Where tradition meets innovation
IX CONGRESSO NAZIONALE IG-IBD

Drug withdrawal IBD: few evidence, lots of strategies

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Why should we stop biologics/immunosuppressants in IBD? (… if they keep working on a patient)

- **Medical reasons (Benefit/Risk)**
  - Over-treatment of long-time remitters
  - Safety concerns (infections, malignancies: lymphoma, skin)
  - Specific situations (e.g. pregnancy, elderly, previous cancer)
- **Patients may ask for it**
  - Convenience
  - Patients do not like to take drugs
  - Patients may be afraid of complications
- **Payor push back/cost**
  - Medical costs

Drug withdrawal IBD

Few evidence

Lots of strategies (?)

Few evidences: 3 possible scenarios

1. Patients on immunomodulator monotherapy;
2. Patients on anti-TNFα monotherapy;
3. Patients on combo therapy.

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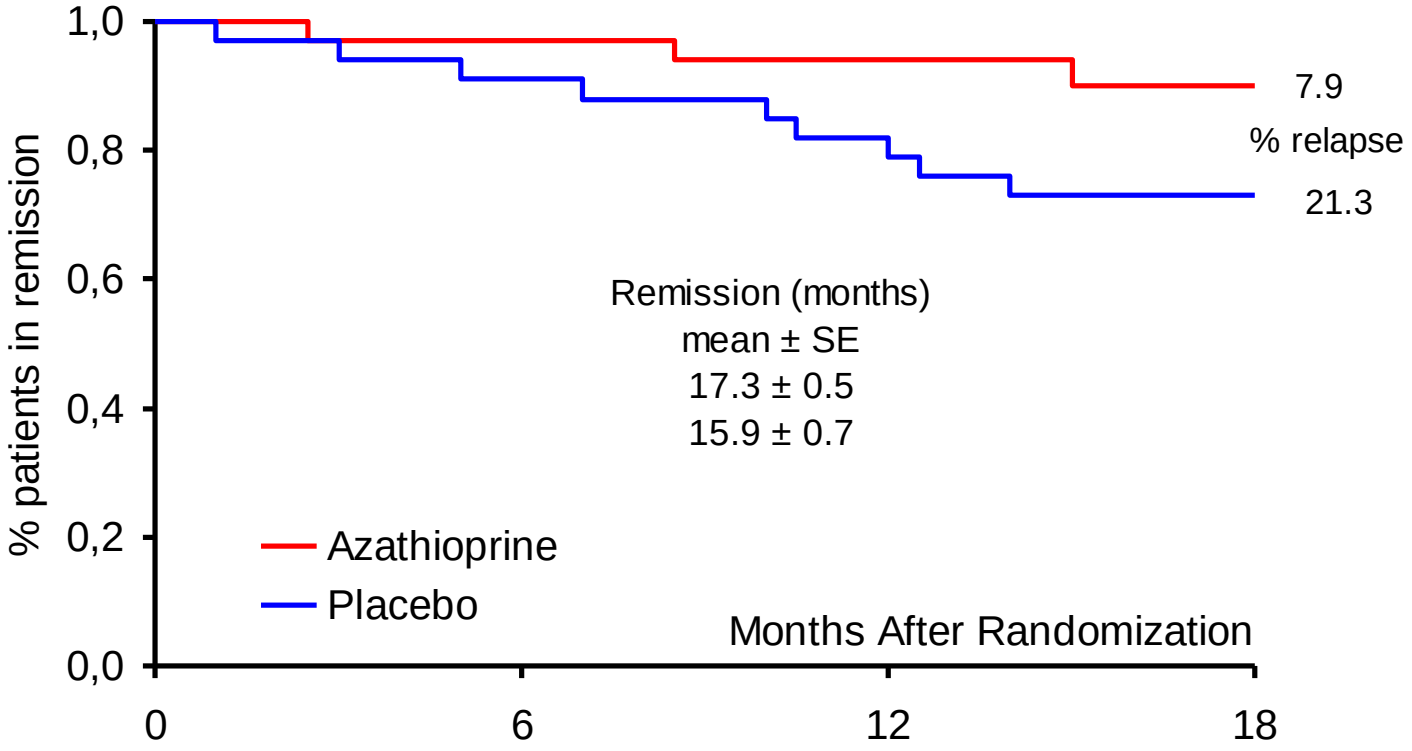
Controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine



83 patients in clinical remission with AZA for at least 3.5 years before randomisation

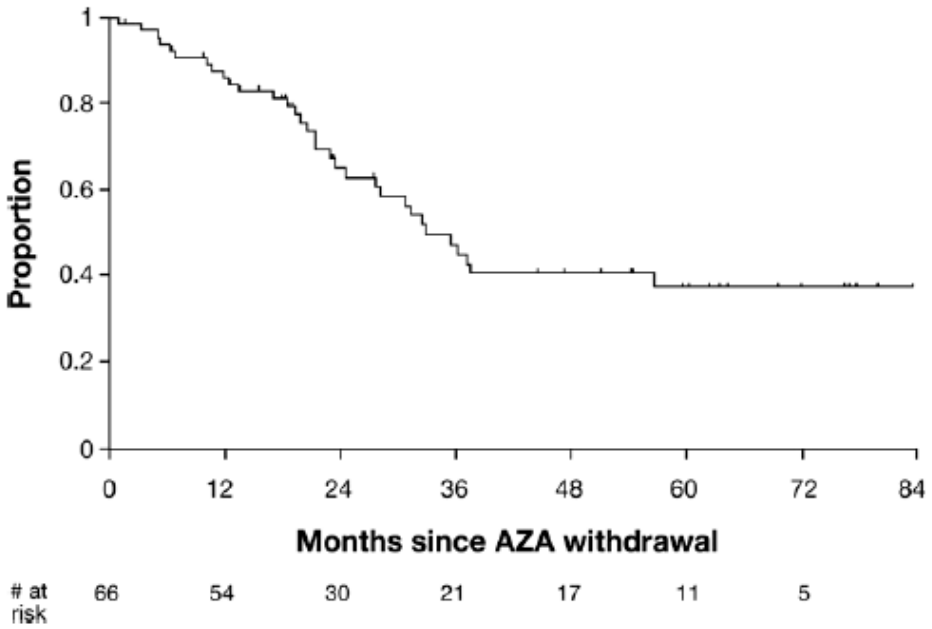
CRP >20 mg/L: RR 16.9 (95% CI 2.7-104.3), p<.0001
Haemoglobin <12 g/dL: RR 8.7 (95% CI 1.6-48.8), p=.0034
Time without steroids <50 months: RR 5.2 (95% CI 1.5-18.1), p=.004

Independent predictors of relapse

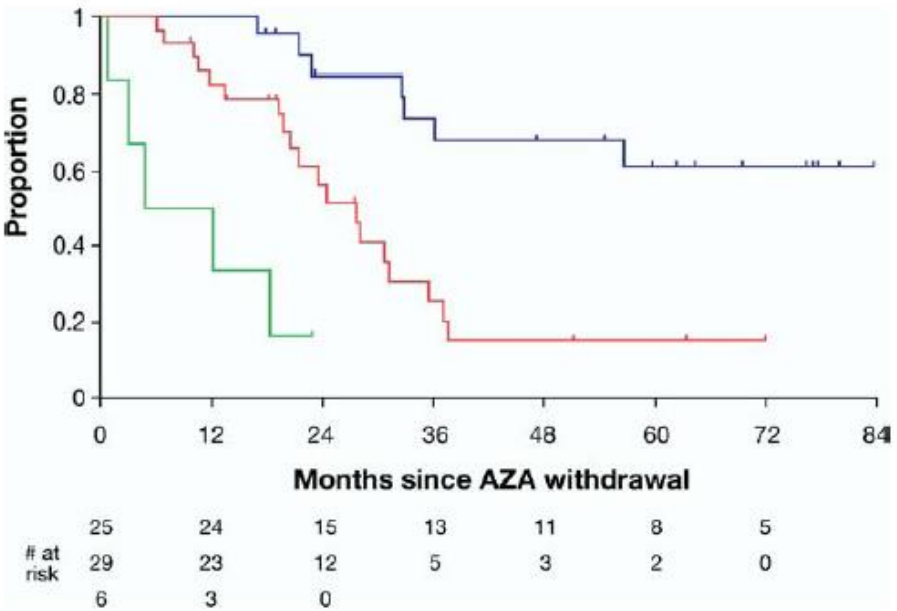
Lemann M, et al. Gastroenterology 2005

Azathioprine withdrawal in Crohn's disease

66 patients in clinical remission with AZA for 63.6 months
Stop AZA and 54.5 months of median FU: 32 of 66 (48.5%) relapse



