How to Heal IBD

Gastroenterology Institute,

Sheba Medical Center, Ramat Gan, Israel

Dr. Bella Ungar & Zohar Ben-Shatach

Therapeutic Drug Monitoring in IBD

Gastroenterology Institute,

Sheba Medical Center, Ramat Gan, Israel

Dr. Bella Ungar & Zohar Ben-Shatach

What are we going to talk about?

What is ***therapeutic drug monitoring (TDM)?***

TDM in anti-TNFα (infliximab, golimumab) therapy

TDM in ***vedolizumab therapy***

Open questions

Take home messages

Therapeutic drug monitoring (TDM)

A branch of clinical pharmacology, specializes in measurement of medication concentrations

Focuses on drugs with narrow therapeutic window

Improving patient care by adjusting the dose for which clinical experience / trials have shown improved outcome

---

Marshall et al, Clinical Chemistry, 2008

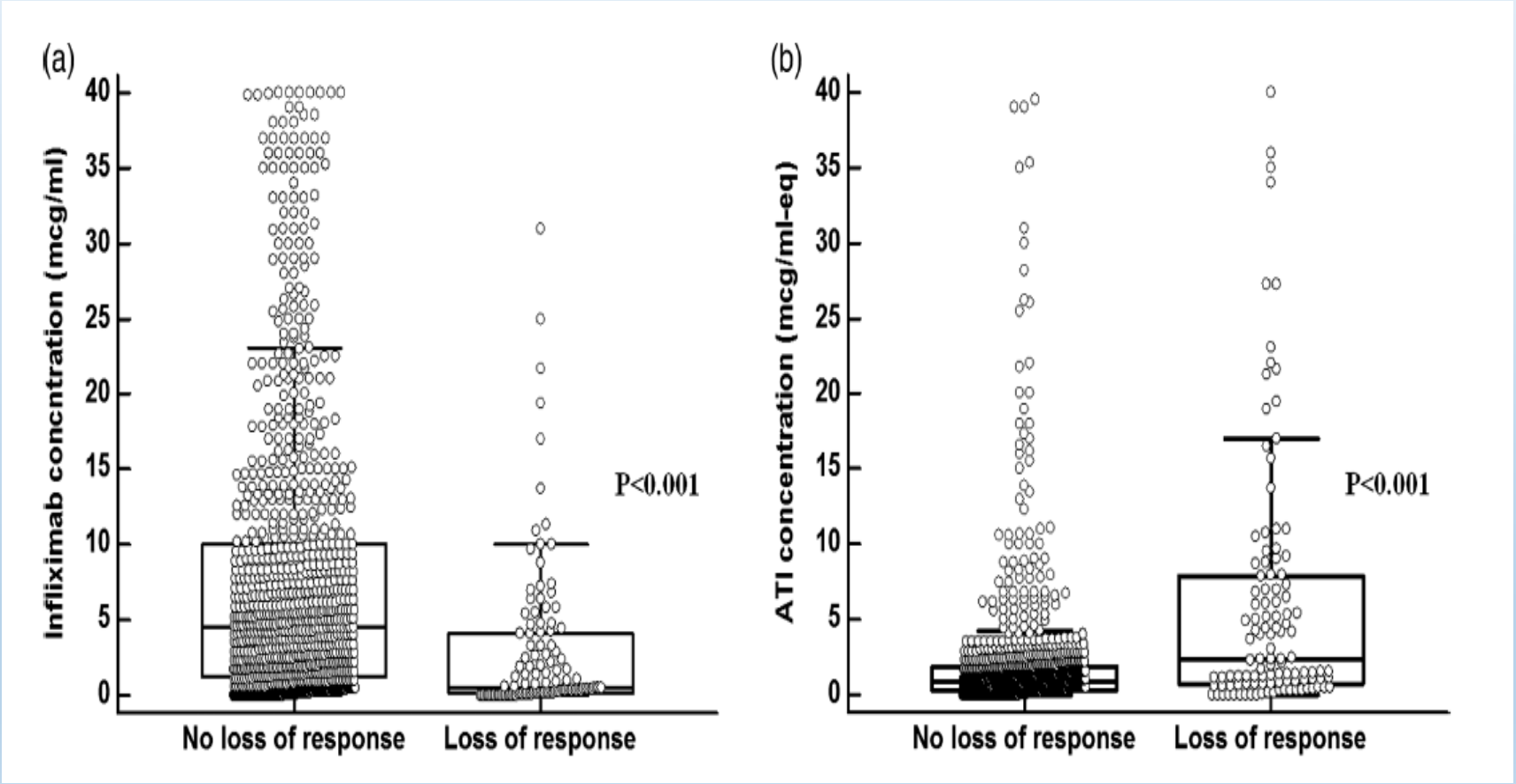
Therapeutic drug monitoring (TDM)

Drug concentration data influenced by:

- ***Age, Gender, Weight***
- ***Clinical status***
- ***Co-medications*** } patient
- ***Timing***
- ***Route*** } drug
- ***Dose***
- *Analytical method*
- ***Anti-drug antibodies***

