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Centre, Stellenbosch



Use of Anti-TNF Antibodies, Drug Levels, and Other Serological Markers in IBD

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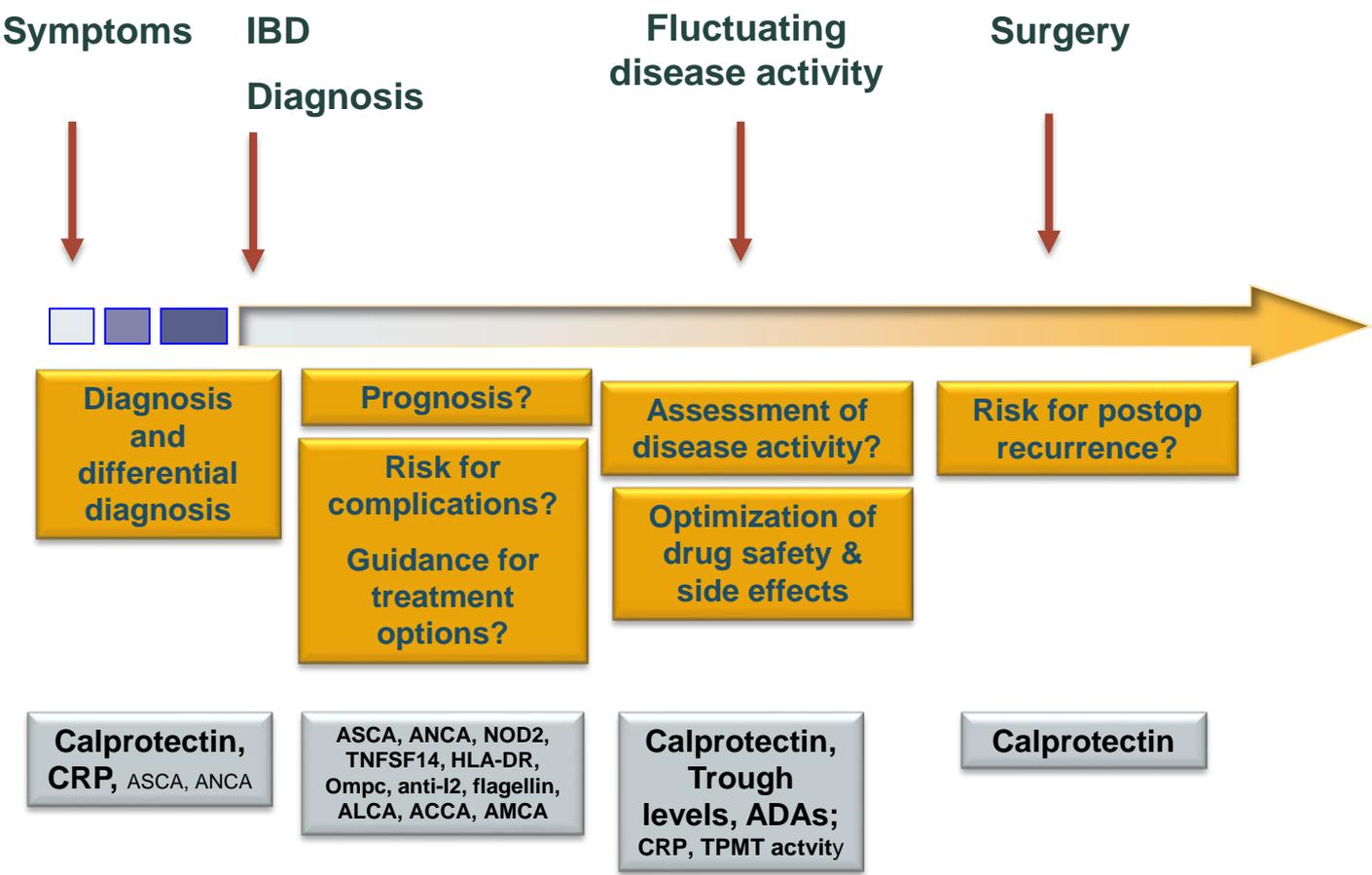


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When do we need diagnostic and therapeutic markers in IBD patients?



Why do drug levels vary between patients?