Cumulative probability of remaining in remission after AZA withdrawal

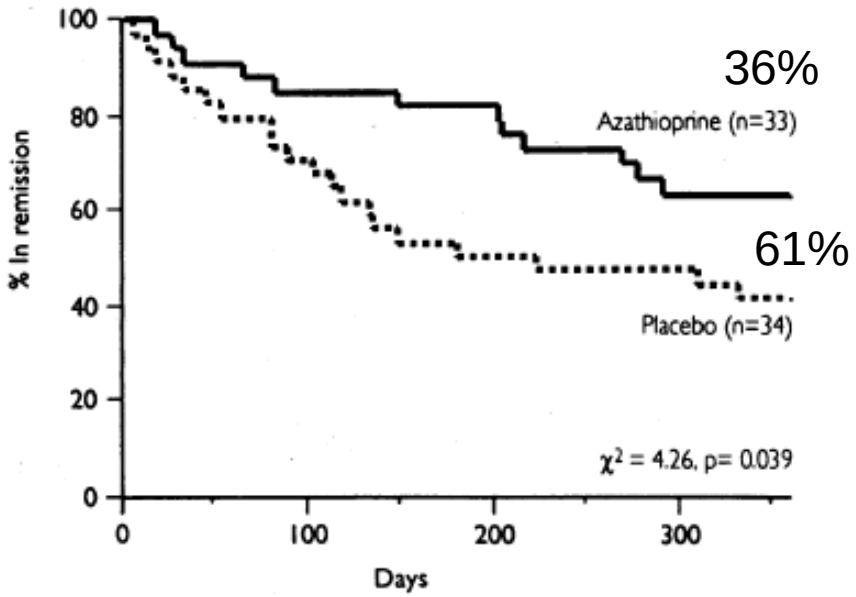


Relapse predicting classification according to the presence of risk factors (CRP, Hb, Neutrophils levels) after AZA withdrawal

23 out of the 32 relapsing patients were retreated with AZA and 22 were put into remission again

Treton X et al. Clin Gastroenterol Hepatol 2009

Azathioprine withdrawal in UC



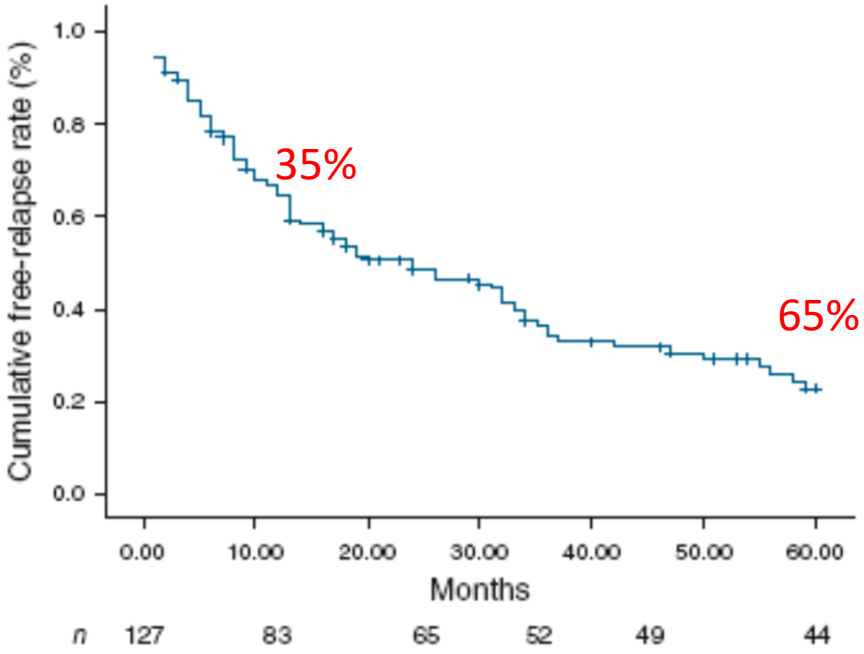
Kaplan-Meier survival plot of the rate of relapse over one year for 67 patients with ulcerative colitis in remission after taking azathioprine

67 patients on AZA for at least 6 months

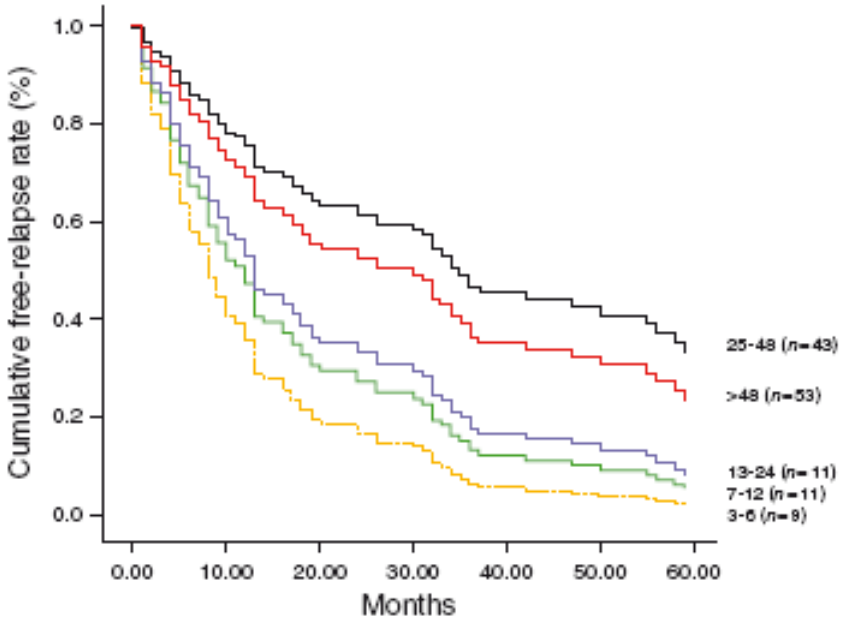
Steroid-free clinical remission for at least 2 months

Hawthorne AB,et al. BMJ 1992

Azathioprine withdrawal in UC



127 UC



Median AZA treatment: 47 mo (3–105)
Median follow-up: 55 mo (1–182).

