The clinical relevance of immunogenicity to anti TNF agents in IBD

Gert Van Assche, MD, PhD, AGAF

IBD Leuven

Clinical relevance of immunogenicity in IBD

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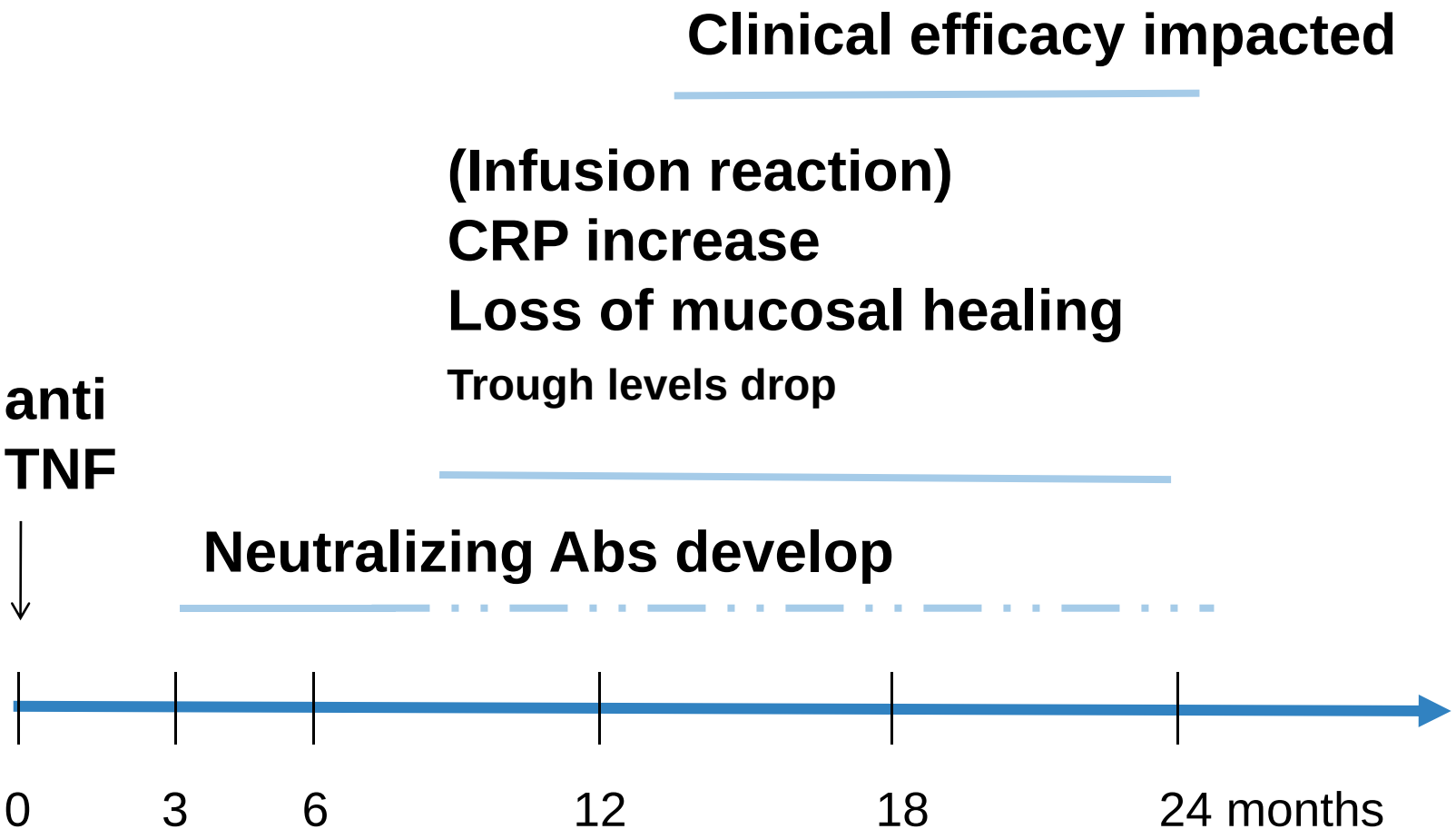
- Immunogenicity to biological therapy: a universal phenomenon
- Impact on IBD: Safety vs. Efficacy
- Serum levels or anti drug antibodies

Immunogenicity: Clinical Relevance

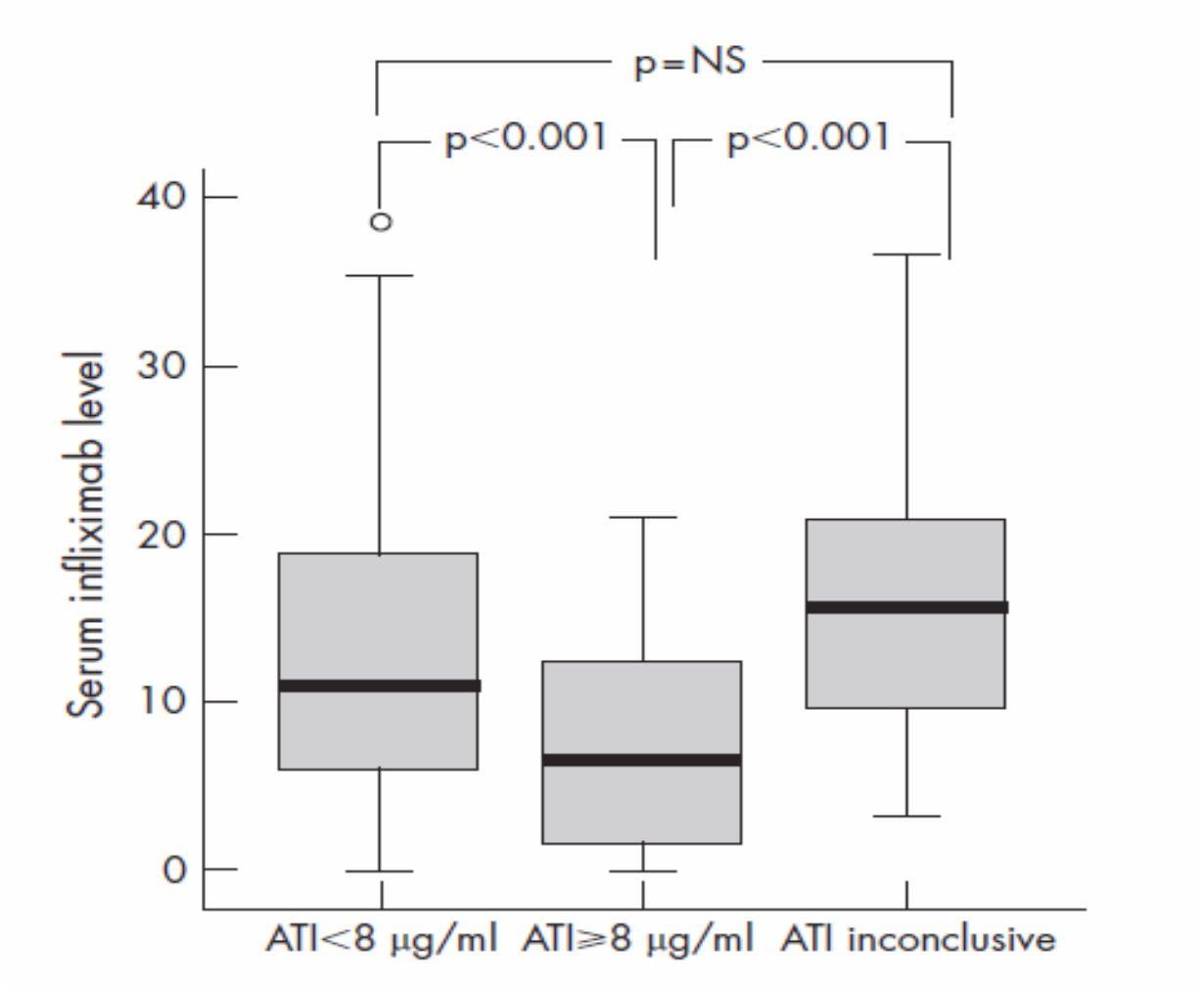
Biologic agent	Therapeutic indication	Clinical relevance of immunogenicity
Rh-Growth hormone	Growth retardation	No impact
Rh-Insulin	Diabetes mellitus	Alteration of the pharmacokinetics
IFN-α IFN-β	Hepatitis B/C Multiple sclerosis	Reduction of clinical efficacy
Rh-EPO	anemia	Cross-reaction with endogenous protein
Infliximab	IBD, RA, SPA, psoriasis	Reduction of efficacy Infusion reactions
Adalimumab	CD, RA, SPA, psoriasis	Reduction of efficacy
Natalizumab	MS, CD	Reduction of efficacy Infusion reactions