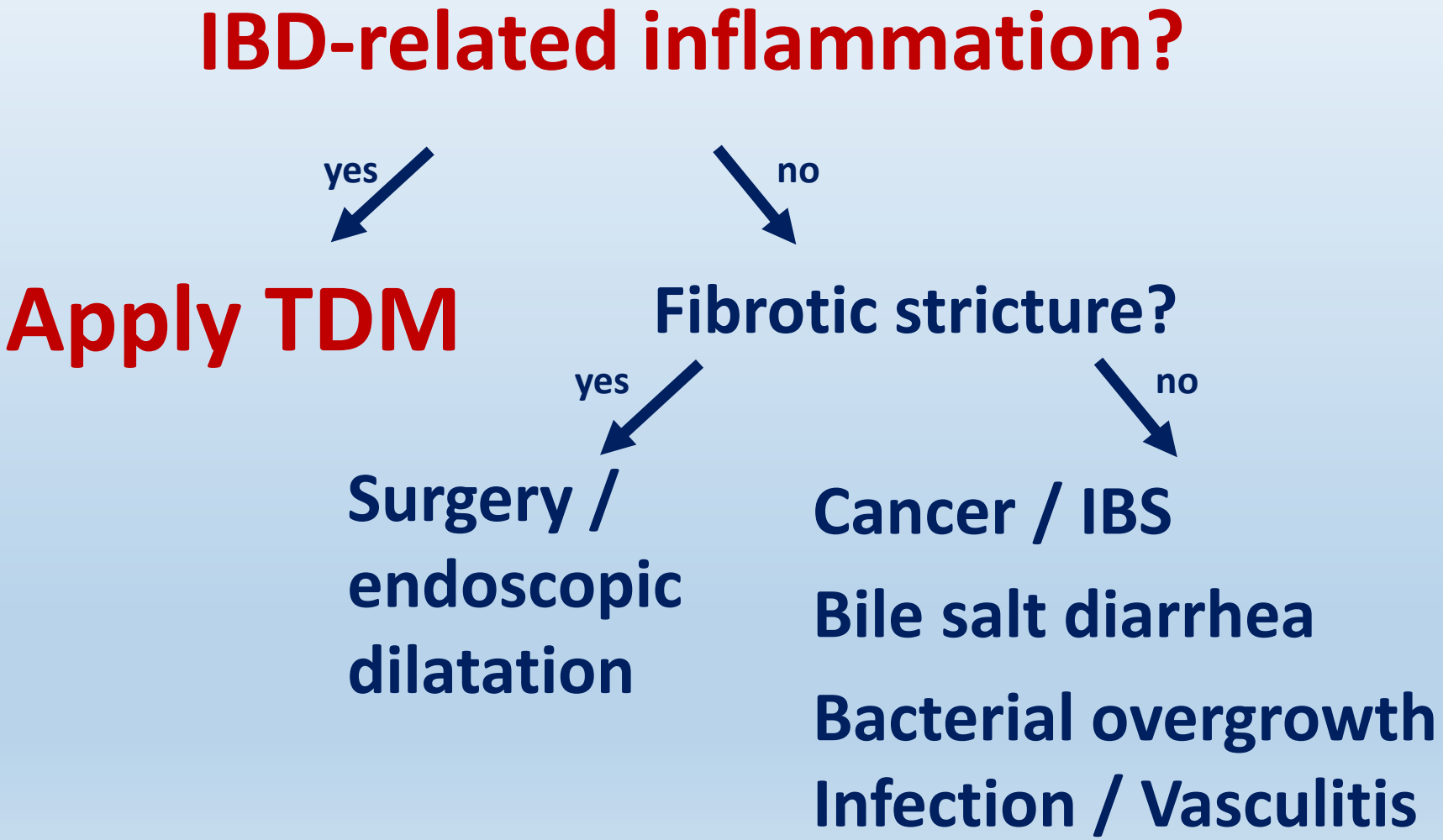
Burton et al, Applied Pharmacokinetics & Pharmacodynamics , 2006
TDM executive committee, 2004

Immunogenic LOR to anti-TNFs



Ungar, Gut, 2014

How to address different mechanisms of LOR?



TDM in anti-TNFα therapy – infliximab & adalimumab

Minimal infliximab trough level *for clinical / CRP / endoscopic remission:* ***3-7 µg/ml***

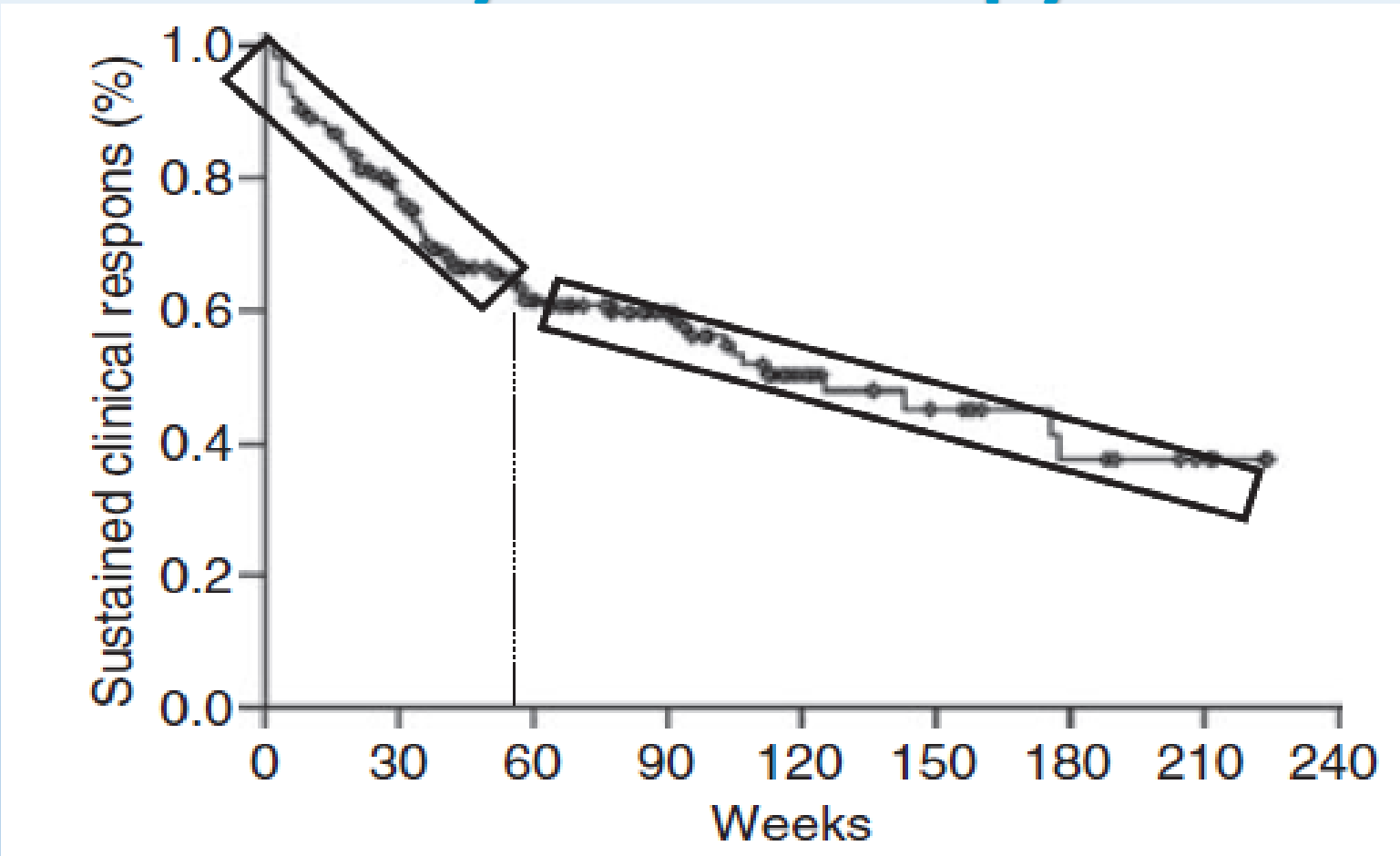
Anti-infliximab-antibodies » lower drug levels, worse outcome

Drawbacks: *different assays, endpoints, IBD/CD/UC*

* Undetectable drug levels in patients with long-term remission predict successful withdrawal

Adedokun, Gastroenterology2014 | Levesque, APT, 2014 | Yanai, CGH, 2015 | Papamichael, CGH, 2016 | Ben-horin, APT, 2015 | Vande Casteele, Gut, 2015