- Antidrug antibodies causing clearance
- Immunosuppression decreasing clearance
- High concentrations of TNF causing clearance
- Drug loss through inflamed colonic mucosa
- Male gender – increased drug loss
- Body size – either high or low

Sandborn Dig Dis 2014



Anti-TNF drug levels and anti-drug antibodies

Trough levels of anti-TNF

- Are significantly lower in patients losing response to this treatment
- Are significantly lower in patients without mucosal healing

Antibodies against anti-TNF

- Are more frequent in patients losing response to anti-TNF
- Are associated with low trough levels of anti-TNF
- Are associated with infusion reactions
- May fluctuate over time



Customising treatment dependent on drug and antibody levels

Subgroup of patients with detectable HACA or subtherapeutic IFX concentrations in whom changes were instituted and outcome was assessable

	Response to test	Response	P value
Detectable HACA	Increase IFX	1/6 (17%)	<0.004
	Change anti TNF	11/12 (92%)	
Subtherapeutic	Increase IFX	25/29 (86%)	<0.016
	Change anti TNF	2/6 (33%)	

Aff Am J Gastro 2010;105:1133-39



When to measure “trough levels” with s.c. preparations?

Hintergrund und Fragestellung

- ADAs- and Adalimumab serum levels were measured in 20 IBD-patients at different time points after s.c. injection (eow)
day 1 after injection, day 5, day 10–13, day 14 („trough level“).

	Day 1	Day 5	Day 10– 13	Day 14
Adalimumab Concentration in Serum ($\mu\text{g/mL}$, Median)	3,7	3,95	4,4	4,25
Anti Drug Antibody- Cocncentration in Serum ($\mu\text{g/mL}$, Median)	1,2	0,95	1,3	0,78

Only mild variation of serum levels. Under s.c. therapy time point of measurement seems to be less crucial

ECCO 2016; P526: B. Ungar, M. Yavzori, O. Picard, E. Fudim, U. Kopylov, Y. Chowers, R. Eliakim, S. Ben-Horin: Sampling not at trough: adalimumab serum drug and antibody levels remain relatively stable in between injections

Predictors of a “loss of response”

Prospective, monocentric study in Essen, 82 patients, 29 (35.4%) had a stable remission and 46 patients (56.1%) developed SLR (defined as dose escalation, interval shortening or change of therapy)

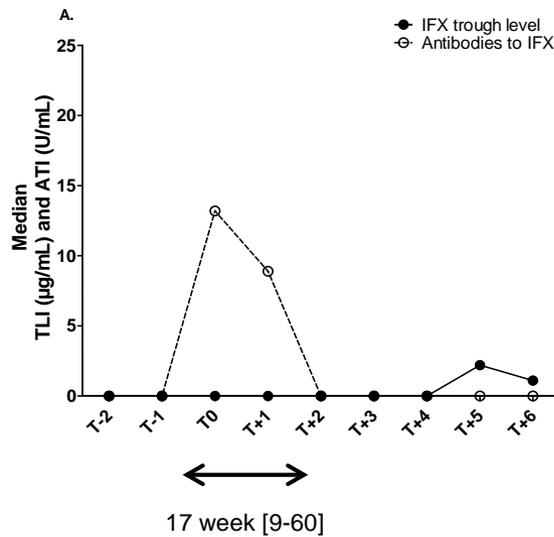
	Stable remission	SLR	p-value
albumin	37,6 g/dL	34,4 g/dL	<0,05
gamma-globulin	12,8 g/dL	17,4 g/dL	0,001

Low albumin levels and high gamma-globulin levels BEFORE therapy start are associated with a LoR