Cumulative relapse rate:
35 % at 1 year
65 % at 5 years

Cox regression

AZA duration: HR 2.8
No sustained remission: HR 2.3
Disease extent: HR 2

Predictors of relapse after withdrawal

Cassinotti A, et al. AJG 2009

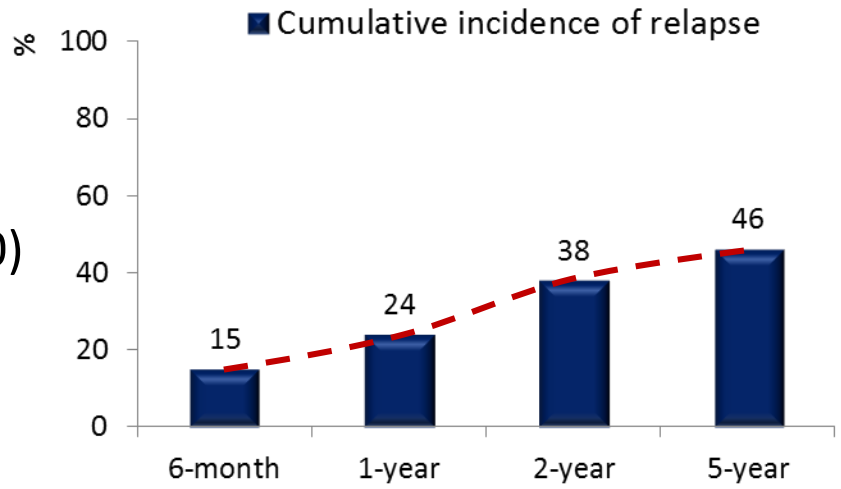
Few evidences: 3 possible scenarios

1. Patients on immunomodulator monotherapy;
2. Patients on anti-TNFα monotherapy;
3. Patients on combo therapy

Evolution after anti-TNF drug discontinuation in IBD (multicenter retrospective observational study – Spain)

1055 IBD (69% CD) in which anti-TNFs had been withdrawn after clinical remission

1) **Relapse after discontinuation**:
Incidence rate: **19% per pts-yr** (95%CI 17-20)



2) **Risk of relapse** (multivariate) in CD:
IM treatment after discontinuation (HR 0.7)
Colonic localization (HR=1.51)
Stricturing behavior (HR=1.5)
Ada (HR=1.29)

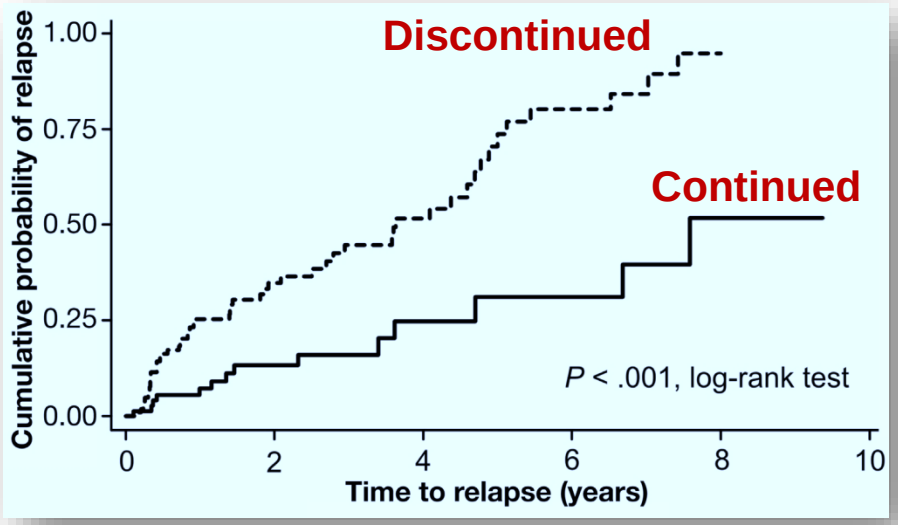
3) 69% of **relapsers retreated** with the same agent:
75% remission at FU, 11% mild adverse events

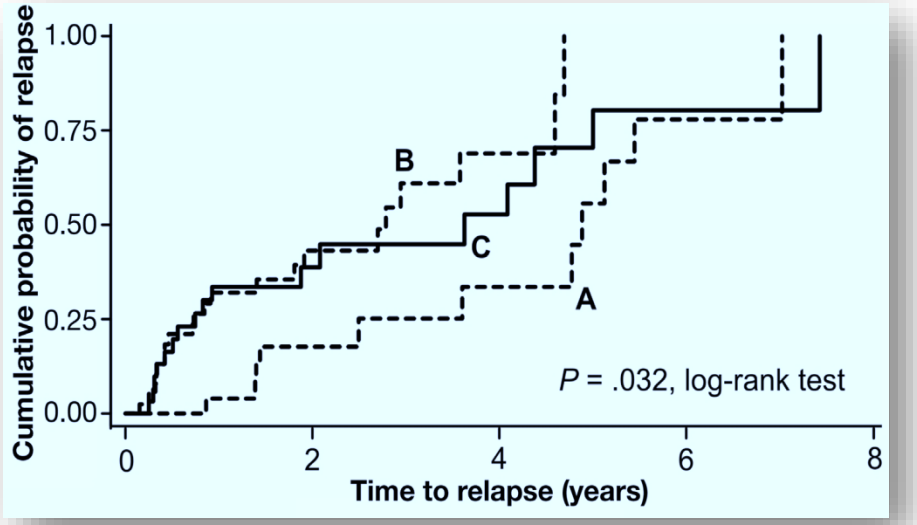
Casanova MJ, et al. Am J Gastroenterology 2017

Discontinuation of IFX in Patients With UC Is Associated With Increased Risk of Relapse

A Multinational Retrospective Cohort Study

193 UC patients in remission (> 12 months) on IFX:
111 (57.5%) discontinued – 82 (42.5) continued





HR of relapse:
- IFX discontinuation
HR 3.7 (95% CI 2.02-6.77); P< .001
- Concomitant thiopurines
HR 0.61 (95% CI0.37-0.99); P= .048