Kinetics of anti drug Abs



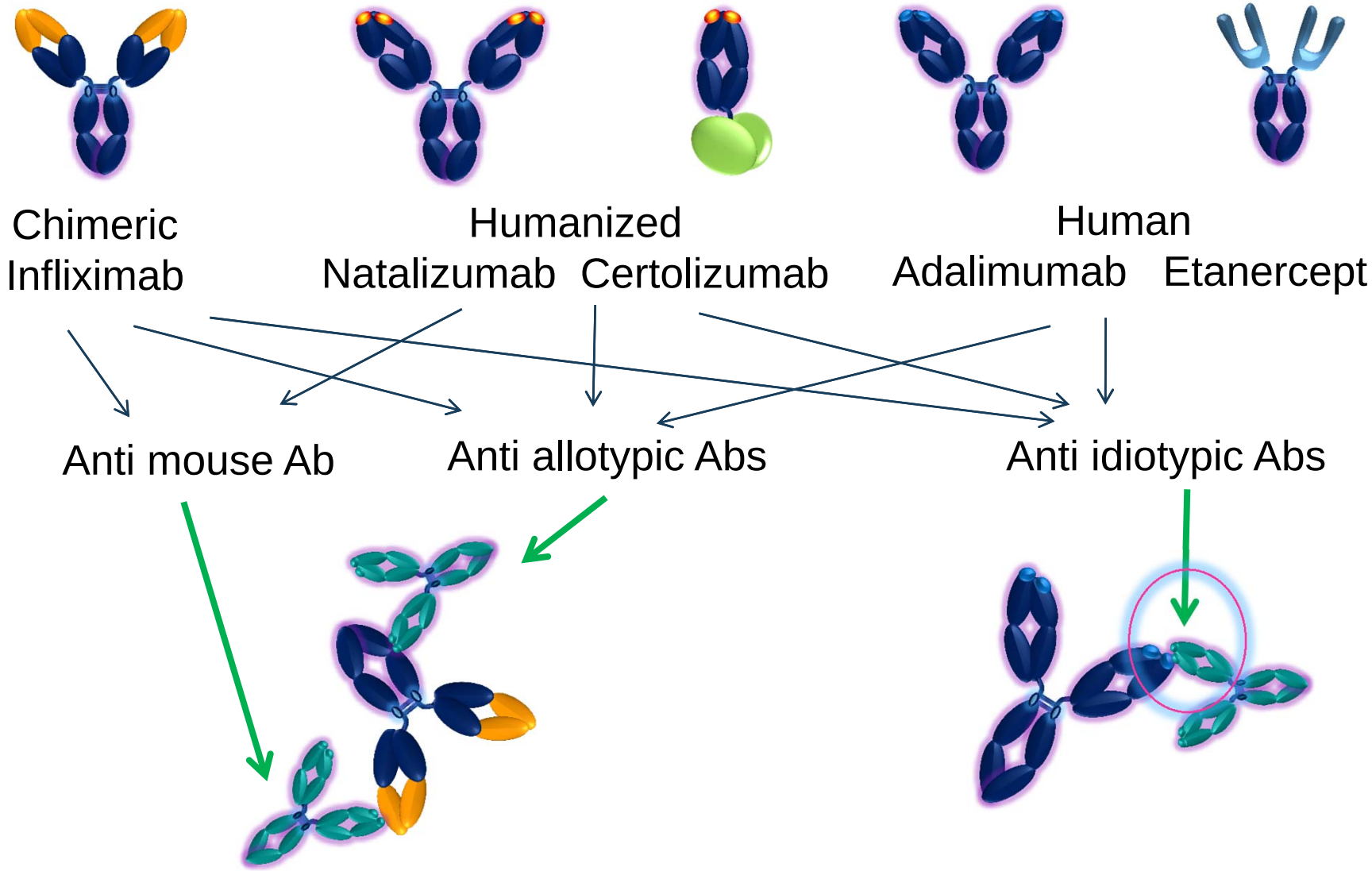
Serum levels after first IFX infusion are related to ATI development during follow up

n= 174



Vermeire S et al. Gut 2007

Mechanisms of Immunogenicity



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What is the relevance of Immunogenicity in IBD