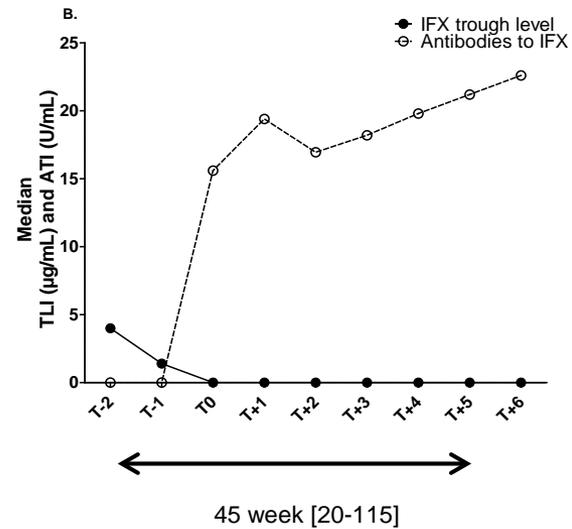
ECCO 2017 DOP035 Schoenefuss F., Hoffmann P. : High gammaglobulin and low albumin serum levels independently predict secondary loss of response to anti-TNF α therapy in IBD

Transient vs. Sustained ADAs

Transient ADA (n=15)

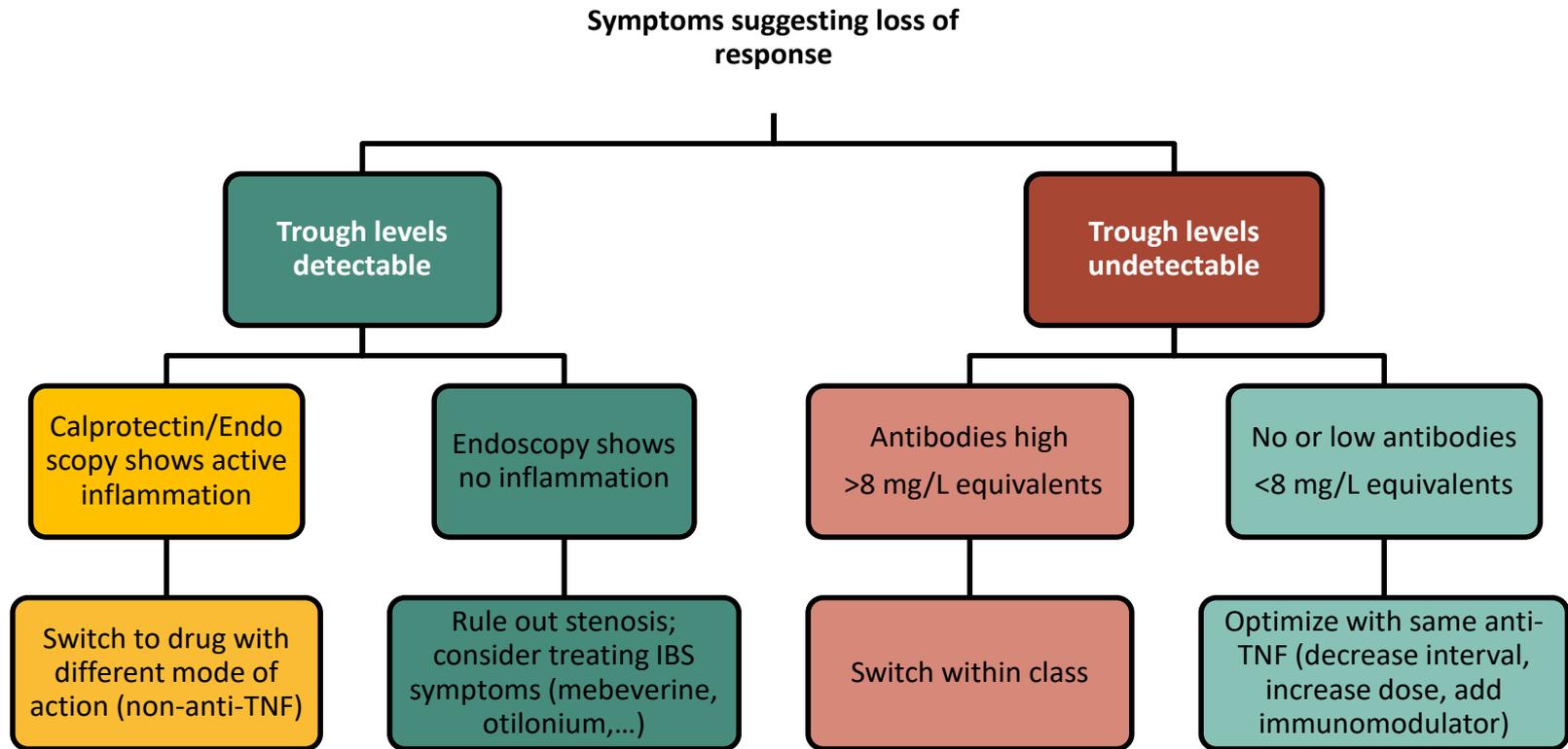


Sustained ADA (n=38)