A: thiopurines
B:aminosalicylates
C: combination

Fiorino G, et al, Clin Gastroenterol Hepatol 2016

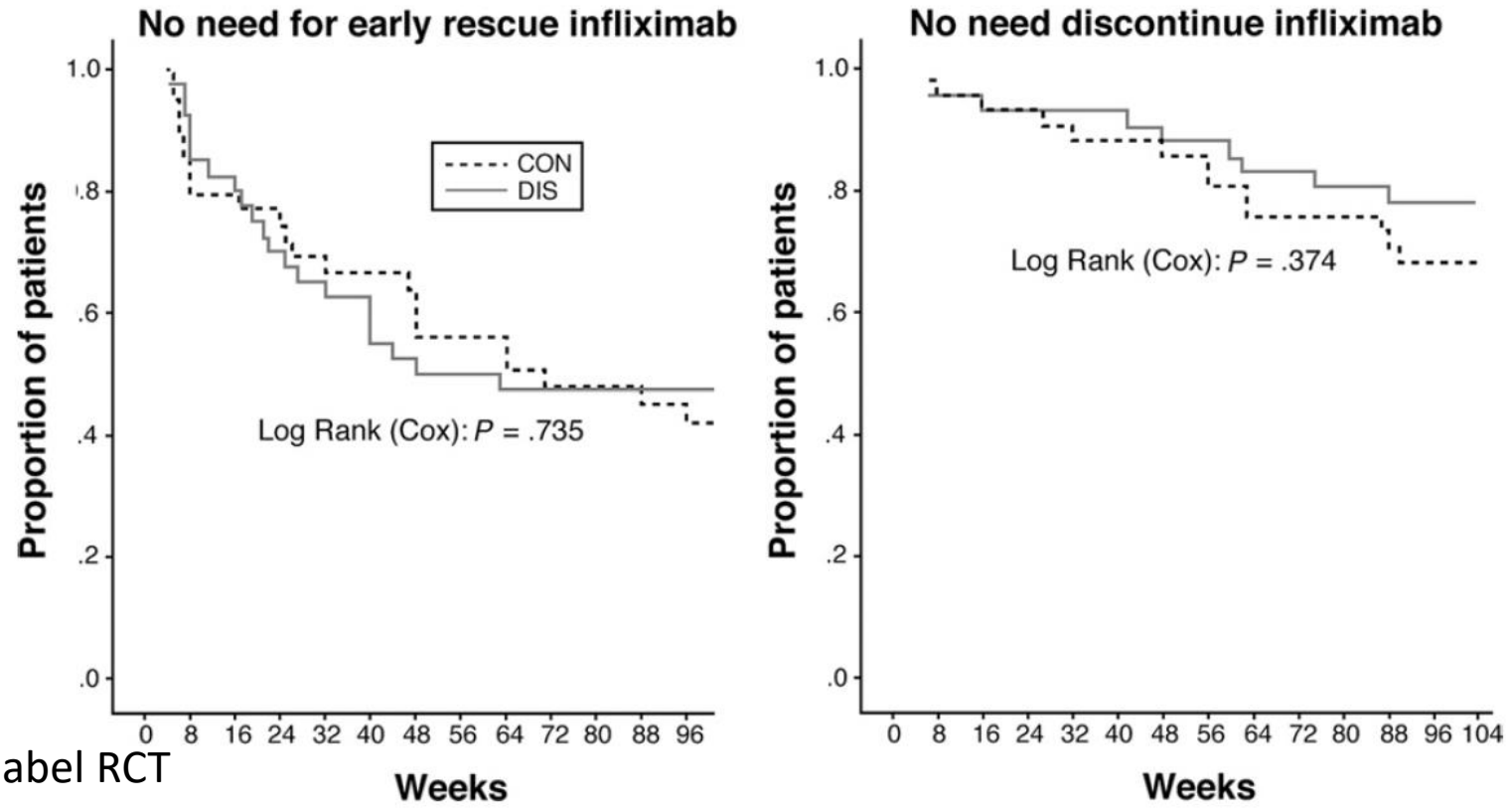
Few evidences: 3 possible scenarios

1. Patients on immunomodulator monotherapy;
2. Patients on anti-TNFα monotherapy;
3. Patients on combo therapy

Which drug can be stopped in a patient receiving combination therapy (anti-TNFs + AZA)?

1. Immunosuppressant

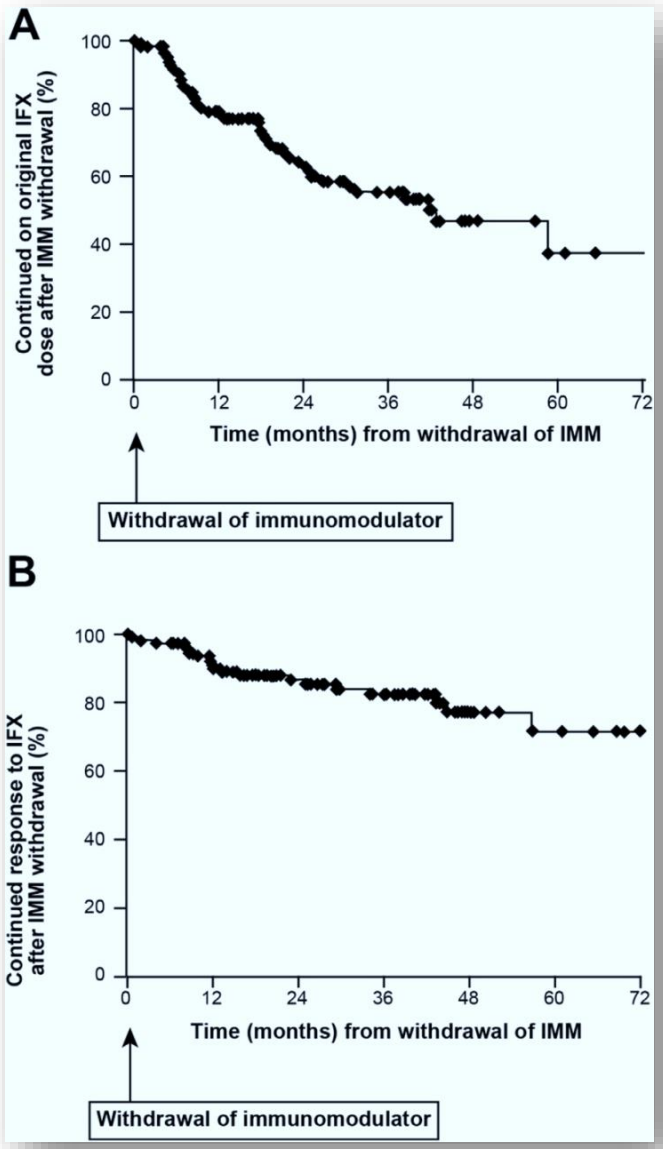
Withdrawal of Immunosuppression in CD Treated With Scheduled IFX Maintenance

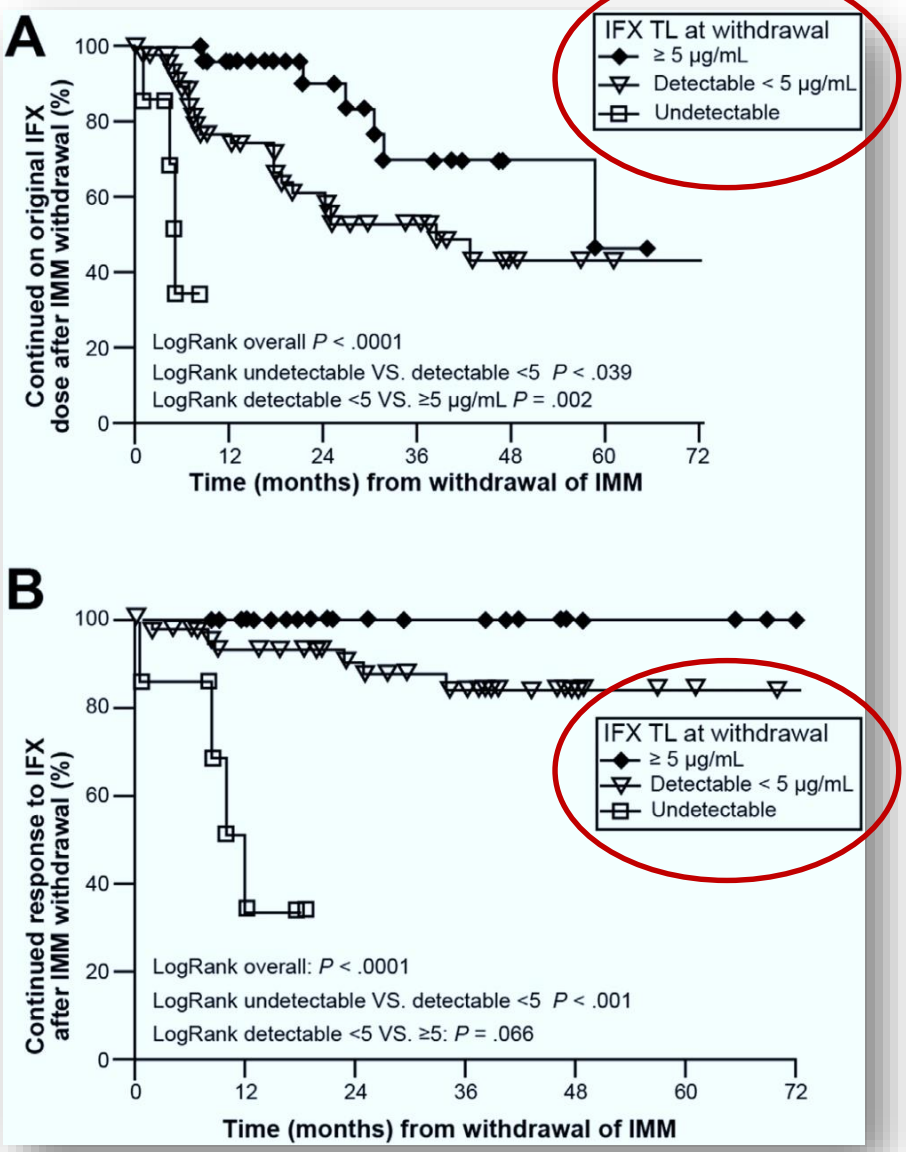


- Open-label RCT
- n=80 CD in remission, treated with combo ≥6 months
- Randomisation: IS cessation *vs*. continuation

Van Assche G, et al. Gastroenterology 2008

Withdrawal of IM in CD After Combination therapy and Trough Level of Infliximab at withdrawal