hypersensitivity reactions

secondary loss of response

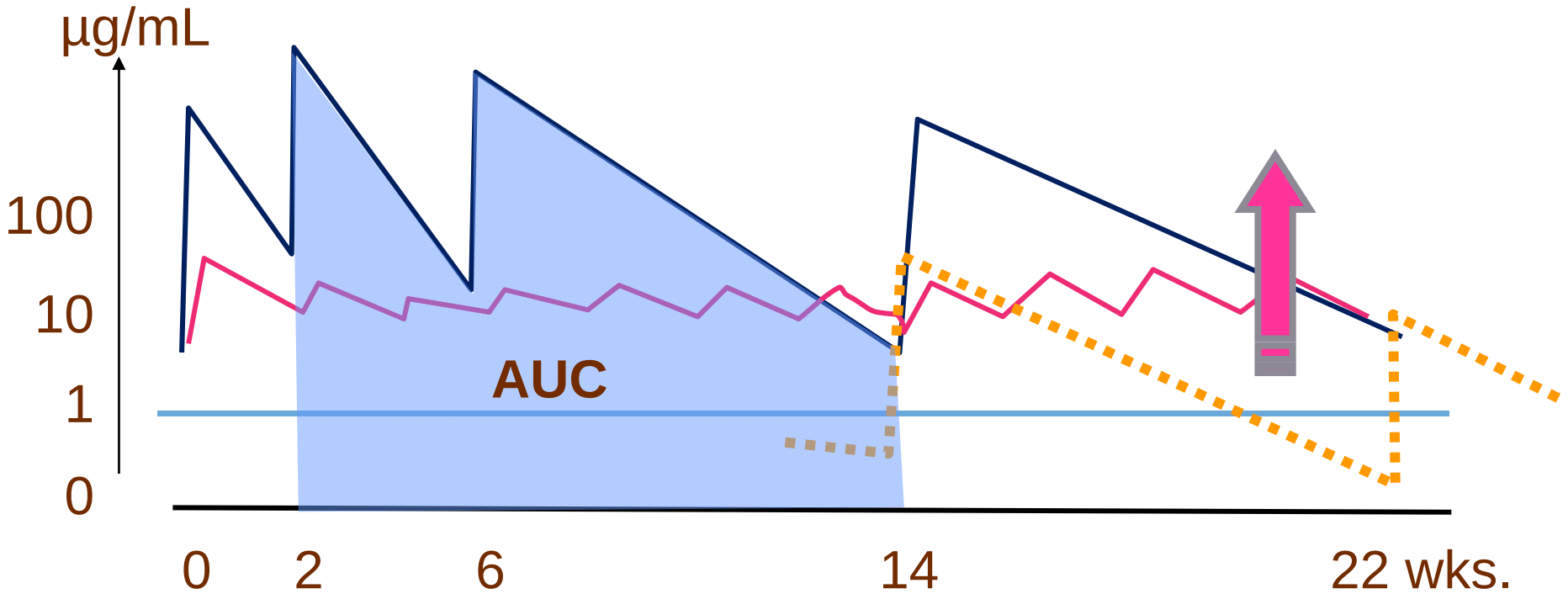
Maintenance therapy

Subcutaneous Rx

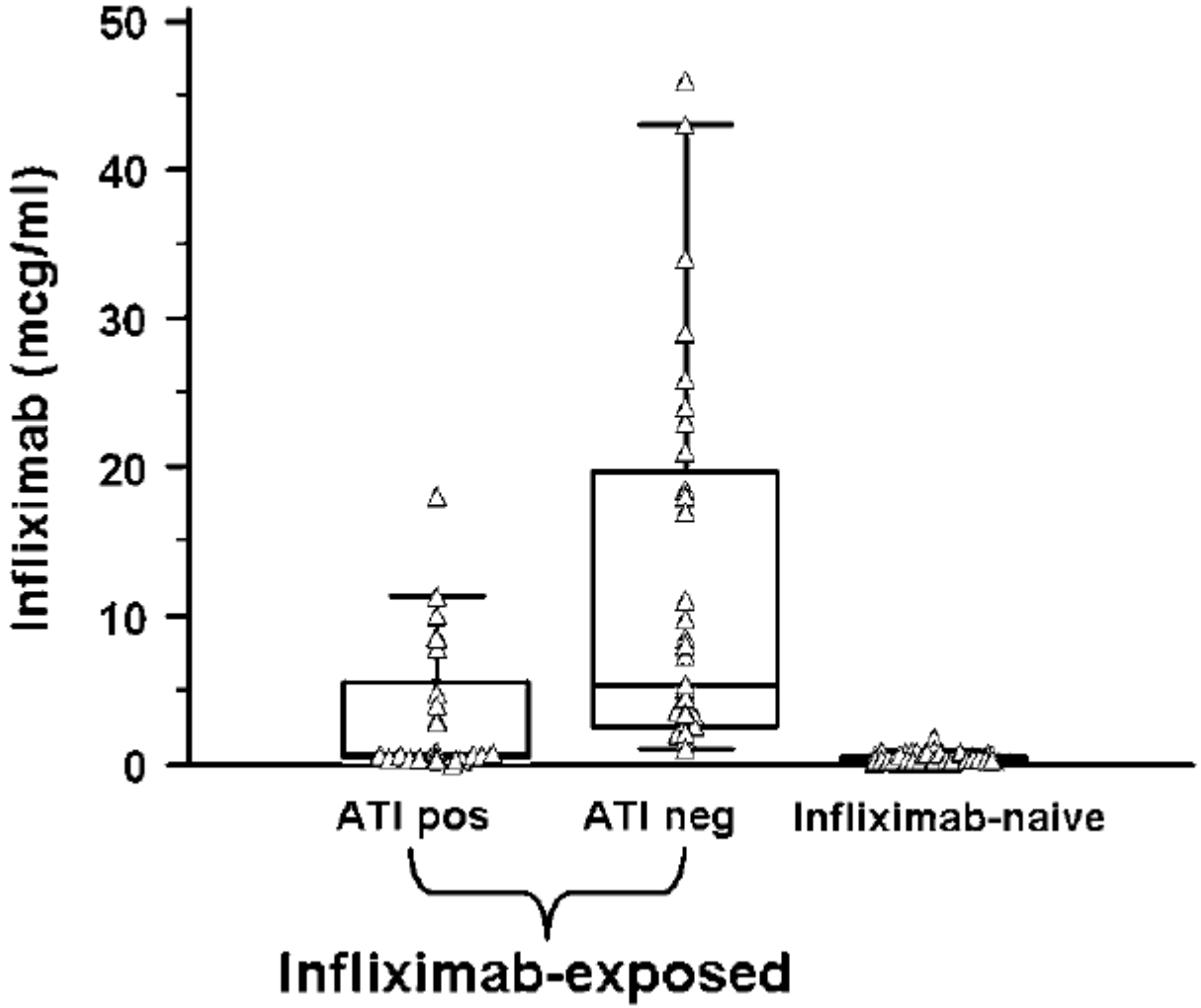
Safety

Efficacy

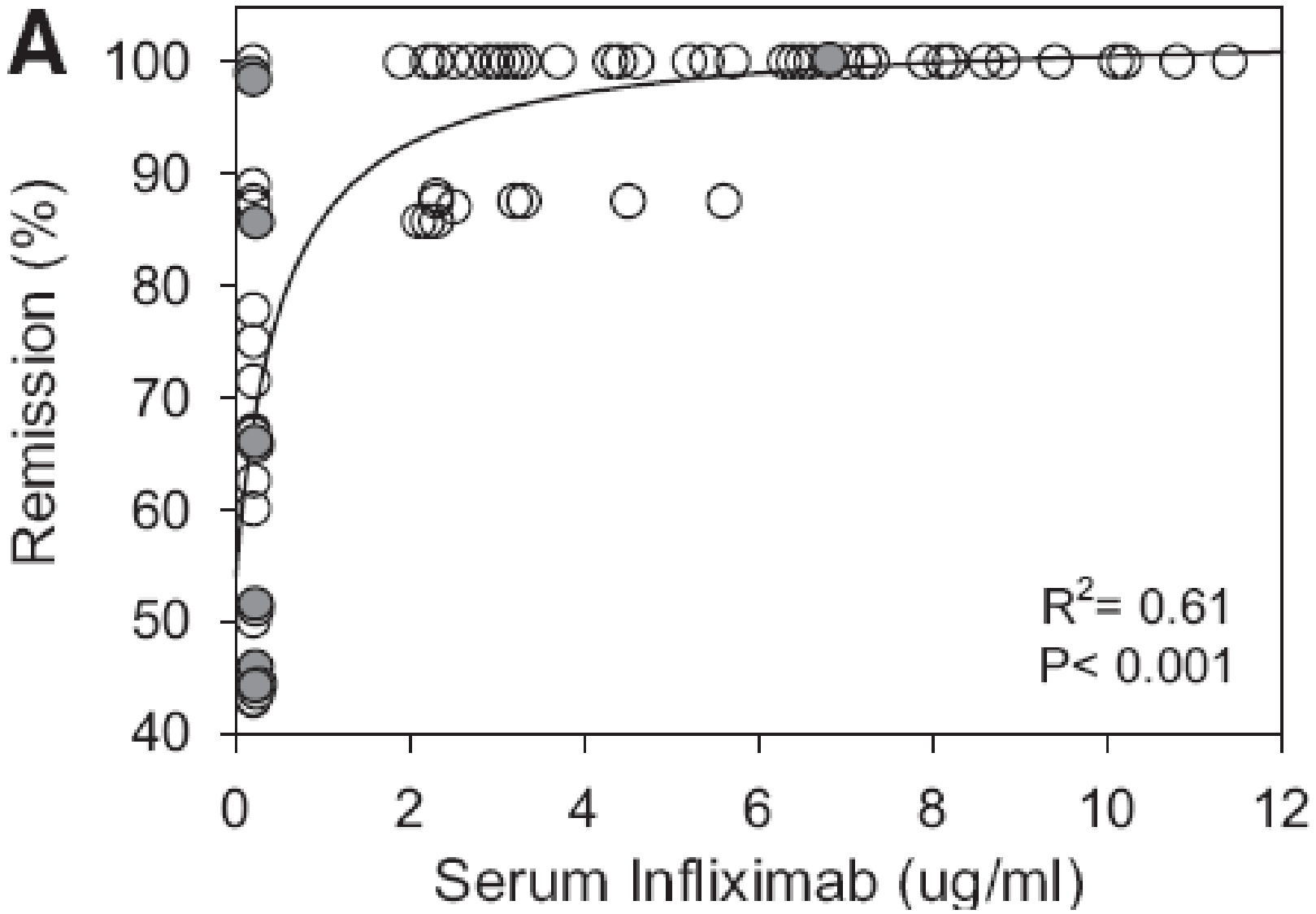
The therapeutic window concept



- Sub-treshold trough levels: predict LOR but not absolute
- Are consistently elevated trough levels associated with toxicity?