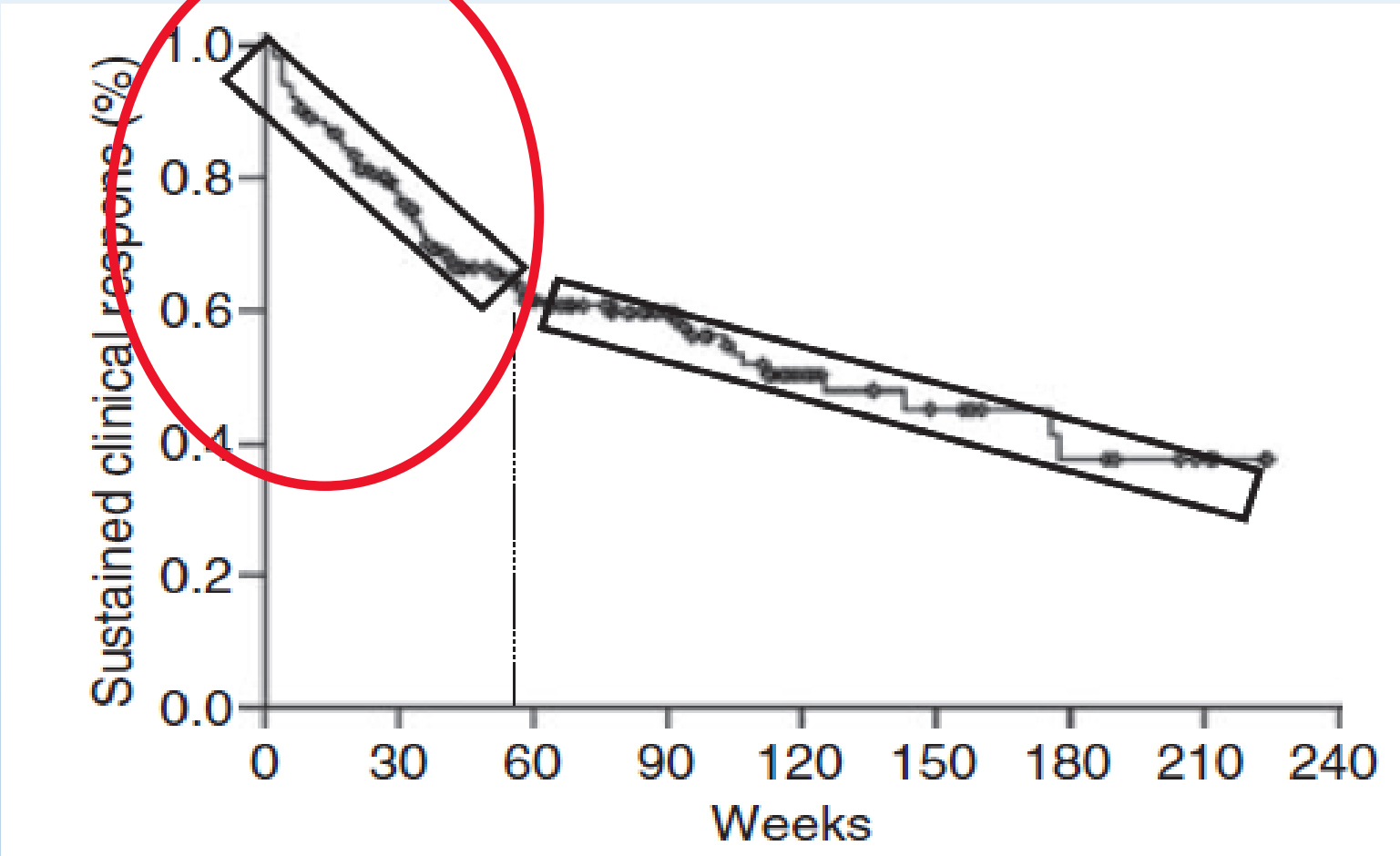
Antibodies & LOR occur mostly during 1st year of therapy