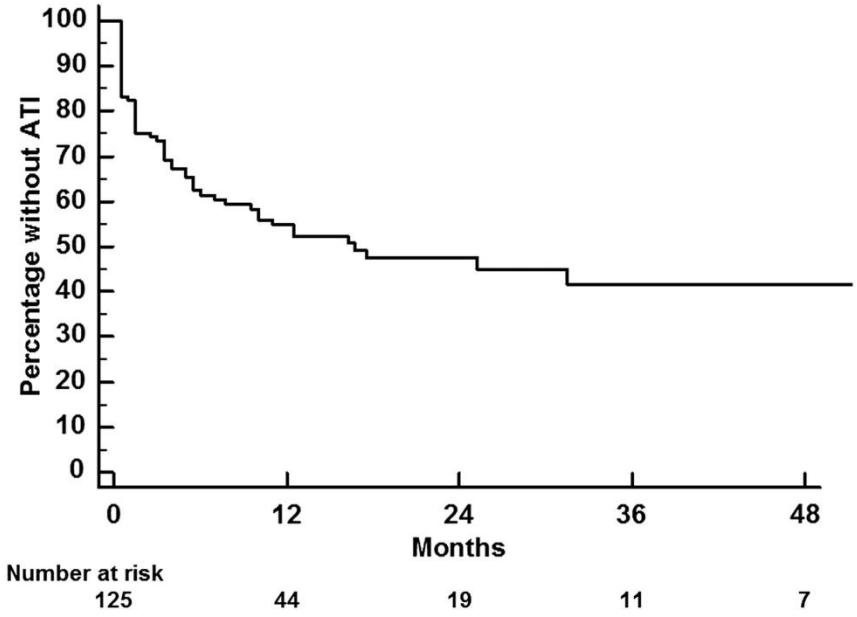


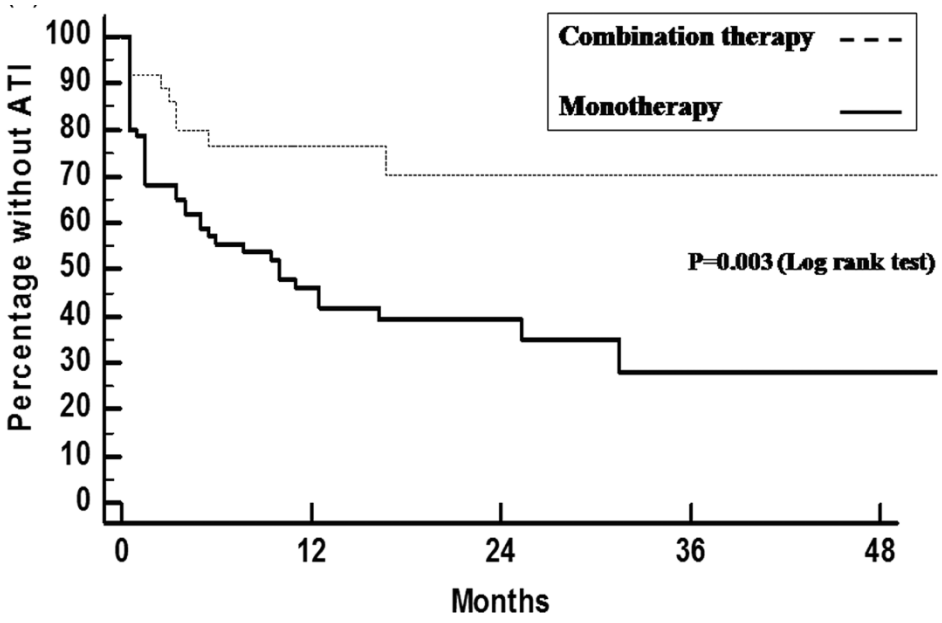


Drobne D, et al. Clin Gastroenterol Hepatol 2015; 13(3):514-521

The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab

Prospective IBD cohort (n=125)





1) 90% of the patients who developed ATI did so within the first 12 months of therapy
2) transient ATI were detected throughout the duration of infliximab therapy

Combotherapy (IM+IFX) resulted in longer ATI-free survival compared with monotherapy

Ungar B, et al. Gut 2014

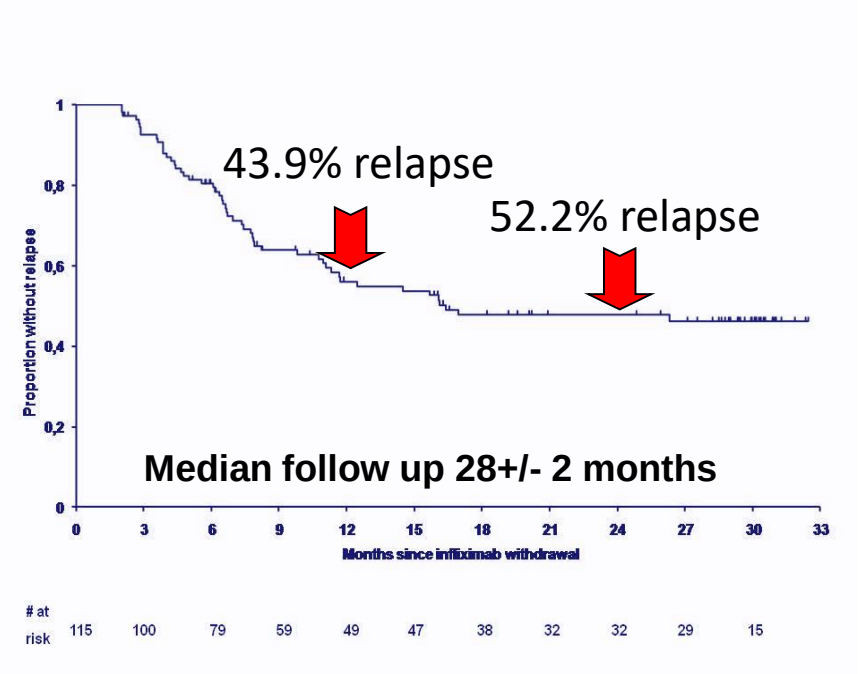
Which drug can be stopped in a patient receiving combination therapy (anti-TNFs + AZA)?

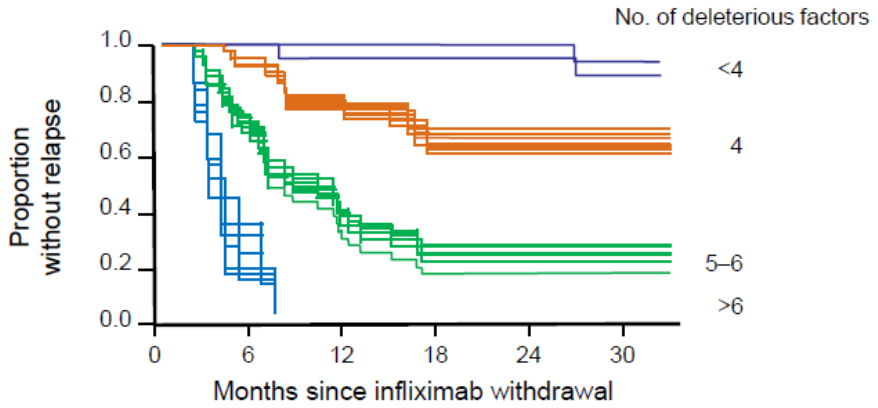
2. anti-TNF

IFX withdrawal in patients receiving prolonged combination (IFX+AZA) therapy in CD

115 CD patients in remission on IFX+AZA (CDAI<150 and steroid free ≥6 months)

Deleterious Factor	HR (95%CI)	P
No previous surgery	4.0 (1.4-11.4)	0.01
Steroids (month -12 to -6)	3.5 (1.1-10.7)	0.03
Hemoglobin ≤ 14.5 (g/dl)	6.0 (2.2-16.5)	<0.001
Male Gender	3.7 (1.9-7.4)	<0.001
Fecal calpro ≥ 300 µg/g	2.5 (1.1-5.8)	0.04
Infliximab TL ≥ 2 mg/L	2.5 (1.1-5.4)	0.02
WBC > 6 (10^3/ml)	2.2 (1.2-4.2)	0.01
CRP hs > 5 (mg/l)	3.2 (1.6-6.4)	<0.001
CDEIS > 0	2.3 (1.1-4.9)	0.04