Ben-Horin S et al. Gut 2010



Maser E et al. Clin Gastroenterol Hepatol 2006

Trough levels and clinical Response to infliximab in UC

	Clinical response	p	Colectomy	p
Antibodies to IFX	0.15 (0.06-0.40)	<0.001	2.71 (1.22-6.01)	<0.05
Detectable trough [IFX]	12.0 (4.76-30.26)	<0.001	0.13 (0.05-0.35)	<0.001
Baseline Mayo score >10	0.36 (0.15-0.83)	<0.05	3.42 (1.56-7.51)	<0.01
Baseline CRP > 5 mg/L	0.60 (0.21-1.69)		1.94 (0.65-5.81)	
pANCA positive	0.89 (0.36-2.16)		0.58 (0.25-1.33)	
Pancolitis	1.23 (0.48-3.16)		1.56 (0.61-3.97)	

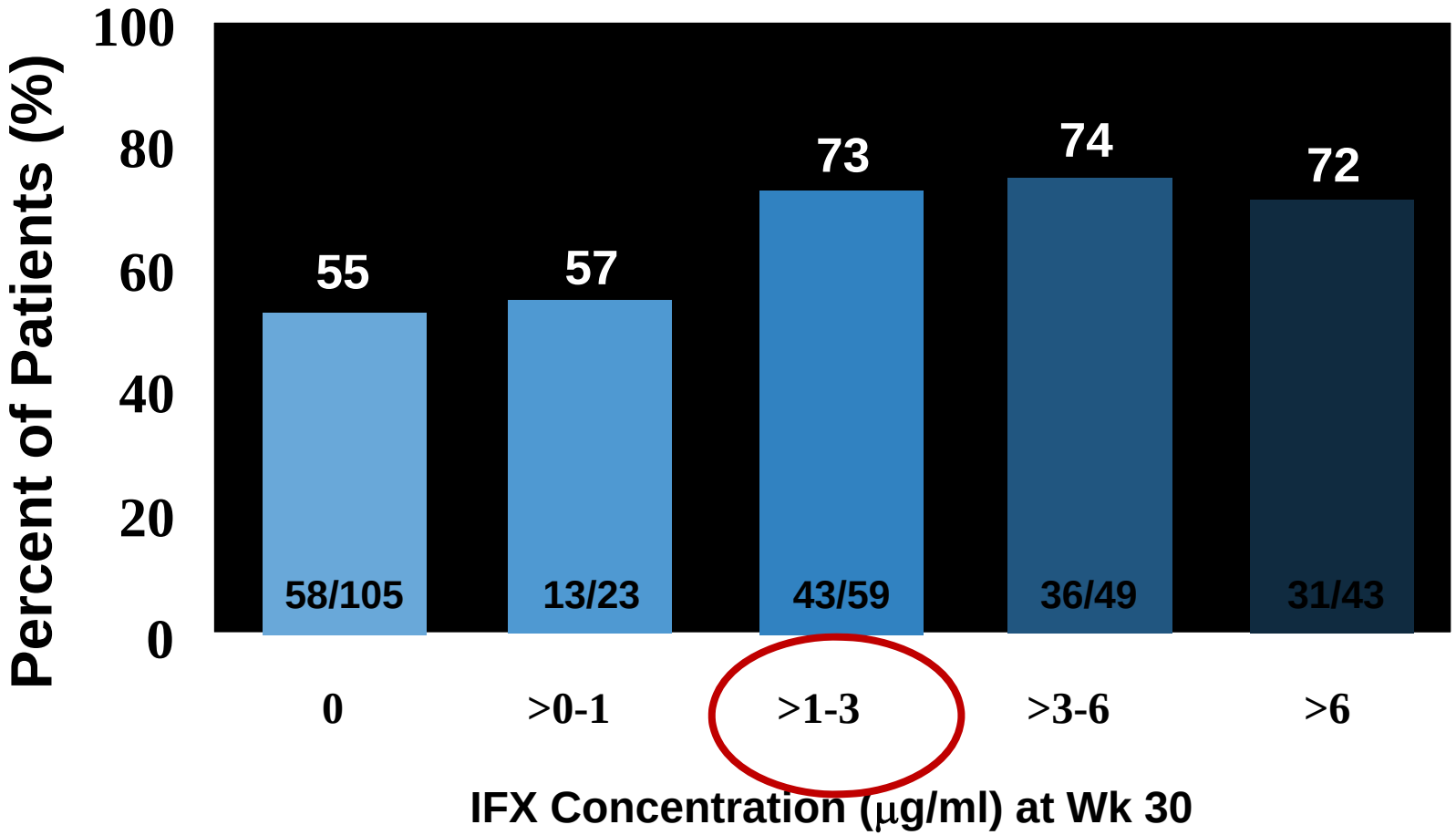
N= 115
Clinical response overall : 59% wk 10 and 48% wk 54
Clinical remission overall: 32% wk 10 and 37 % wk 54
Colectomy rate: 40% by wk 54

Seow CH et al. Gut 2009

SONIC

Clinical Remission Without Corticosteroids by Trough IFX Concentration

Primary Endpoint - All Patients – Wk 26



Mono or Combo: Why is the pendulum swinging?

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Immunogenicity of episodic IFX

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Combined clinical trials and cohorts with IFX

Hepatosplenic T-cell lymphomas

'Human' mAbs

Modified from G Greenberg, MD

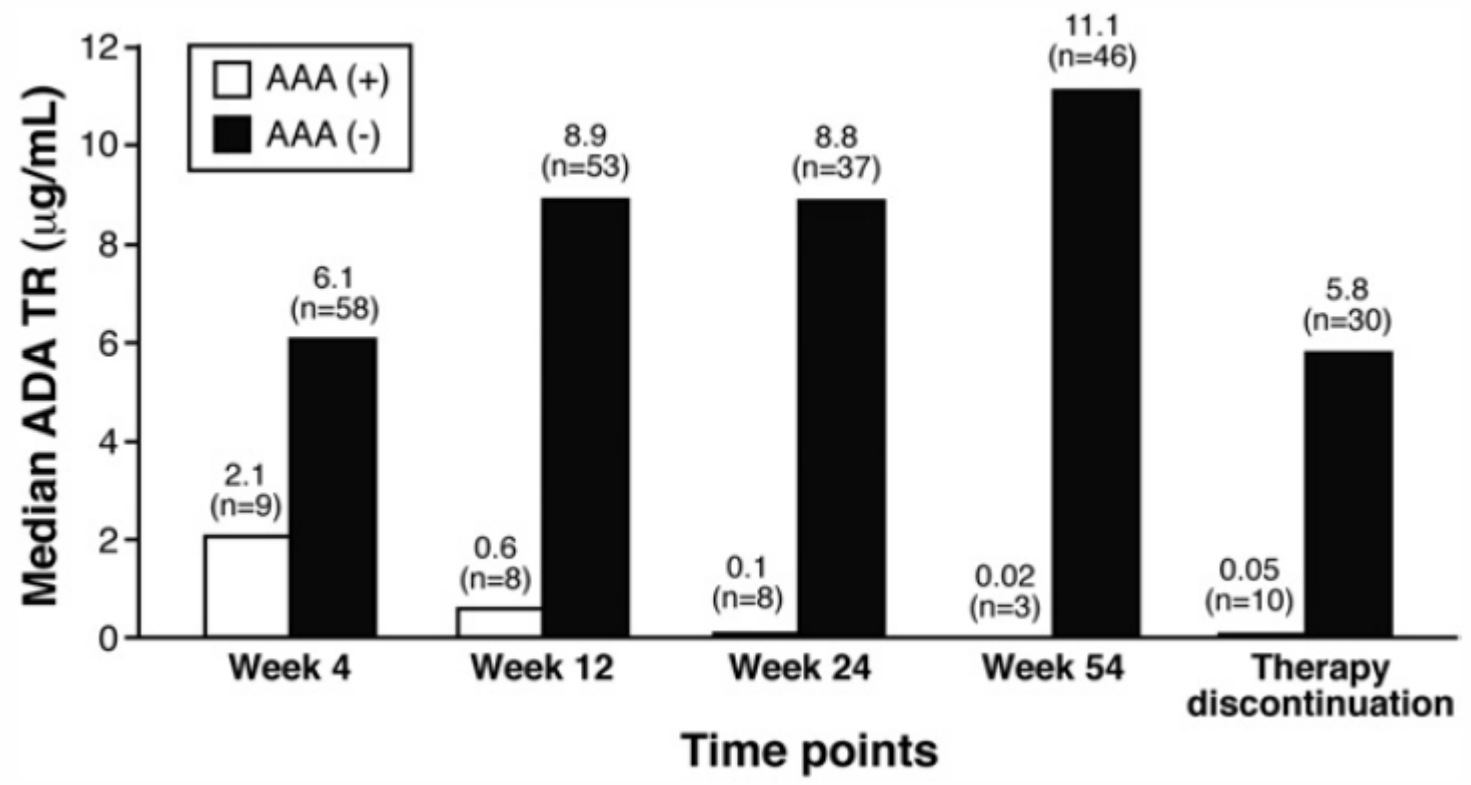
Concomitant immunosuppressives and IFX trough levels