LOR to adalimumab

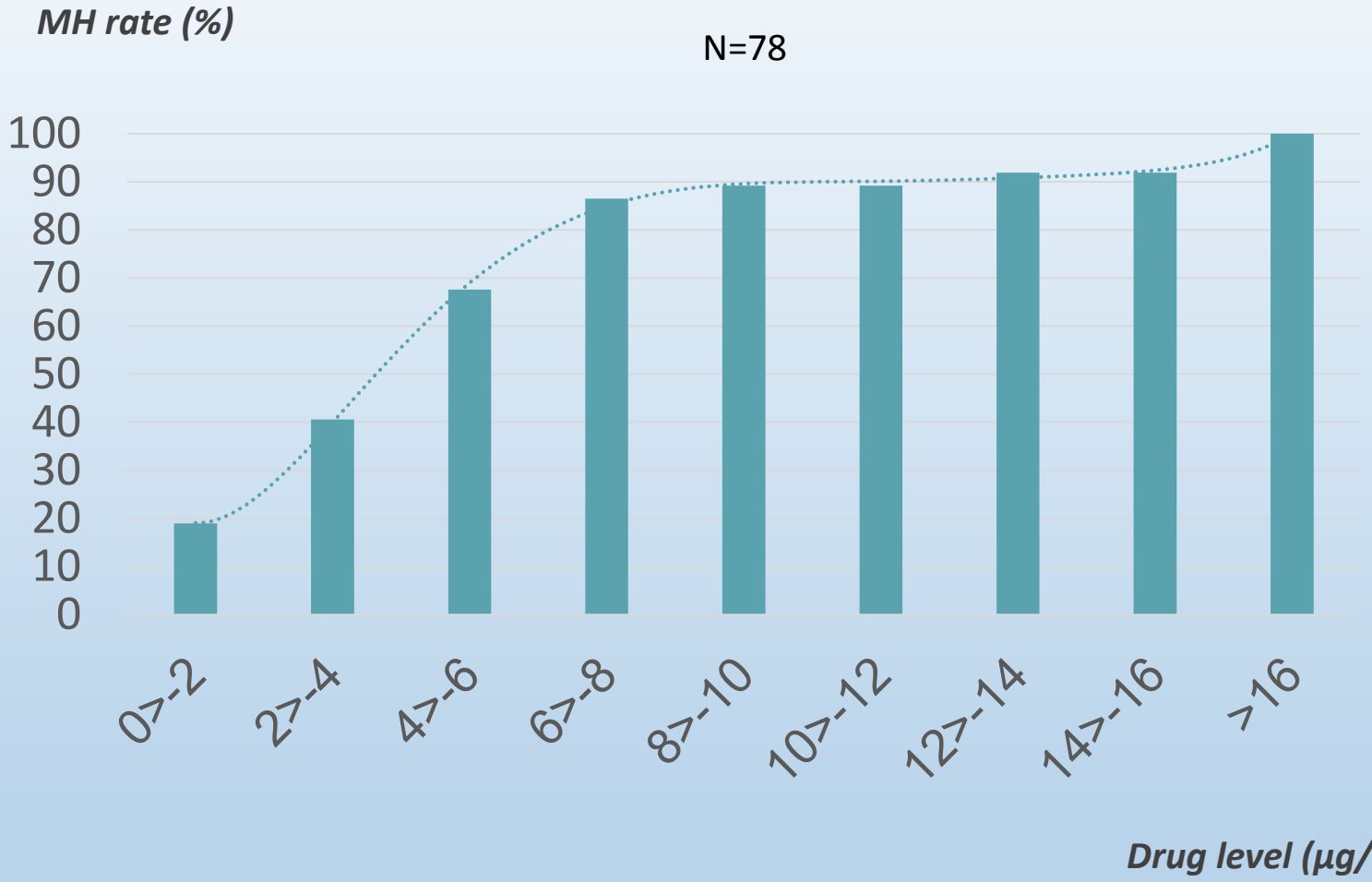
Karmiris, GE, 2009

Antibodies & LOR occur mostly during 1st year of therapy



LOR to adalimumab