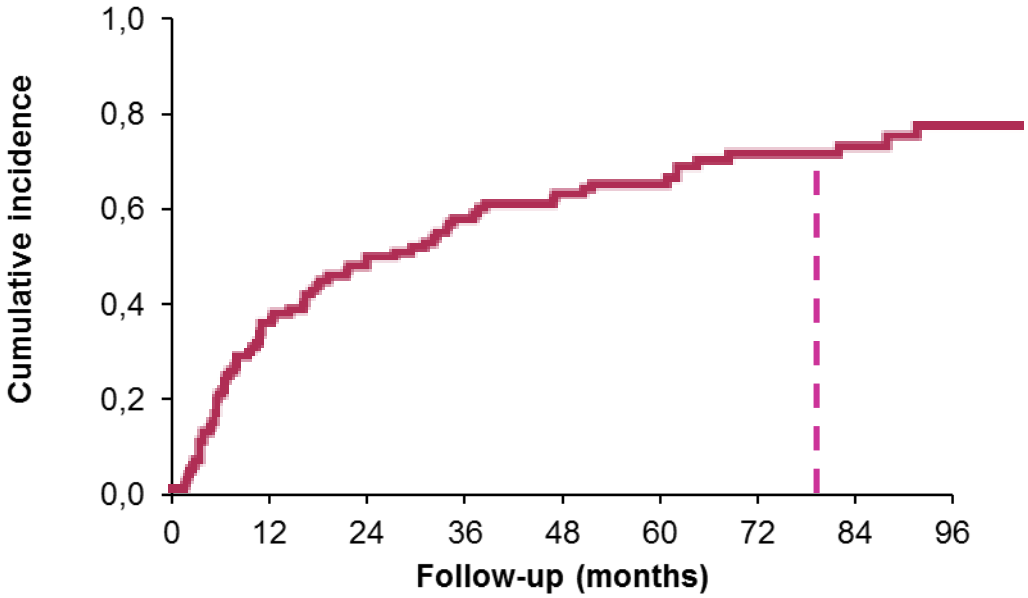


Louis E, et al. Gastroenterology 2012

STORI: long-term follow-up (retrospective)

- 102 CD patients receiving combotherapy
- Median FU duration: 78 months

Survival without failure of the de-escalation strategy*



Long-term outcomes	
Absence of any anti-TNF	22%
Major complications	18.5%
Anti-TNF retreatment	71%
IFX retreatment	
Success	66%
Failure (including 45% of severe relapse)	34%

*Ifx restart failure + major complications

GETAID

Reenaers C et al., Clin Gastroenterolgy and Hepatology 2018

Drug withdrawal IBD

Few evidence

Lots of strategies (?)

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1. Assess the risk of relapse
2. TDM
3. Dose reduction
4. Biocycle

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Factors associated with relapse of IBD after discontinuation of thiopurines monotherapy

Table 1. Factors associated with higher relapse rates in CD [left column] and UC [right column] following withdrawal of thiopurine IM monotherapy. Based on Torres *et al.* 2015.[87]

Factors associated with higher CD relapse risk	Factors associated with higher UC relapse risk
Elevated C-reactive protein level[23,77,89]	Increased leukocyte count[23,91]
Increased leukocyte or neutrophil count[23,89]	
Low haemoglobin level[77,89]	
High-risk disease [peri-anal involvement]	Extensive disease [pancolonic/extensive][84]
Younger age[76]	Younger age[83]
Male gender[76]	Male gender[84]
Short duration of remission[76]	Number of relapses on azathioprine[84,91]
Shorter time since latest steroids[77]	Shorter duration of azathioprine[84,91]
Higher dose of azathioprine[79]	Longer time from diagnosis to azathioprine[91]
Thiopurine tapering before de-escalation[23]	
Smoking cessation[90]	

Bold type identifies factors observed consistently.

Doherty G et al, JCC 2018

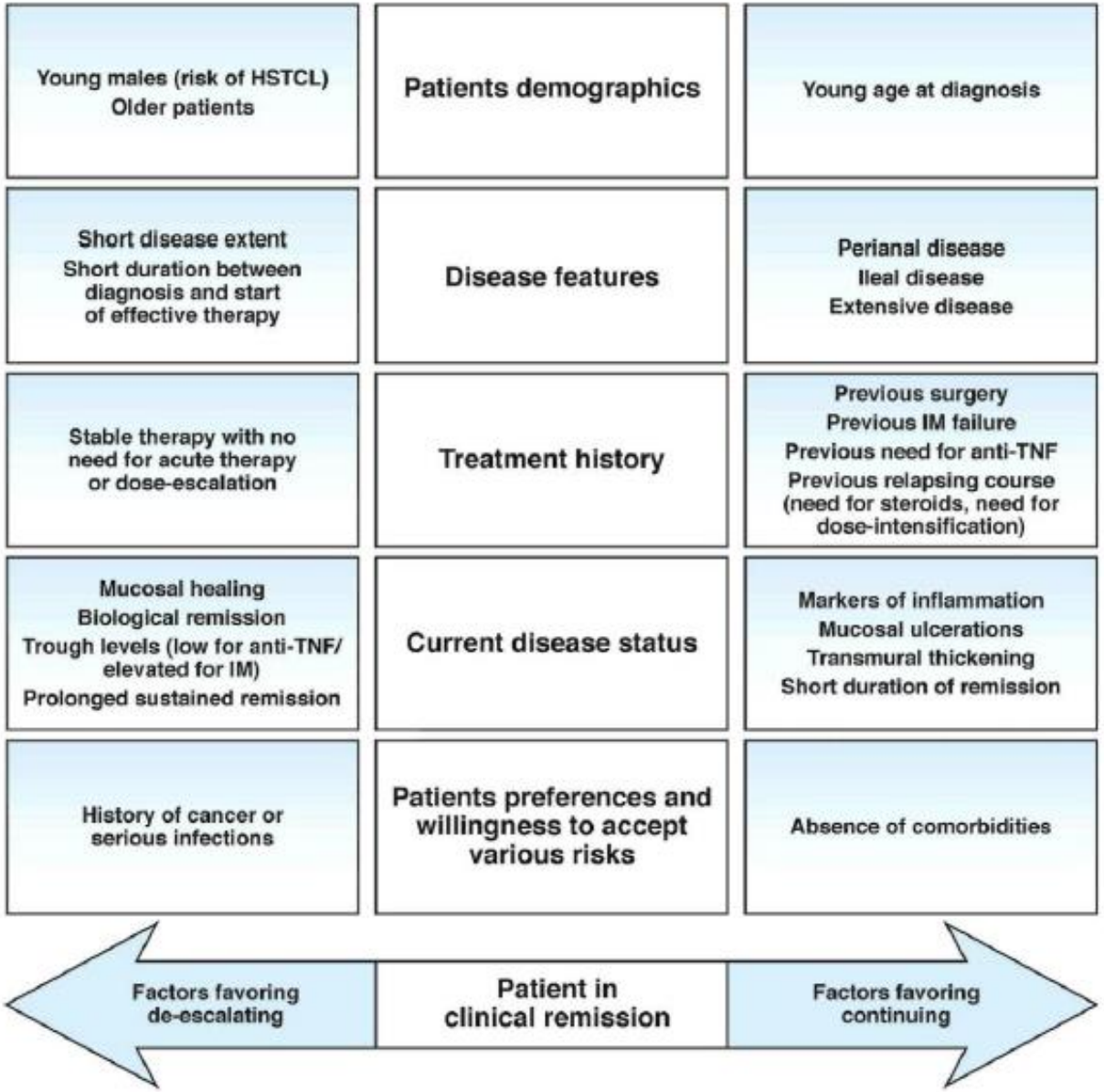
Factors associated with relapse of IBD after discontinuation of anti-TNFs

