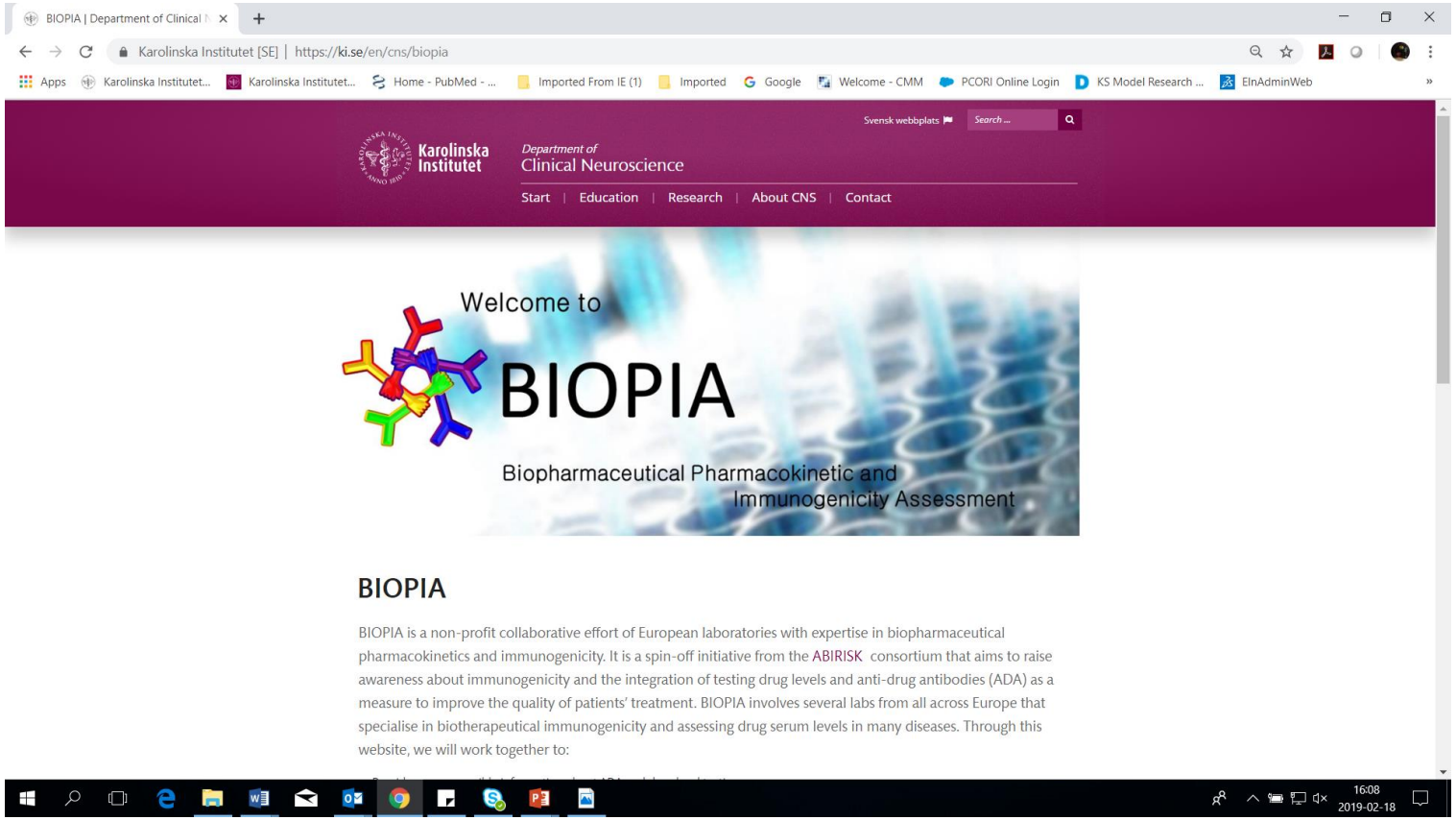
How do we move forward?

BIOPIA https://ki.se/en/cns/biopia

Contact: Anna.Fogdell-Hahn@ki.se



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The BIOPIA map

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Examples of tests you can find on the BIOPIA home page

Karolinska University Laboratory

Biologic	Drug level	ADA
	Service	Service
Abatacept	-	-
Adalimumab	√	√
Certolizumab	-	-
Etanercept	√	-
Golimumab	-	-
Infliximab	√	√
Natalizumab	-	-
Nivolumab	-	-
Omalizumab	-	-
Rituximab	√	-
Tocilizumab	-	-
Ustekinumab	√	-
Vedolizumab	√	-

ADA Lab Karolinska Institutet/CMM

Biologic	Drug level	ADA	nADA (NAb)	Immune Complexes
	Service	Service	Service	Service
Abatacept	-	-	-	-
Adalimumab	-	-	√	-
Certolizumab	-	-	-	-
Etanercept	-	-	-	-
Golimumab	-	-	-	-
Infliximab	-	-	√	√
Interferon beta	-	-	√	-
Natalizumab	-	√	-	-
Nivolumab	-	-	-	-
Omalizumab	-	-	-	-
Rituximab	-	√	-	-
Tocilizumab	-	-	-	-
Ustekinumab	-	-	-	-
Vedolizumab	-	-	-	-

nADA (Nabs) - Neutralizing anti-drug antibodies

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Commissariat a L'Energie Atomique et aux Energies Alternatives- France
www.cea.fr

DRK-Blutspendedienst Baden-Württemberg – Hessen gemeinnützige GmbH - Germany
www.blutspende.de