	IFX trough NO IS median (IQR) µg/mL	IFX trough with IS	IS used
SONIC (Colombel JF, NEJM 2010)	1.6	3.5 (p<0.001)	AZA (+prednis.)
COMMIT (Feagan B, DDW 2010)	3.75	6.35 (p<0.08)	MTX + prednis.
IMID (Van Assche G, Gastro 2008)	1.65 (0.54-3.68)	2.87 (1.35-4.72) p<0.0001	AZA/MTX withdrawal
Toronto (Maser E, Clin Gastro Hepatol 2006)	5.6	5.2	AZA/(MTX) concomitant
U of Leuven mucosal healing cohort (Van Moerkercke W, ECCO 2010)	2.78 (0.35-8.71)	4.03 (0.38-9.42) p=0.365	AZA (MTX) concomitant

Antibodies against adalimumab: comparison between studies

Study	N patients	% AAA	disease
CLASSIC I	225	0.04%	CD
CLASSIC II	269	2.6%	CD
CHARM	517	-	CD
GAIN	159	0%	CD
Leuven	130	9.2%	CD
Bartelds	121	17%	RA

Karmiris K et al. Gastroenterology, 2009;137:1628-1640



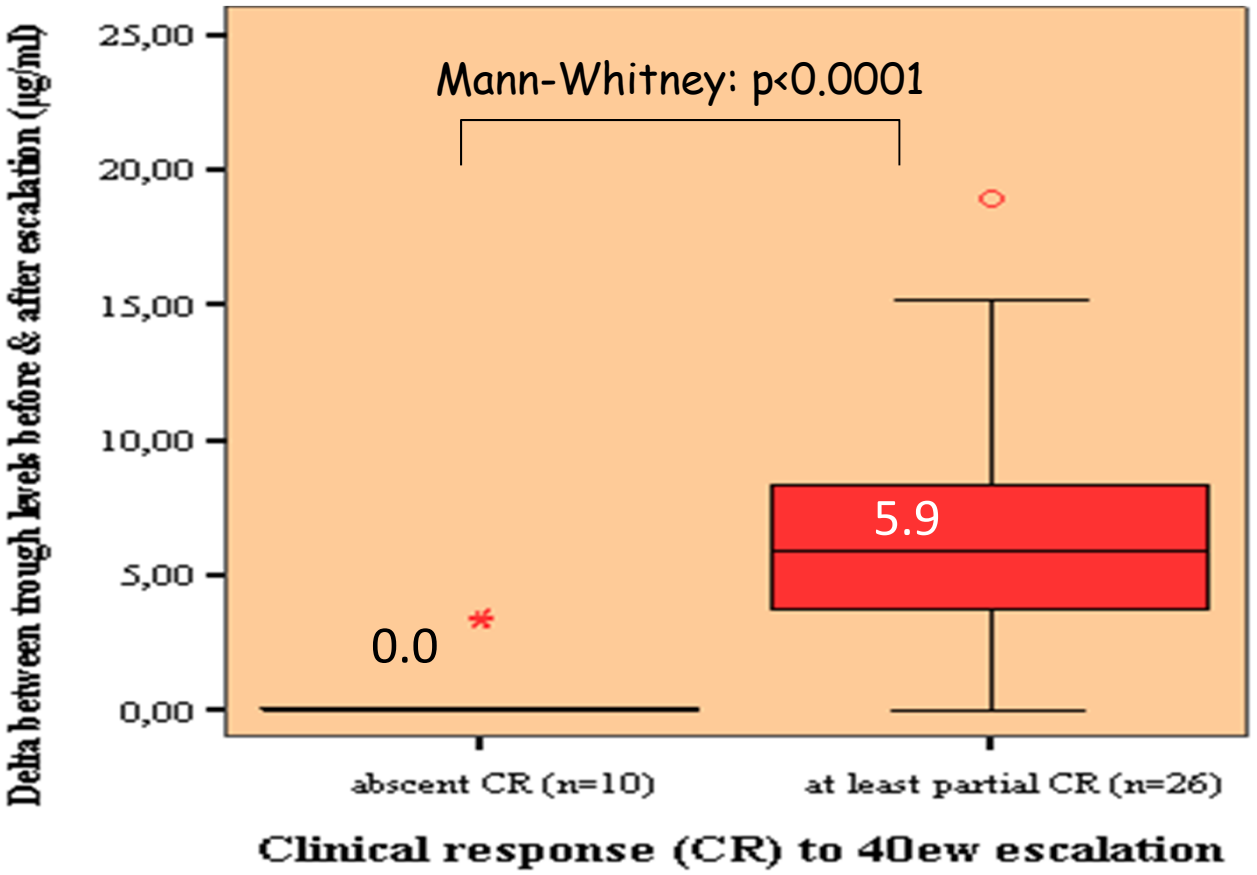
- 12/130 patients (9.2%) undetectable serum [ADA] at least once

- 11/12 AAA positive and all discontinuated therapy

Adalimumab trough levels and clinical response

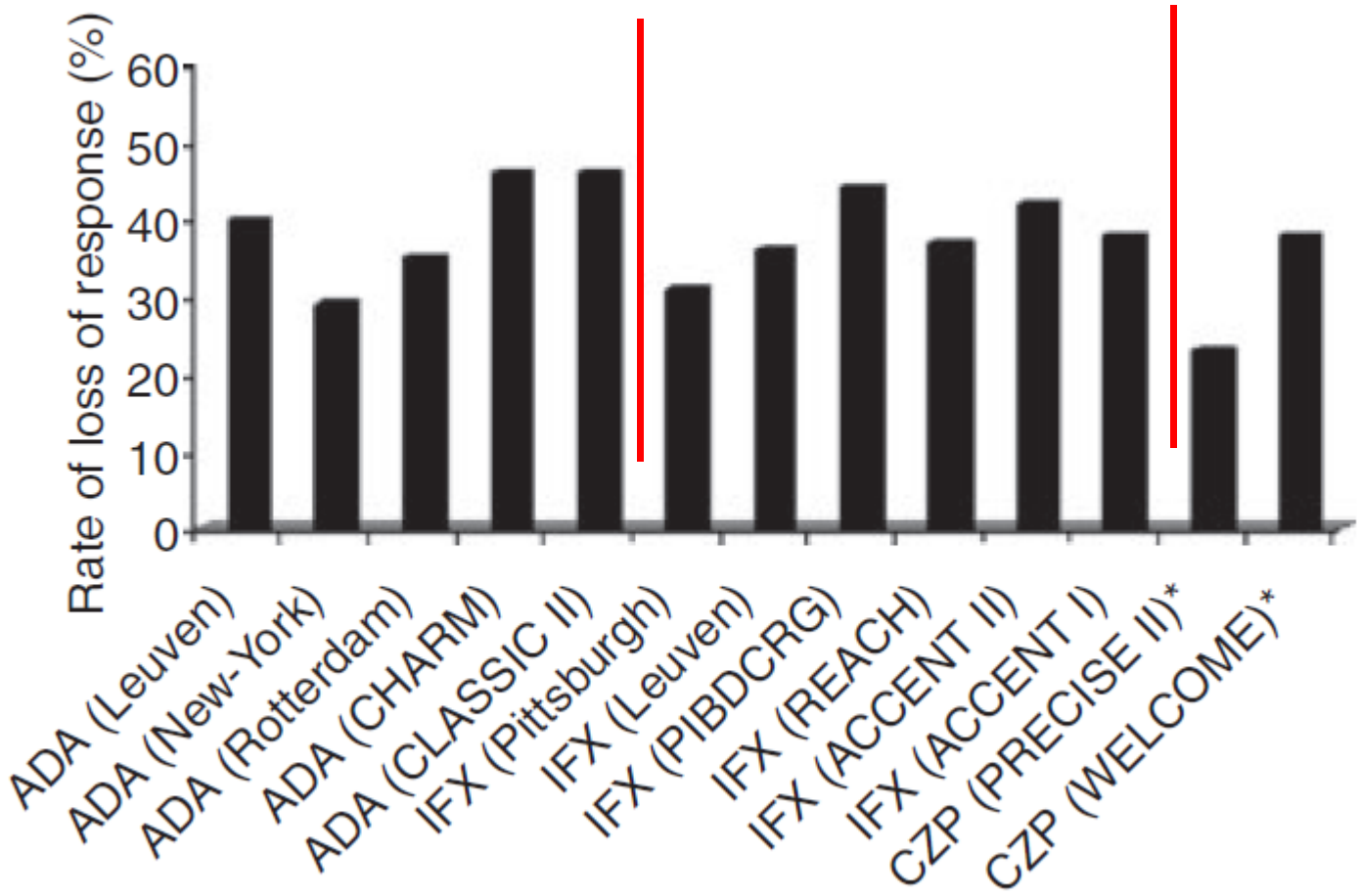
- **Median (IQR) TR before dose/time escalation (μg/mL): 4.7 (1.5-8.9)**
- **Median (IQR) TR after dose/time escalation (μg/mL): 9.2 (1.1-16.7)**