Factor	Risk of relapse	IBD type	Association (and corresponding references)	Comments
Clinical variables				
Younger age	Higher	CD	HR 1.83 (1.03–3.25) (age ≥25 years at diagnosis associated with remission)[39]	Evidence based on few studies
Smoking	Higher	CD	OR 2.74 (0.99–7.59)[22]; HR 1.91 (1.11–3.27)[27]	Evidence based on few studies
Longer disease duration	Higher	CD	Early introduction of anti-TNF therapy is associated with less severe intestinal tissue impairment and restored mucosal immune homoeostasis[45]	Evidence based on few studies
Fistulising perianal CD	Higher	CD	Incidence of relapse in perianal vs. luminal CD: 66% vs. 31%[17]; 65% vs. 42%[54]	Stop anti-TNF not recommended unless radiological healing confirmed
Escalated anti-TNF doses	Higher	CD	Incidence of relapse in patients with escalated dose: 90%[15] and 100%[78] OR 13 (1.39–120)[22]	Stop anti-TNF not recommended
Prevention of post-operative CD	Higher	CD	Incidence of relapse in patients with intestinal resection: 100%[81] and 83%[82]	Stop anti-TNF not recommended
Laboratory markers				
Low haemoglobin levels	Higher	CD	HR 6.0 (2.2–6.5) (haemoglobin level ≤145 g/L)[20]	Evidence based on few studies
High leucocyte count	Higher	CD	HR 2.4 (1.2–4.7) (leucocyte count >6 × 10^9/L)[20]	Evidence based on few studies
High CRP levels	Higher	CD	HR 3.2 (1.6–6.4) (hsCRP level ≥5 mg/L)[20] OR 2.38 (0.92–6.19)[22] HR 4.2 (1.9–9.2) (CRP > 5 mg/L)[58]	False-negative results limit clinical application
High faecal calprotectin	Higher	CD	PPV for relapse 67% (FC > 50 µg/g)[15] HR 2.5 (1.1–5.8) (FC 300 µg/g)[20] HR 6.5 (2.7–15.6) (FC > 250 µg/g)[58]	Lack of validated cut-off point limits clinical application
High serum anti-TNF levels	Higher	CD	HR 2.5 (1.1–5.4) (infliximab trough levels ≥2 µg/mL)[20] Higher relapse risk if trough levels >3 µg/mL[14] or >6 µg/mL[39]	Lack of validated cut-off point limits clinical application
Endoscopic factors				
Mucosal healing	Lower	CD & UC	When anti-TNFs were stopped based on achievement of *clinical* remission, 42% of CD patients relapsed during the following year.[12] However, if patients discontinued anti-TNFs after achieving also *endoscopic* remission, this figure decreased to 26%.[12] Similar differences were observed for UC at 12–24 months: relapse rates were 50% and 33% after therapy withdrawal based on clinical and endoscopic remission, respectively[12]	Lower risk not confirmed by some studies Degree of mucosal healing necessary unclear

The overall risk of relapse after discontinuation of anti-TNF:
- 44% for CD
(FU range: 6–125 months)
- 38% for UC
(FU range: 6–24 months).

Gisbert JP, et al. APT 2015

What about our decision?

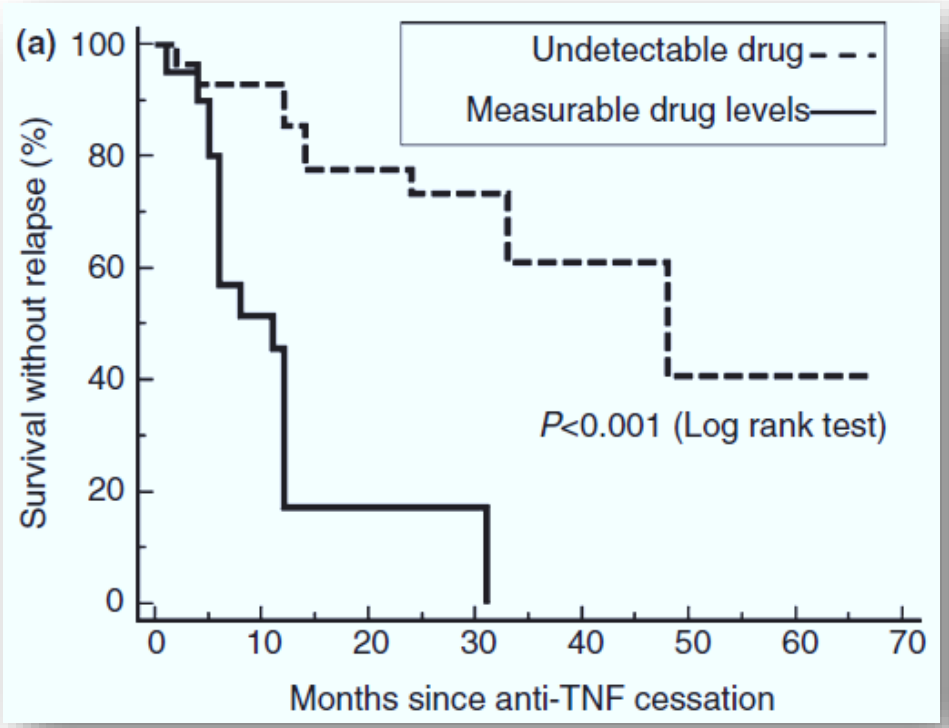


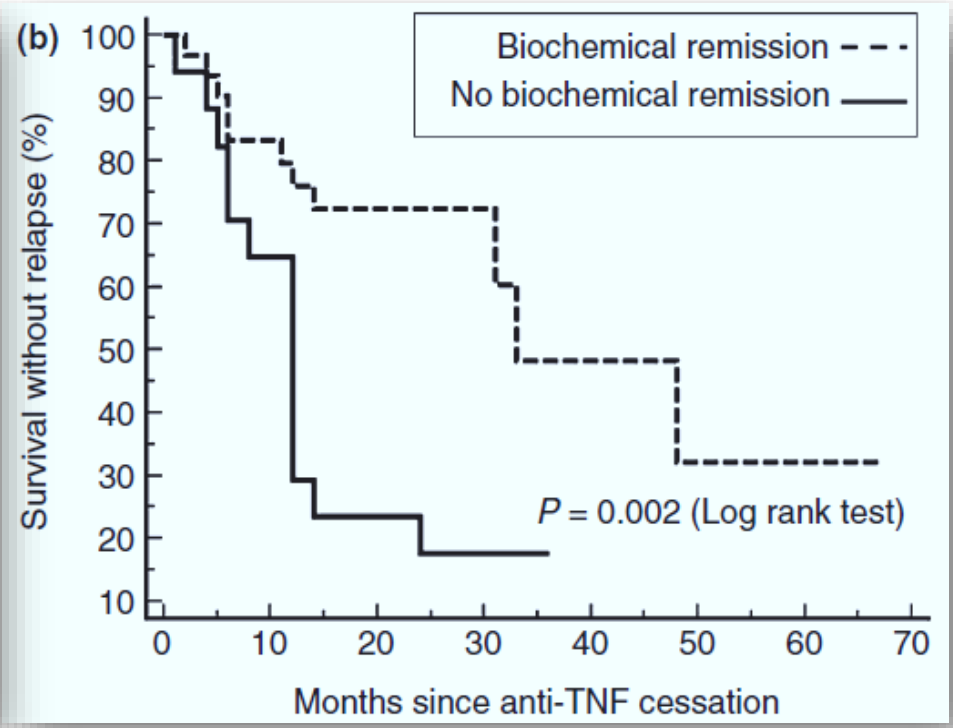
Torres J. et al, Gastroenterology 2015

Lots of strategies (?)