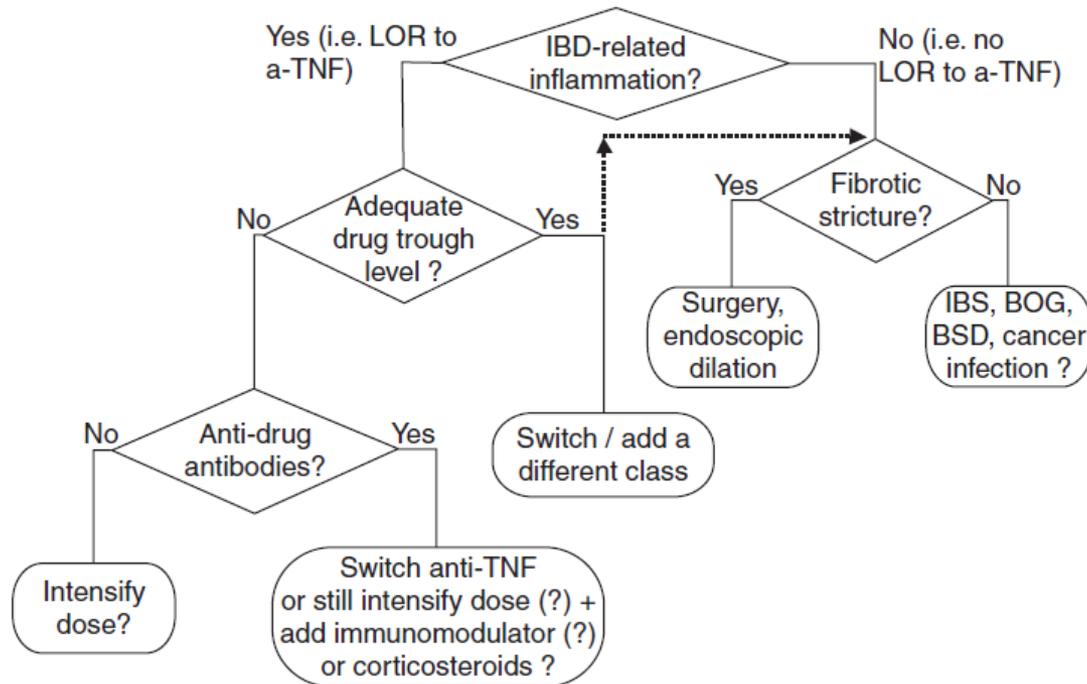


Vande Castele N, et al *American Journal of Gastroenterology* 2013; 108, 962-71

How to interpret levels when loss of response?