p<0.0001



Karmiris K et al. Gastroenterology, 2009;137:1628-1640

Loss of response to anti TNF agents in IBD



Ben-Horim S and Chowers Y. APT 2011

Does the need for dose escalation predict failure ?

Complete loss of response or intolerance after dose escalation

-ACCENT 1 (IFX)

-5 mg/kg to 10 mg: 38%

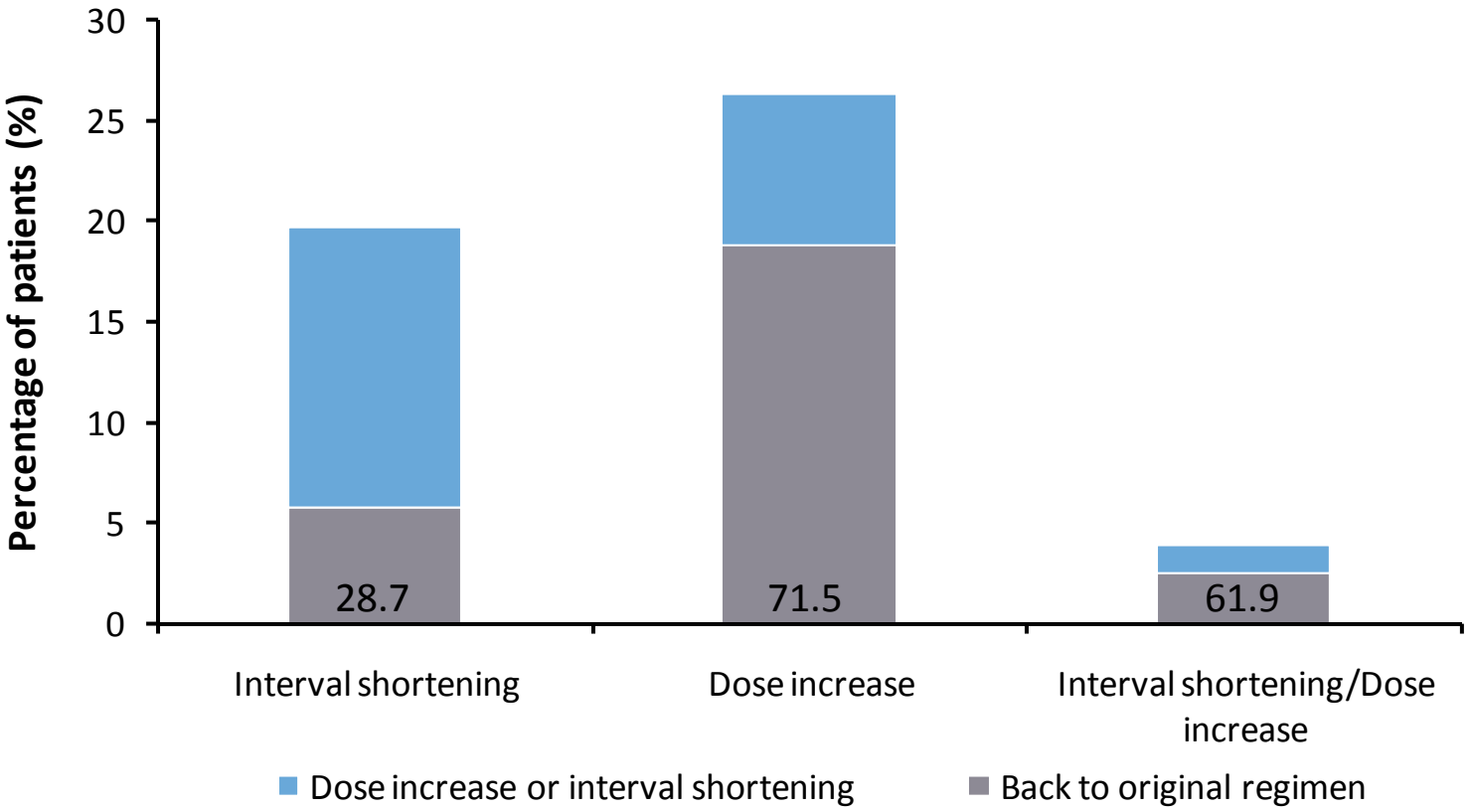
-10 mg/kg to 15 mg: 31%

-Leuven Crohn's disease cohort (n=547):

After interval shortening:	17% immediately
(19.7%, 108)	33% (36/108) long term
After (temporary) dose increase:	50% long term
(26.3%, 144)	23% directly

Hanauer et al. Lancet 2002, Rutgeerts et al. Gastro 2004
Schnitzler et al. Gut 2009

Flexible dosing of infliximab in Crohn's disease



Schnitzler F et al. Gut 2009;58:492-500

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What drives loss of response to monoclonal anti TNF Abs?

IBD Leuven

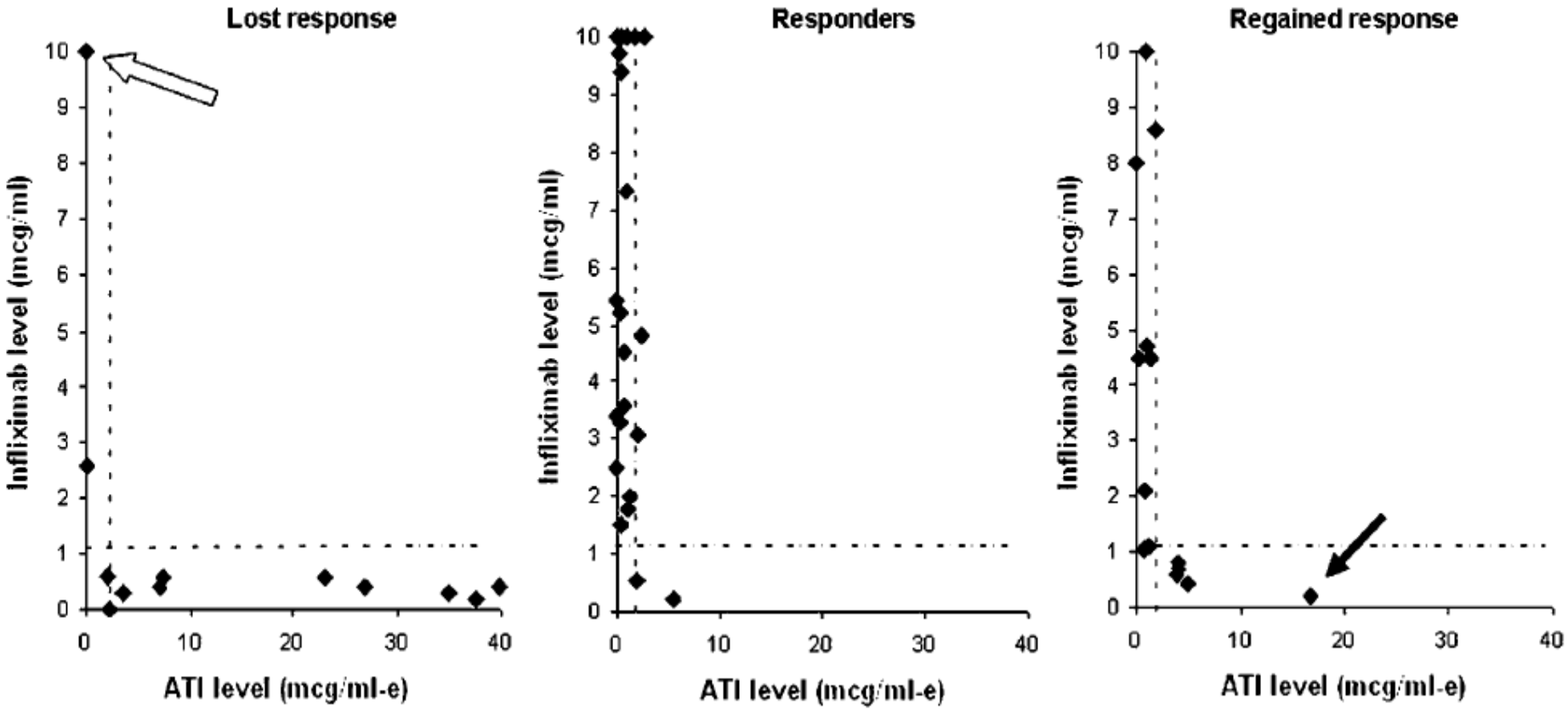
Problems:

- Neutralizing antibodies/low trough levels
- Other immune pathways drive inflammation
- Patient has no residual inflammation

Solutions:

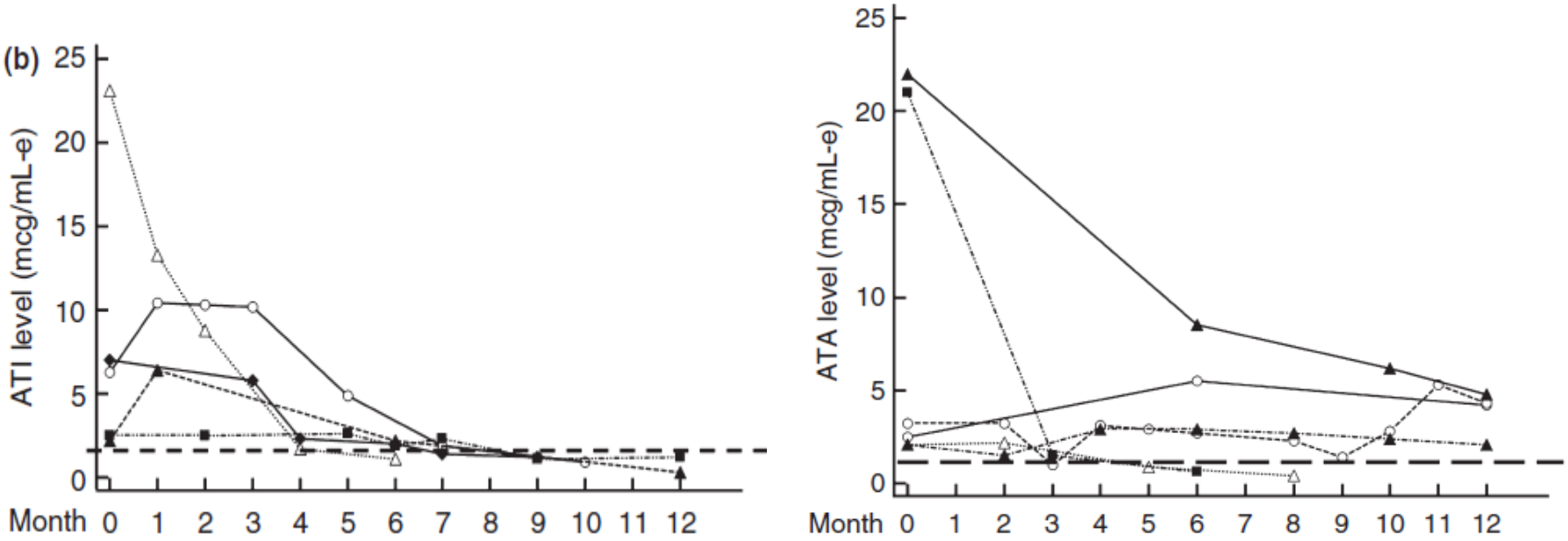
- Increase dose, switch to other anti-TNF
- Biological with other MOA, immunosuppress.
- Surgery

Clinical impact of anti drug Ab and trough levels



Ben-Horin S et al. Gut 2010

Disappearance of anti drug Abs after cessation of treatment.



Anti drug Abs not very useful to predict response or reactions to rechallenge

Ben-Horin S et al. Aliment Pharmacol Ther 2012

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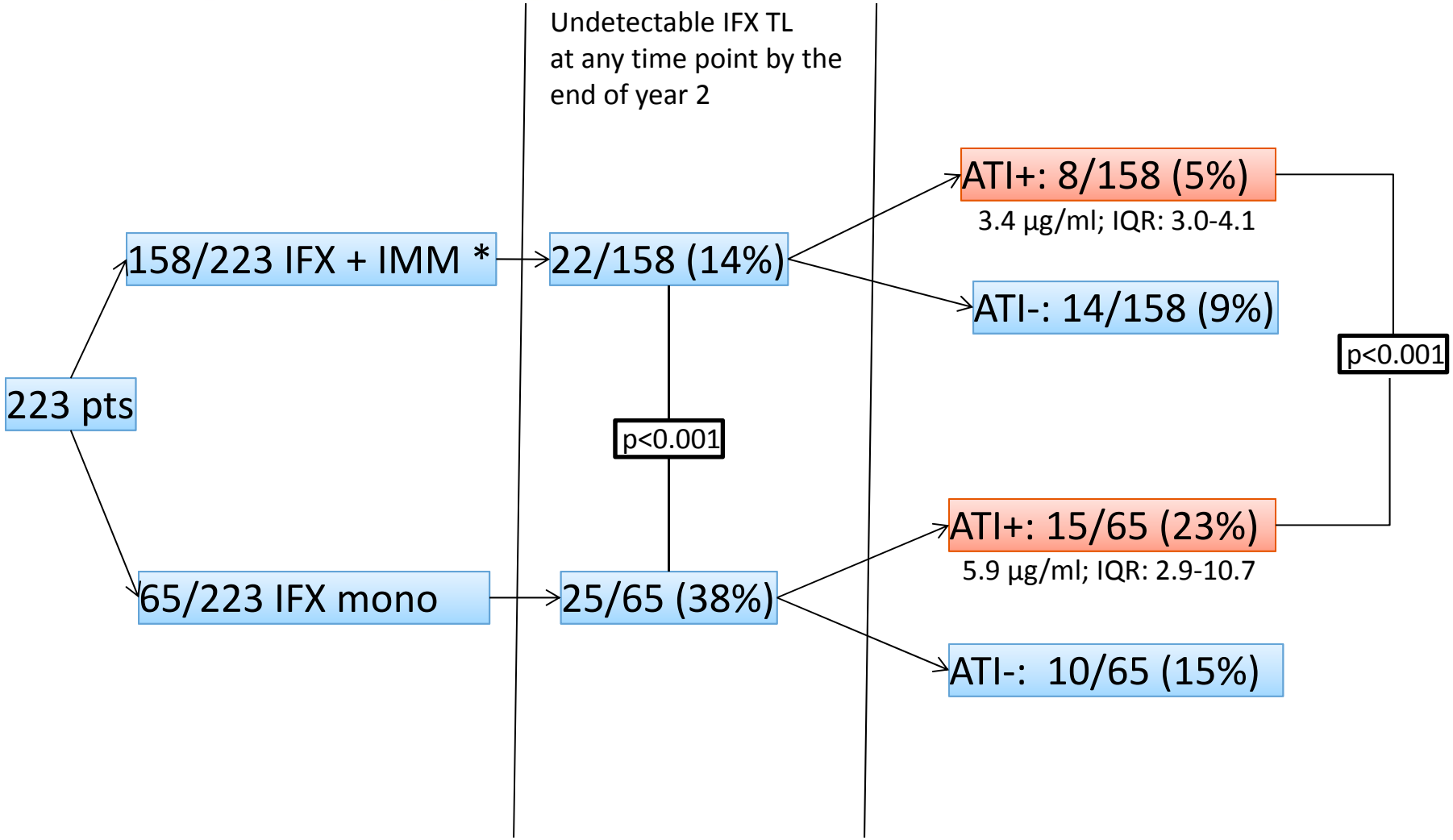
Impact of IMM on ATI formation