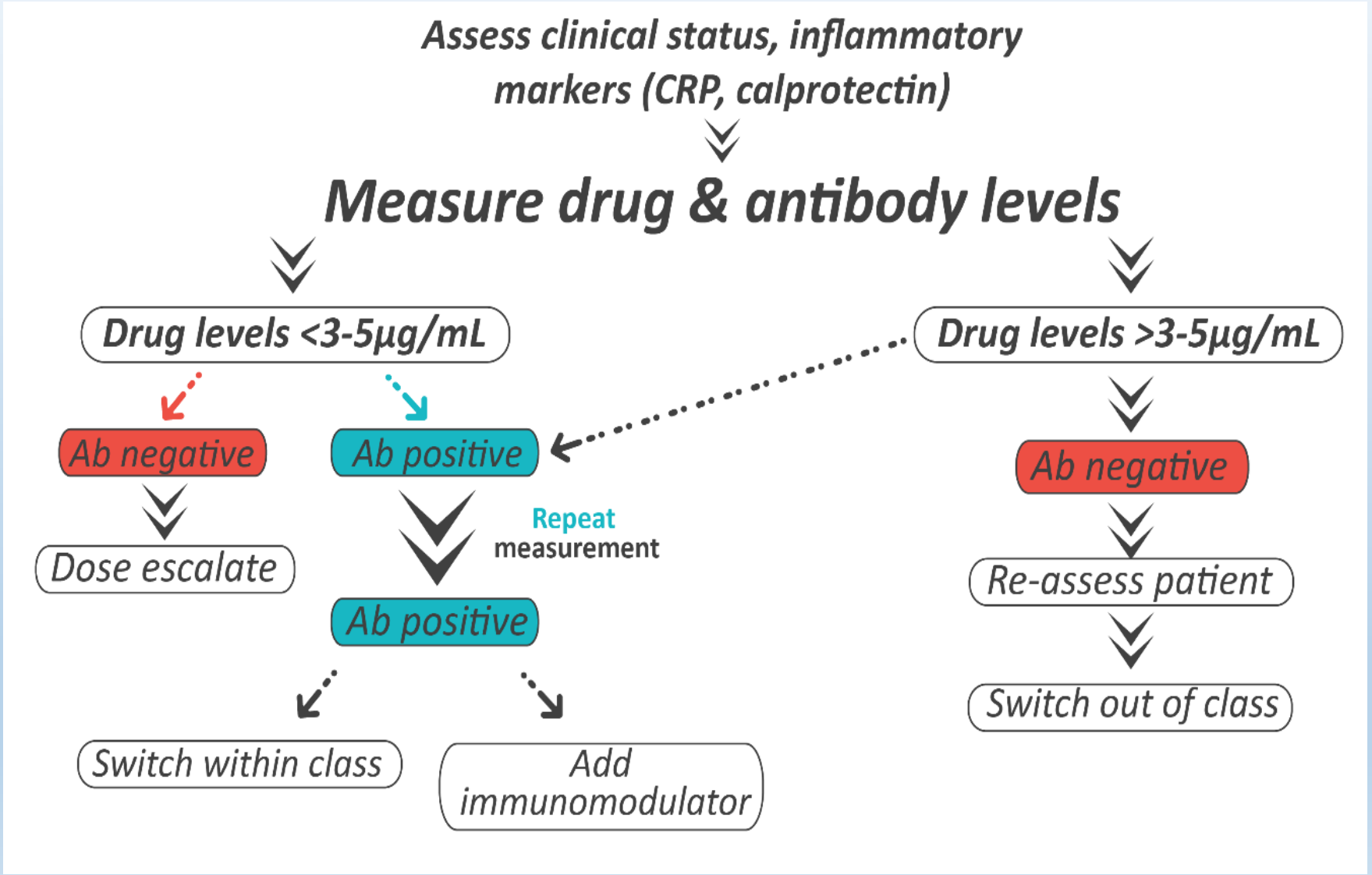
Karmiris, GE, 2009



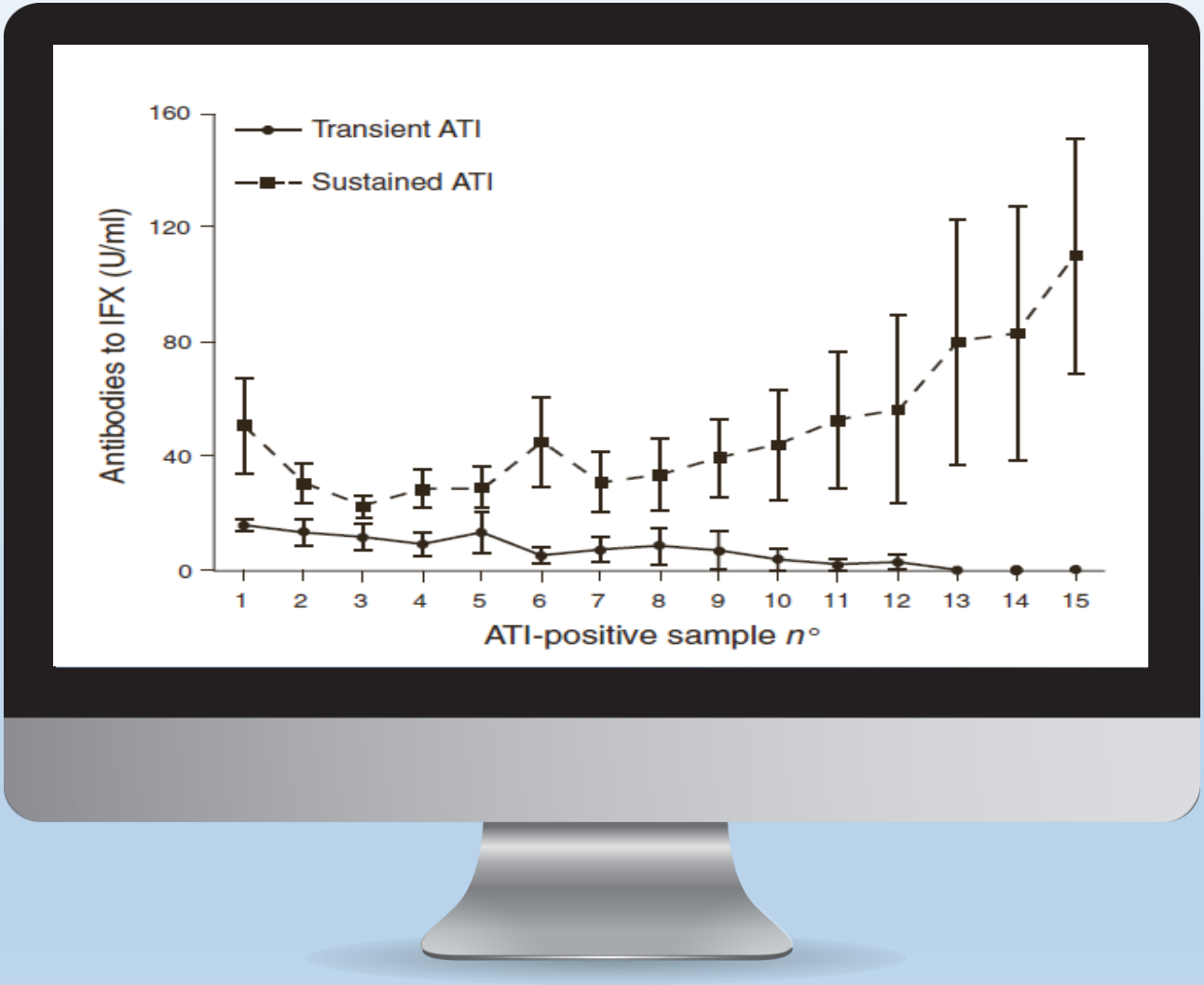
Ungar et al, CGH, 2016

So…how to treat LOR?