Fondazione per l'Istituto di Ricerca in Biomedicina
Switzerland
www.blutspende.de

Fundació Institut de Recerca de L'hospital Universitari Vall D'hebron - Spain
www.vhir.org

Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif - France
www.getaid.org

SME: SciCross

Assistance-Publique-Hôpitaux de Paris

Istituto Giannina Gaslini
Italy
www.gaslini.org

Johann Wolfgang Goethe Universität - Klinikum und Fachbereich Medizin - Germany
www.kgu.de

Karolinska Institutet
Sweden
ki.se

Klinikum rechts der Isar der Technischen Universitaet Muenchen - Germany
www.med.tum.de

Medizinische Universität Innsbruck
Austria
www.i-med.ac.at

Paul-Ehrlich-Institut, Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel - Germany
www.pei.de

Queen Mary and Westfield - University of London
United Kingdom
www.qmul.ac.uk

Rambam Medical Center
Israel
www.rambam.org.il

Region Hovedstaden
Denmark
www.regionh.dk

Università di Firenze
Italy
www.unifi.it

Universitaetsklinikum Bonn
Germany
www.ukb.uni-bonn.de

Universitätsklinikum Düsseldorf
Germany
www.uniklinik-duesseldorf.de

University College London
United Kingdom
www.ucl.ac.uk

University Hospital Basel
Switzerland
www.unispital-basel.ch

Univerzita Karlova v Praze
Czech Republic
www.cuni.cz

SMEs

ALTA Ricerca e Sviluppo in Biotecnologie S.r.l.u
Italy
www.altaweb.eu

Biomonitor A/S
Denmark
www.biomonitor.dk

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° [115303], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.'

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Not all ADA are neutralizing ADA

Neutralizing ADA (nADA/NAb) are the ADA that block the mode of action of the drug

- Bioassays
- Titer level as proxy?

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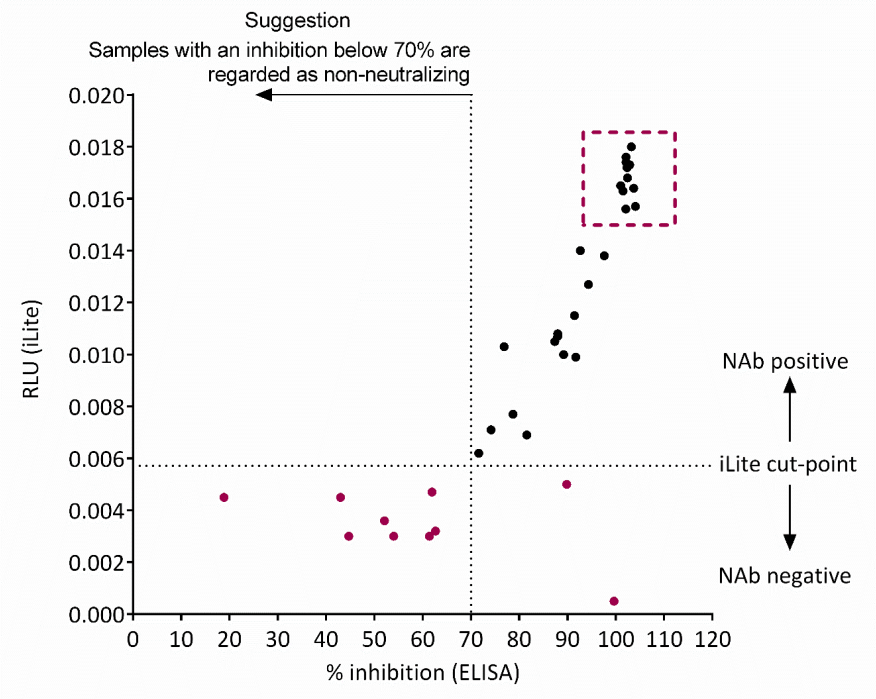
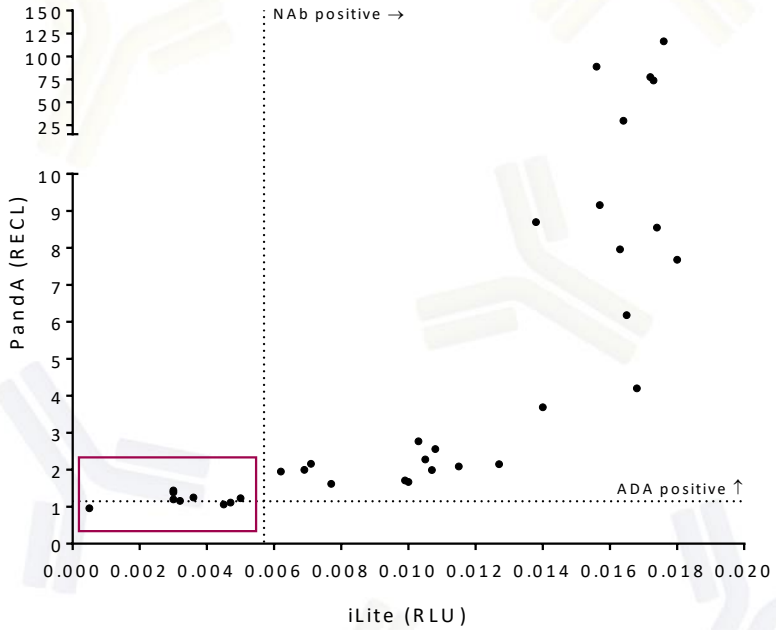
Infliximab neutralizing ADA (iLite) in RA

Correlation bioassay versus ELISA



Correlation bioassay versus PandA



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