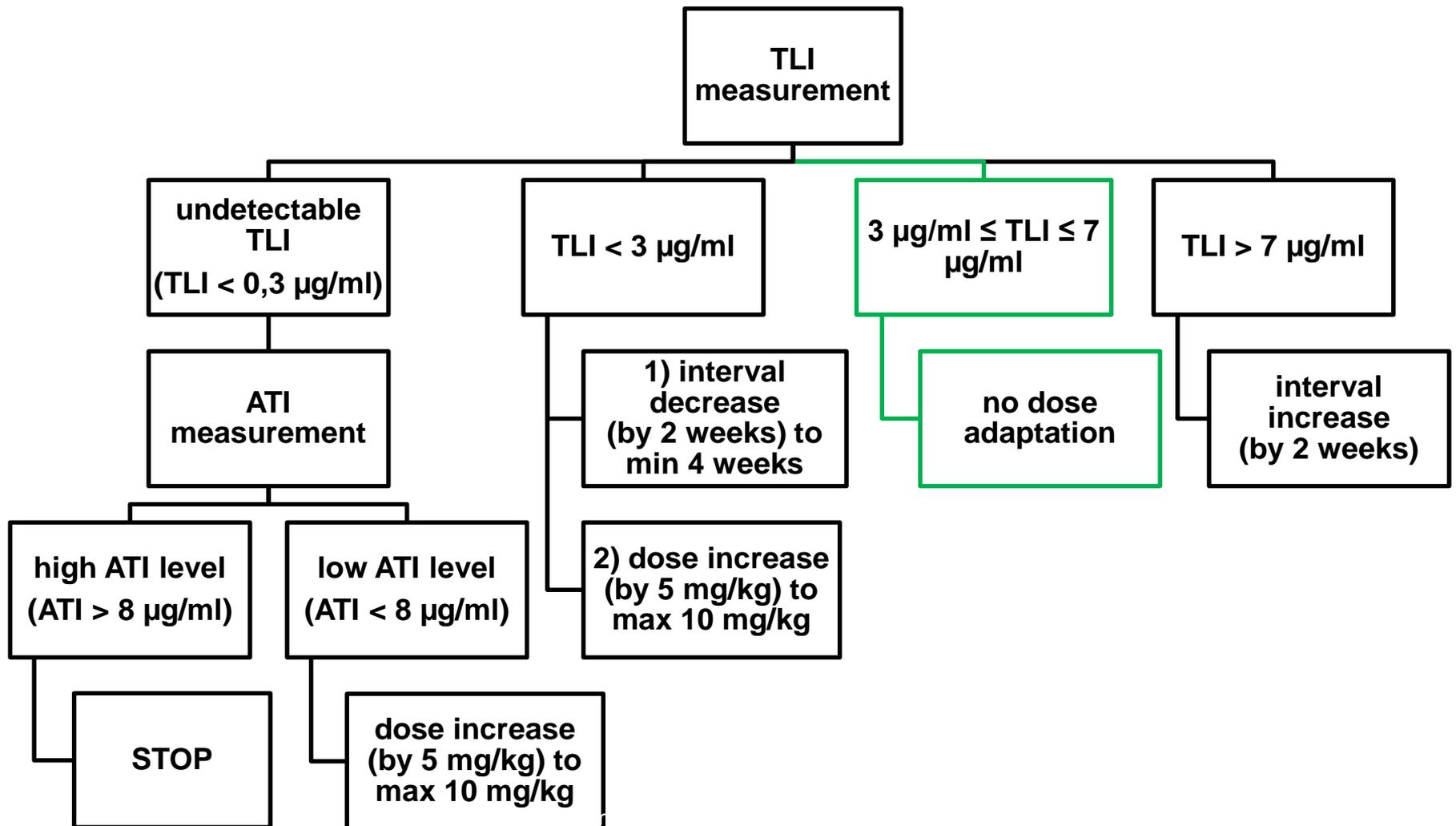


Using trough levels to manage loss of response

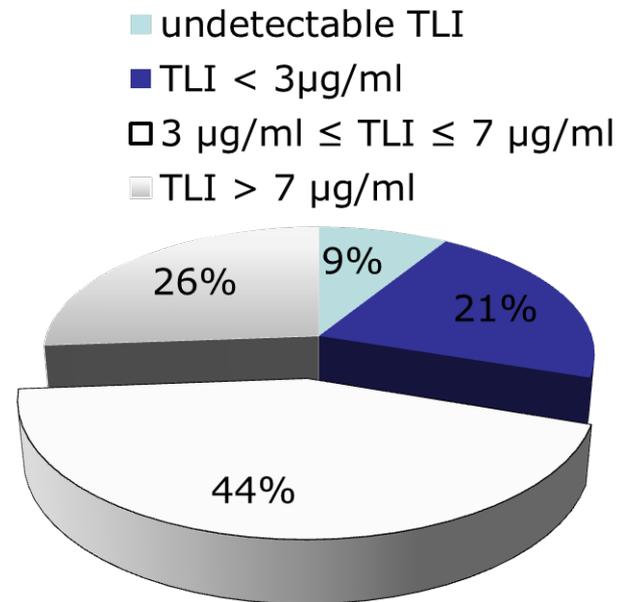


Ben Horin APT 2011

TAXIT algorithm



Testing in patients who are responding to anti-TNF therapy: TAXIT study

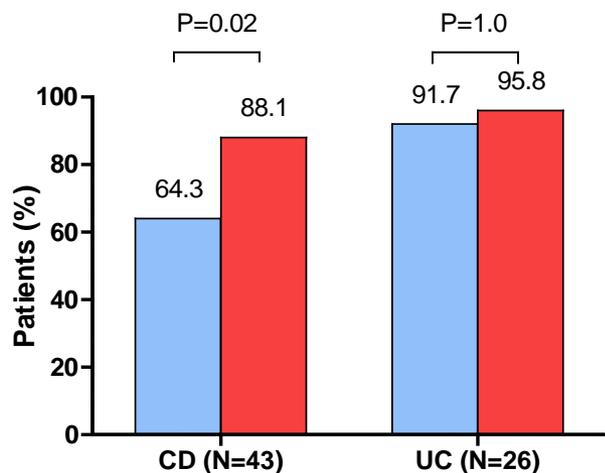


Results optimisation phase

Dose escalation (n=69)

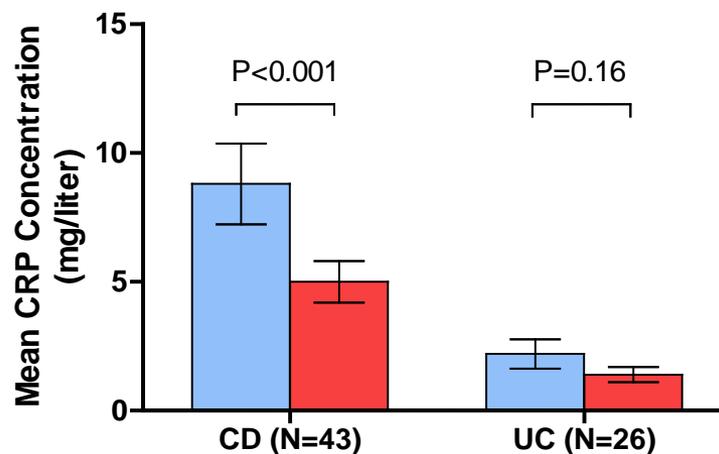