Reactive TDM - Infliximab & Adalimumab

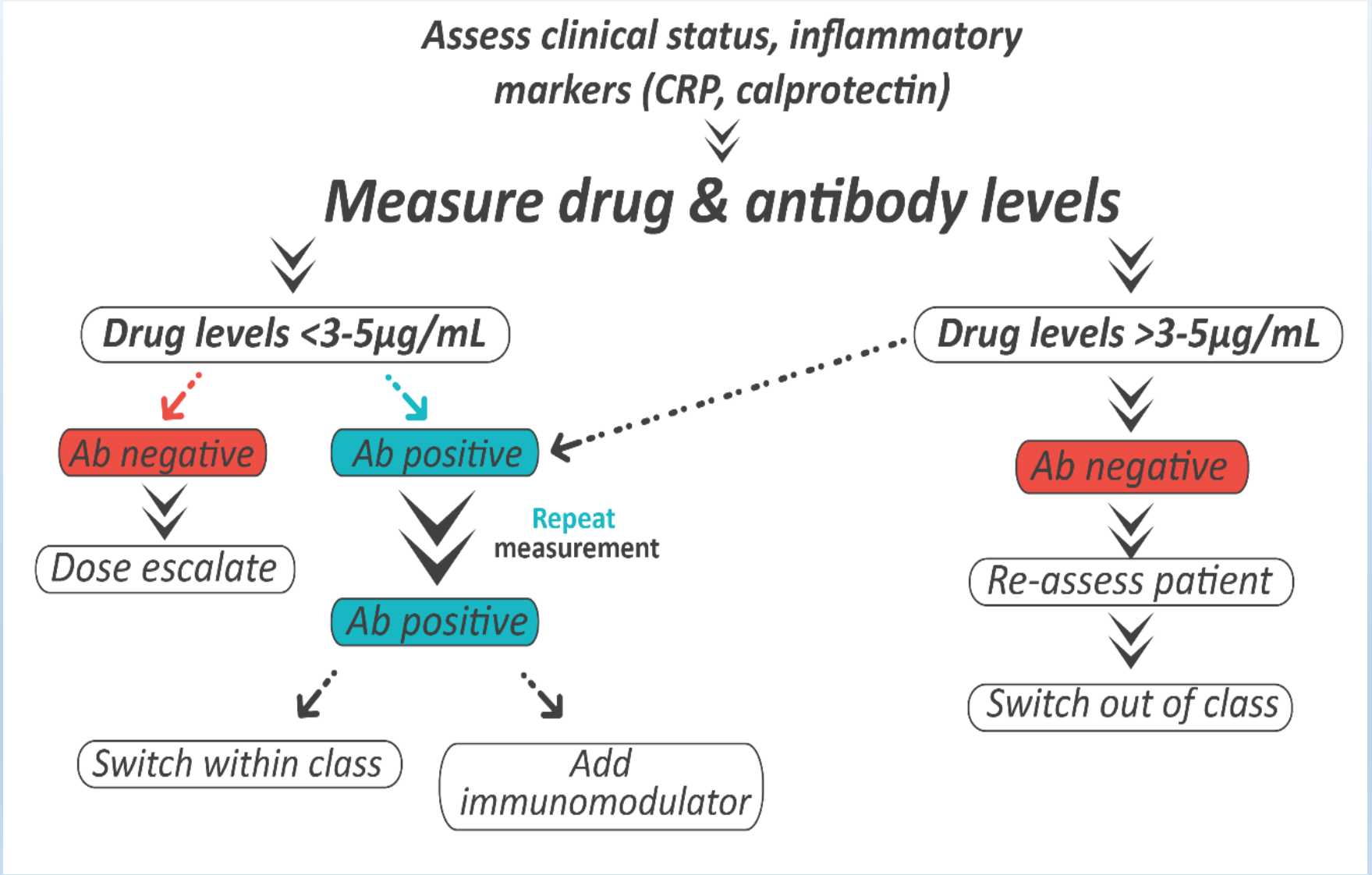


Transient versus sustained Ab



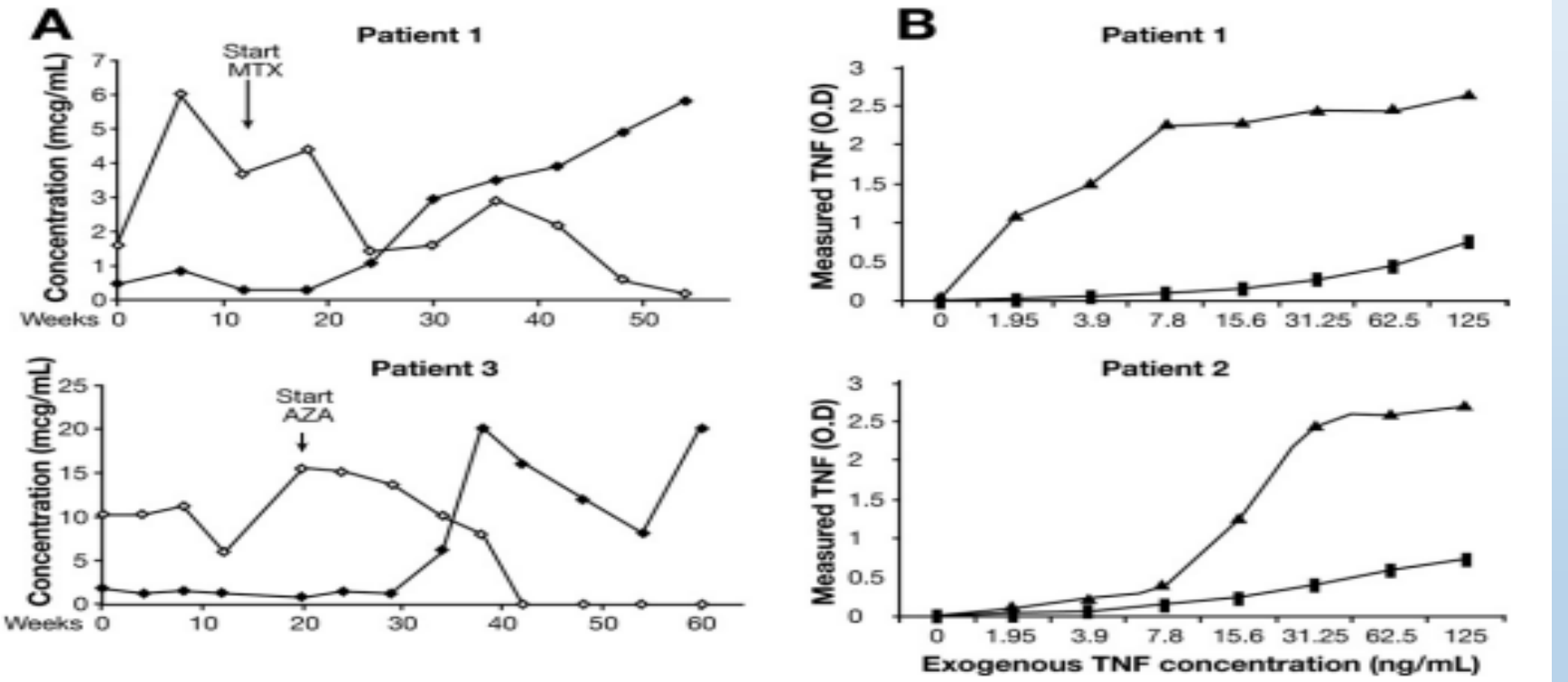
Vande Casteele, AJG, 2013

Reactive TDM - Infliximab & Adalimumab



Addition of an Immunomodulator to Infliximab Therapy Eliminates Antidrug Antibodies in Serum and Restores Clinical Response of Patients With Inflammatory Bowel Disease

SHOMRON BEN–HORIN,* MATTI WATERMAN,‡ URI KOPYLOV,* MIRI YAVZORI,* ORIT PICARD,* ELLA FUDIM,* HALIM AWADIE,‡ BATIA WEISS,* and YEHUDA CHOWERS‡

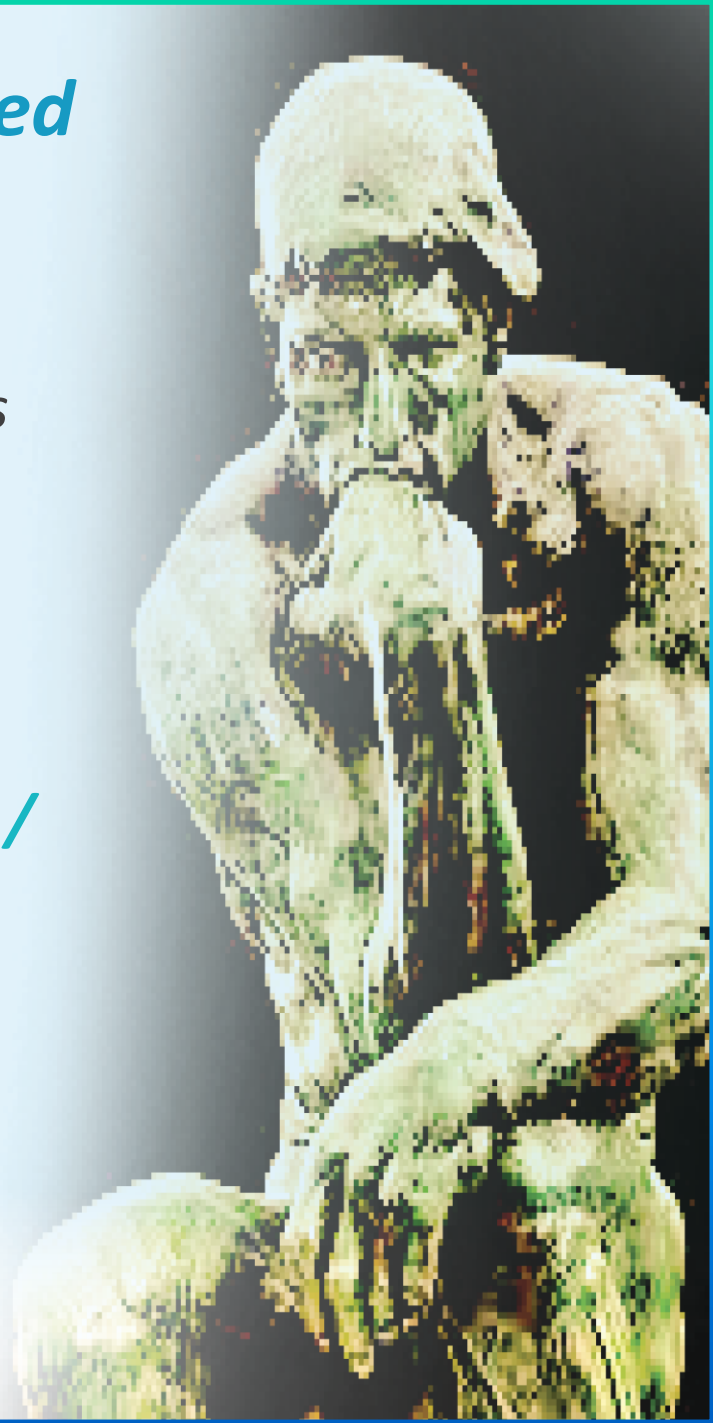


Proactive TDM vs. clinically based dosing

Low adalimumab and infliximab drug levels predict increased future risk of antidrug antibody development and active disease