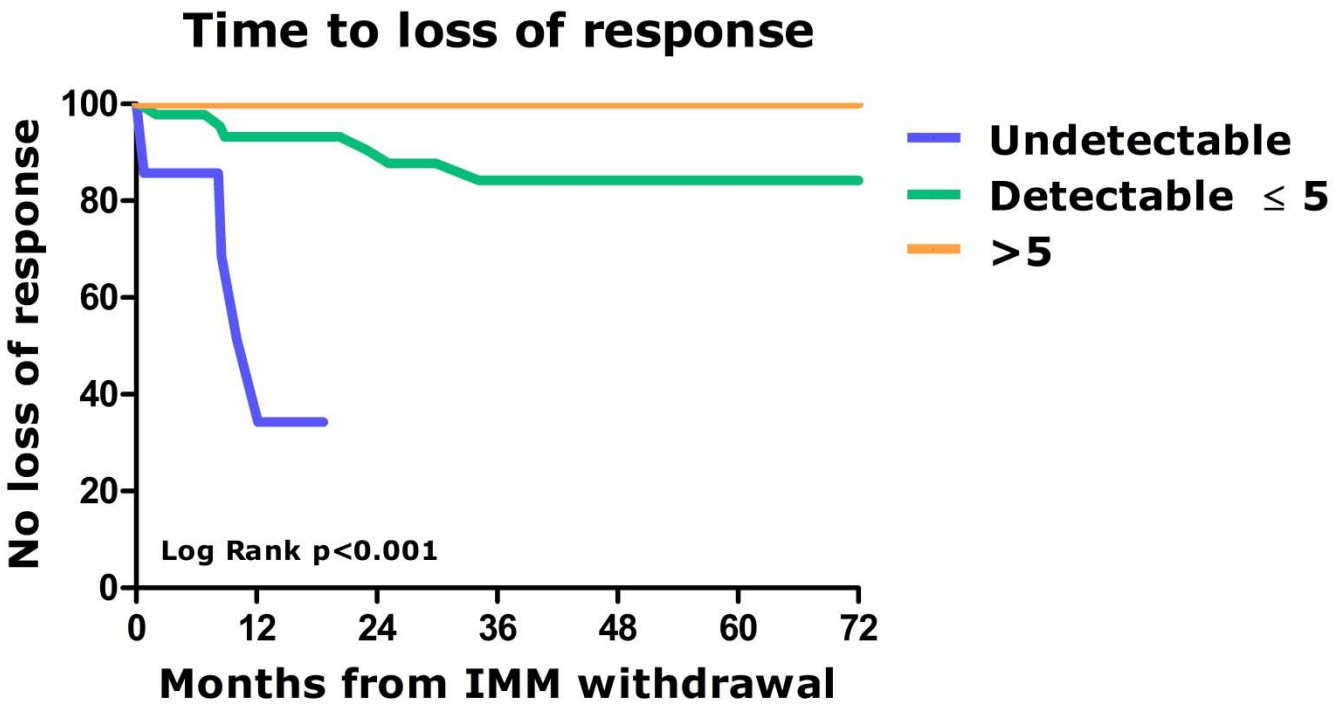
Cumulative incidence at the end of year 2 after start of IFX



*IFX TLs after withdrawal of IMM are censored in this subanalysis

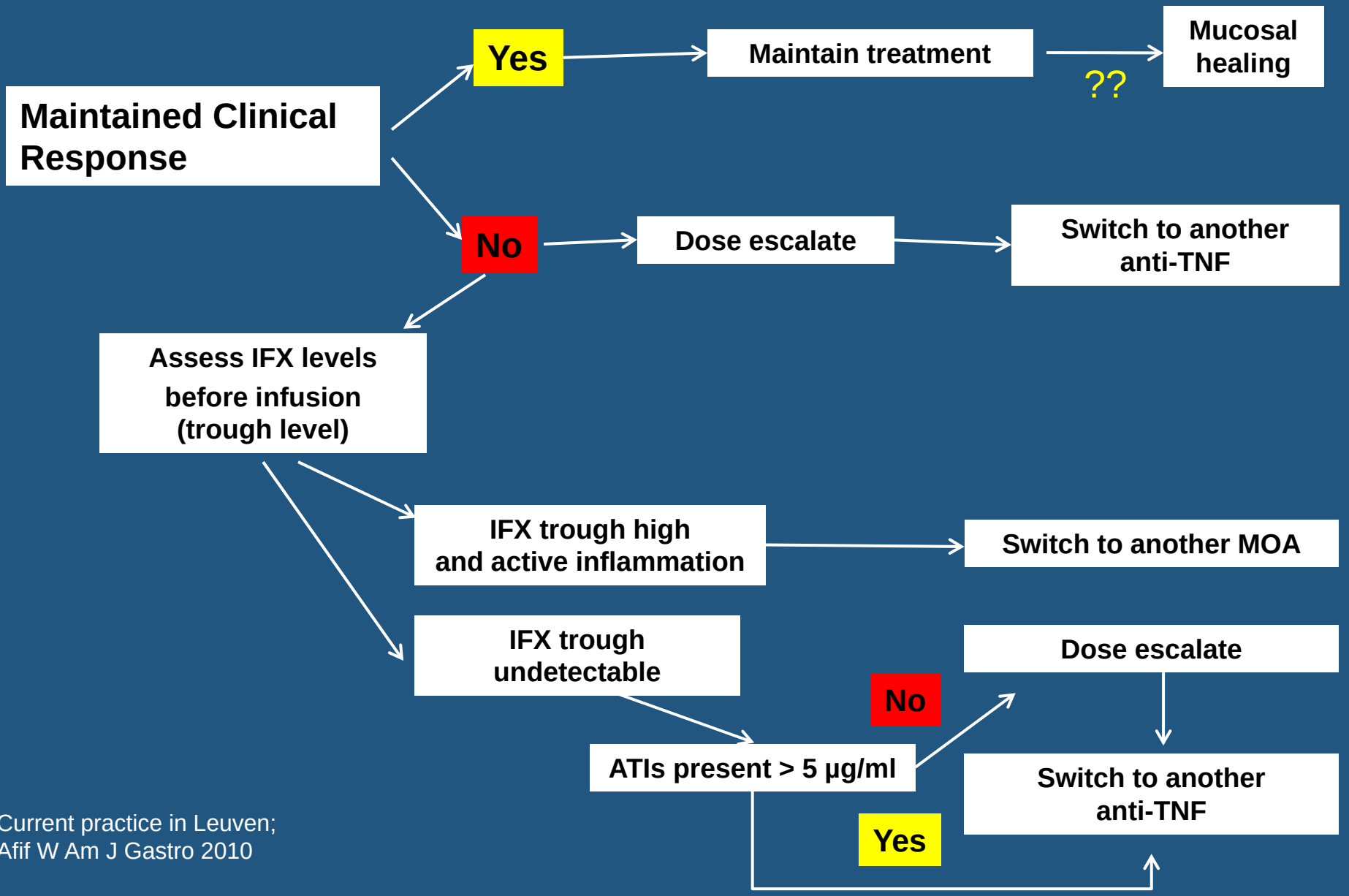
Drobne D DDW 2011

No loss of response after withdrawal of IMM: *IFX trough levels at the time of withdrawal*



Drobne D DDW 2011

Algorithm for Use of Trough Levels/Anti drug Abs during Anti TNF Maintenance in patients with CD



Current practice in Leuven;
Afif W Am J Gastro 2010

Anti TNF serum levels and anti drug antibodies are clinically relevant

IBD Leuven

Scenario 1: Adequate serum levels and negative antibodies

Scenario 2: Undetectable serum levels and high titer Abs

Scenario 3: Low/undetectable serum levels and absent Abs

- Non immune clearance (Fc receptor...)
- Indeterminate for anti drug Abs (ELISA)
- Low patient compliance
- Drug sequestration due to high TNF load: inflammation+++