CD: Harvey-Bradshaw ≤ 4 / UC: Partial MAYO ≤ 2

■ Before optimisation ■ After optimisation



C-reactive protein (CRP) level

■ Before optimisation ■ After optimisation

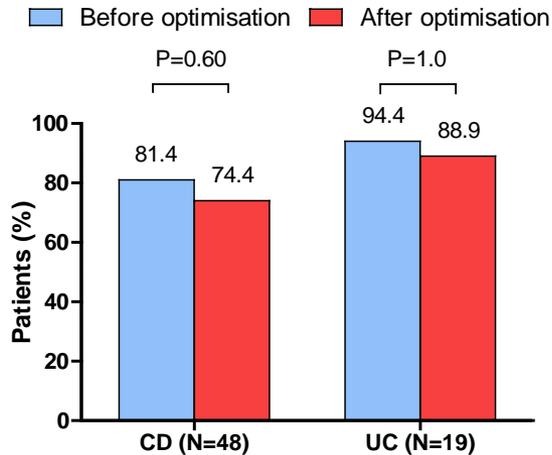


Dose escalation in Crohn's disease patients with subtherapeutic levels results in a better disease control

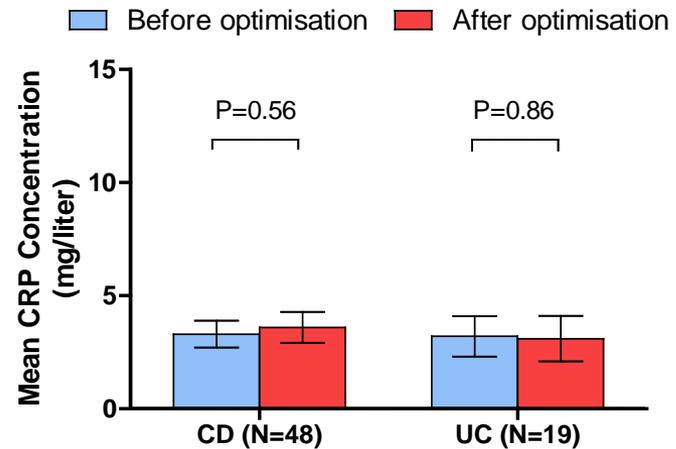
Results optimisation phase

Dose reduction (n=67)