TAXIT
TAILORIX
Additional trials

} ***Proactive approach – not clinically superior / cost - efficient?***



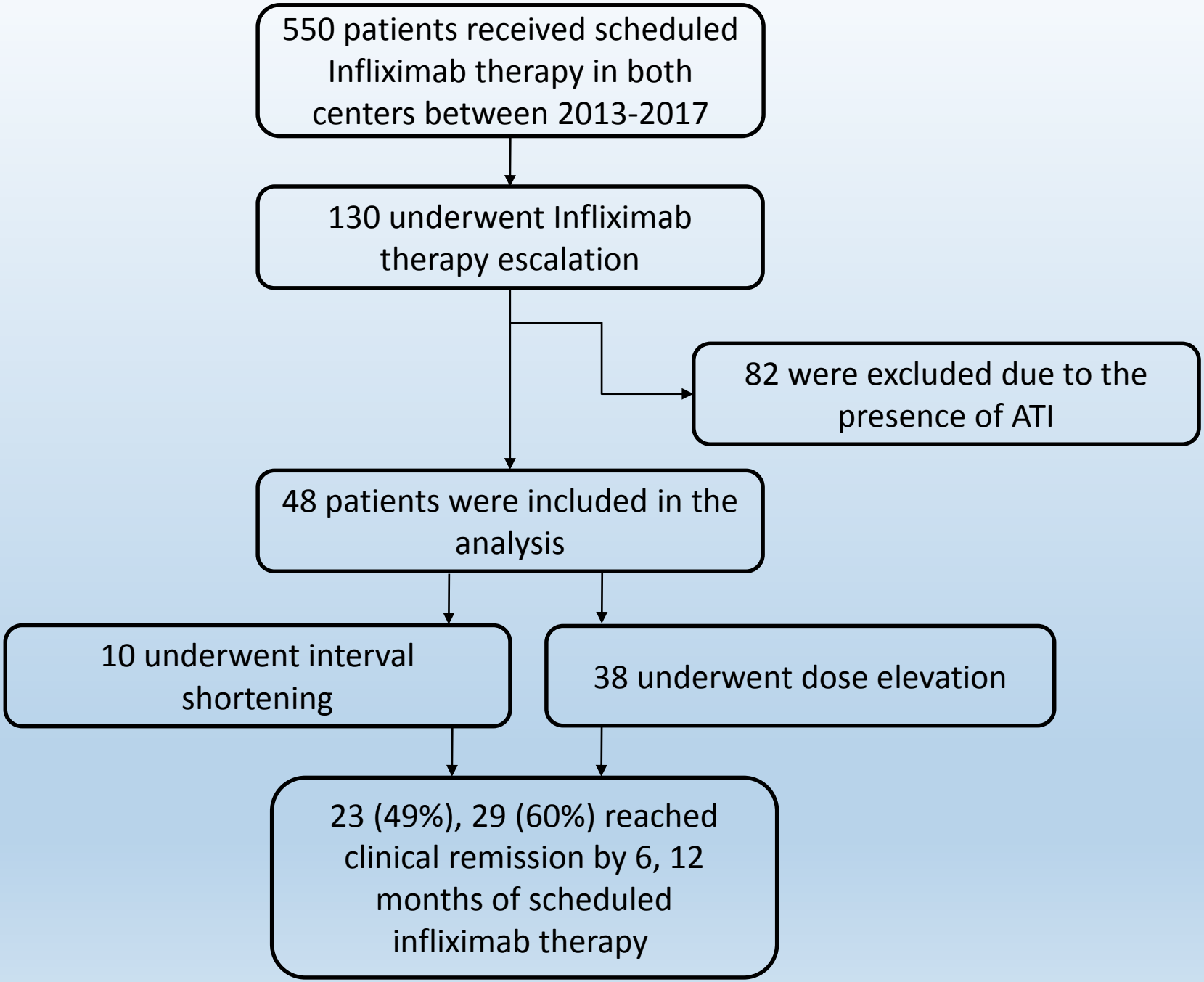
Amiot, Clin Res Hepatol Gastroenterol. 2016 | Vaughn, IBDJ, 2014

Our study- significance

- IFX- a monoclonal Ab
- LOR to IFX- 30% of IBD patients
- At time of LOR, lower IFX TL, in the absence of ATI, have been associated with the need for therapy escalation
- TL of 3-7µg/ml - clinical therapeutic window.
- It is still unclear above which TL further increasing the dose won't be beneficial

Our aim

- To evaluate the **impact of TL on therapeutic efficacy** of dose intensification in IBD patients experiencing LOR to infliximab in the absence of ATI.
- To **define** which infliximab levels correlate best with dose intensification- what is the **cut-off?**


550 patients received scheduled Infliximab therapy in both centers between 2013-2017
130 underwent Infliximab therapy escalation
82 were excluded due to the presence of ATI
48 patients were included in the analysis
10 underwent interval shortening
38 underwent dose elevation
23 (49%), 29 (60%) reached clinical remission by 6, 12 months of scheduled infliximab therapy

Clinical remission assessment

Harvey-Bradshaw Index (HBI)			
remission < 5 mild disease 5–7 moderate disease 8–16 severe disease > 16	general well-being	very well = 0 points slightly below = 1 point poor = 2 points very poor = 3 points terrible = 4 points	
	abdominal pain	none = 0 points mild = 1 point moderate = 2 points severe = 3 points	
	number of liquid stools		
	abdominal mass	none = 0 points dubious = 1 point definite = 2 points definite and tender = 3 points	
	complications	none arthralgia uveitis erythema nodosum aphthous ulcers pyoderma gangrenosum anal fissure new fistula abscess	1 point each

Tab. 3. Simple Clinical Colitis Activity Index (SCCAI).
Tab. 3. Jednoduchý klinický index aktivity kolitidy (SCCAI).

Simple Clinical Colitis Activity Index (SCCAI)			
	bowel frequency (number of stools per day)	0–3 = 0 points 4–6 = 1 point 7–9 = 2 points > 10 = 3 points	
	number of stools per night	0 = 0 points 1–3 = 1 point > 4 = 2 points	
	urgency of stool	none = 0 points hurry = 1 point immediately = 2 points incontinence = 3 points	
	blood in stool	none = 0 points trace = 1 point occasionally (< 50% of stool) = 2 points usually (> 50% of stool)	
	general well-being	very well = 0 points slightly below = 1 point poor = 2 points very poor = 3 points terrible = 4 points	
	extracolonic features	arthritis uveitis erythema nodosum pyoderma gangrenosum	1 point each

- Clinical remission was defined as HBI <5 for CD patients and SCCAI≤ 3 for UC patients

Results

- ROC- Infliximab pre-escalation trough levels <4.8µg/ml were found to be optimal for dose intensification, for clinical remission at 6 months (AUC=0.77, p=0.0001, 91% sensitivity, 66% specificity) and at 12 months (AUC=0.74, p=0.001, 83% sensitivity, 58% specificity).