CD: Harvey-Bradshaw ≤ 4 / UC: Partial MAYO ≤ 2



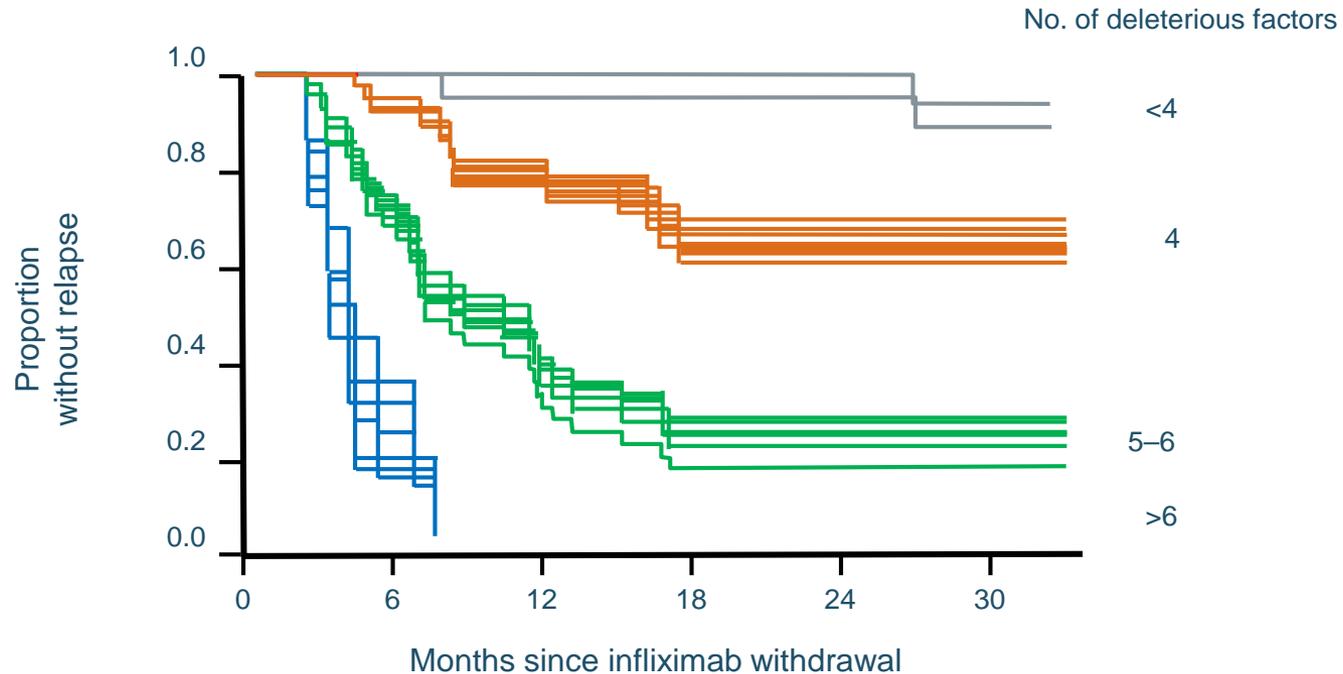
C-reactive protein (CRP) level



Successful dose de-escalation of patients with supra-therapeutic levels whilst retaining disease control

Biomarkers contribute to prediction of relapse in STORI

Predictive model for the time-to-relapse



Deleterious factors were:

no previous surgery, steroid use within 12-6 months before infliximab withdrawal, male gender, haemoglobin ≤ 14.5 g/dl, leukocyte count $>6 \times 10^9/l$, hsCRP ≥ 5 mg/l, faecal calprotectin $\geq 300 \mu\text{g/g}$, CDEIS >0 , infliximab trough ≥ 2 mg/l

Conclusions

Anti TNF trough level and anti drug antibodies

- Show promise as a therapeutic guide
- Are particularly useful in patients losing response
- Require further work to define therapeutic ranges



Thank you for your attention



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