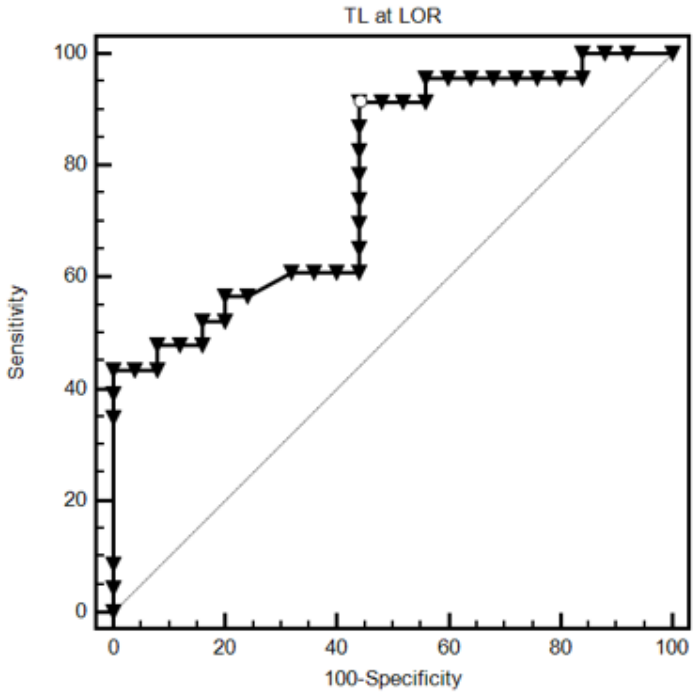


Figure 2a

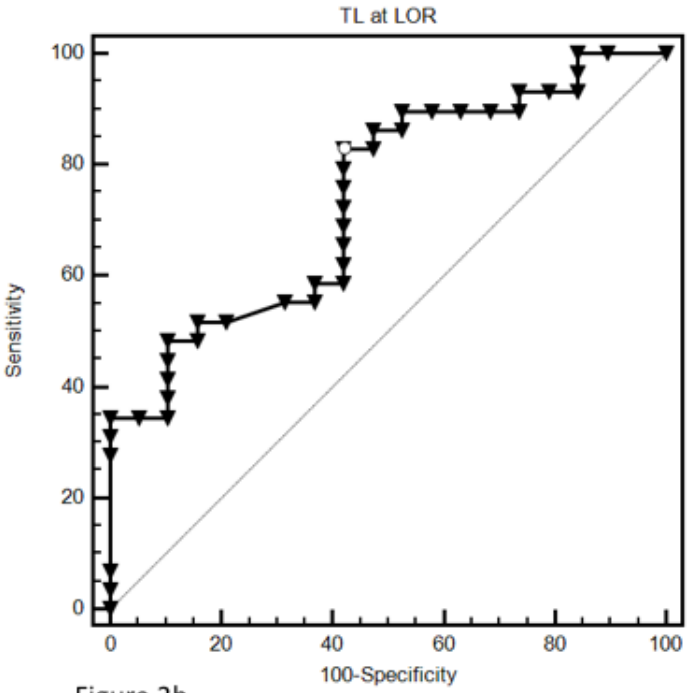


Figure 2b

Results (cont.)

- Multivariable analysis – showed that **only infliximab TL predicted both 6 and 12 months clinical remission** e.g. age, disease duration and location, concurrent use of immunosupressors.

Table 2a - Clinical and demographic parameters among patients who reached clinical remission 6 months post intensification versus those who did not

	Clinical remission at 6 months		
Variable	**Univariate**		**Multivariable**
	OR (CI)/ Median (IQR)	**P value**	**P value**
TL upon LOR	4.73(3.6-8), 8.69(5.3-16)	0.005	0.0037
CD	1.4(0.4-4.9)	0.59	
Male, female ratio	0.86(0.27-2.73)	0.8	
Age at diagnosis	25(20.5-30), 21.5(20-31)	0.58	
Age at intensification	34(27.75-47.5), 45(30.75- 51.5)	0.36	
Disease duration at induction, years	5.5(3-10), 10(4-16)	0.09	0.57
Infliximab therapy duration at intensification	3(1.75-4), 2(1.25-6)	0.83	
Median weight (kg)	72(57.5-82), 65(58.2-71.2)	0.17	
Smoking	0.43(0.07-2.6)	0.36	0.24
Previous biological therapy	2.21(0.58-8.4)	0.23	0.5
Previous surgery	0.66(0.18-2.34)	0.52	0.72
Combination therapy with an immunomodulatory	0.96(0.3-3)	0.95	0.76
Dose escalation*	0.9(0.22-3.6)	0.88	

CD - Crohn's disease, Vs. - Versus, LOR - Loss of response, TL - Trough levels, OR - Odds ratio, CI - Confidence interval, IQR - Interquartile range.

* Versus intervals shortening

Summary

- Therapeutic drug monitoring assists us in selection of the optimal intervention for each specific patient.
- Non immunogenic LOR to infliximab in IBD patients was associated with the need for dose increase when infliximab levels were below 4.8µg/ml
- The only factor significantly associated with successful intensification was lower infliximab TL.

What is our goal?

Clinical / endoscopic / histologic remission?

Deep remission?

Therapeutic Drug Monitoring, Mucosal Healing, Deep Remission: The Path to Nirvana in Crohn's Disease?

Moss, CGH, 2014

Golden rules for successful TDM

- *Timing - trough / in between (adalimumab / golimumab? Ustekinumab?)*
- *Time-point of measurement (induction / maintenance, acute severe colitis); Compare to baseline*
- *What is the patient's clinical status? Inflammatory markers?*
- *Patient adherence*
- *Wait for "steady state" after therapy escalation / de-escalation (4-14 weeks)*
- *Address anti-drug-antibodies (transient?)*

Mitrev & Leong, Expet Opinion j., 2016

Take Home Messages

- ~30% develop LOR
- First ask: is LOR due to IBD related inflammation / other causes?
- For anti-TNFs: if immunogenic LOR → switch within class / add immunomodulator
- For other biologics: higher levels associated with improved outcome, but affect probably not robust. Minor significance of immunogenicity

Thank You!!!

bella.geyshis.ungar@gmail.com