1. Assess the risk of relapse
2. TDM
3. Dose reduction
4. Biocycle

Relapse Rate After Discontinuing anti-TNF in long-term deep remission is lower when nil drug levels



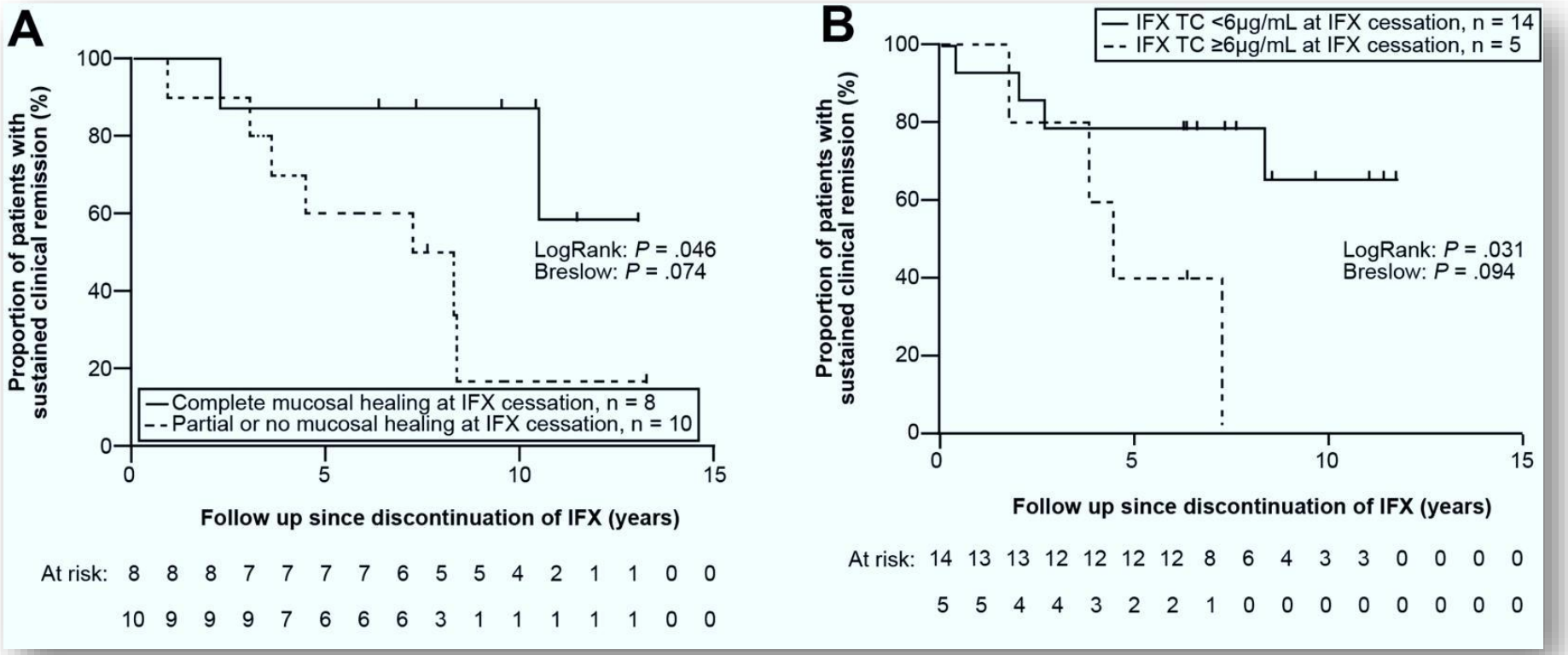


48 patients stopped IFX (n=35) or adalimumab (n=13) in deep endoscopic remission: 41% of relapse at 12 months

Ben-Horin S, et al. APT 2015

Long-Term Outcome of Patients With CD Who Discontinued Infliximab Therapy Upon Clinical Remission

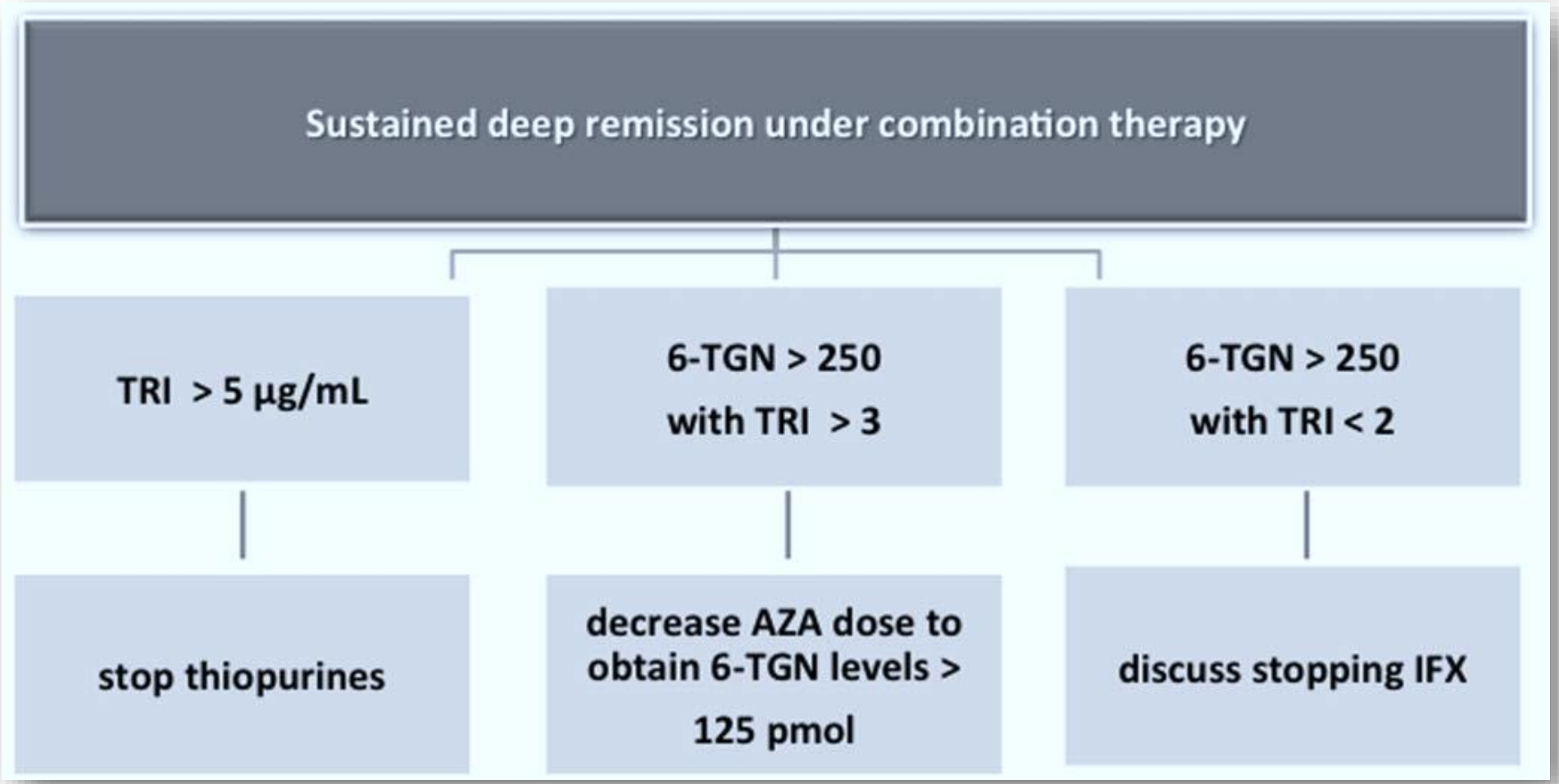
MH **TL**



52% of patients remained in Sustained Clinical Remission after a median FU of 9.7 years (IQR 8-11.5)

Papamichael K, et al. CGH 2015; 13(6):1103-10

Proposed algorithm to guide drug discontinuation or de-escalation in patients with IBD who achieved sustained deep remission while on combotherapy



Roblin X, et al. Inflamm Bowel Dis 2016

Lots of strategies (?)

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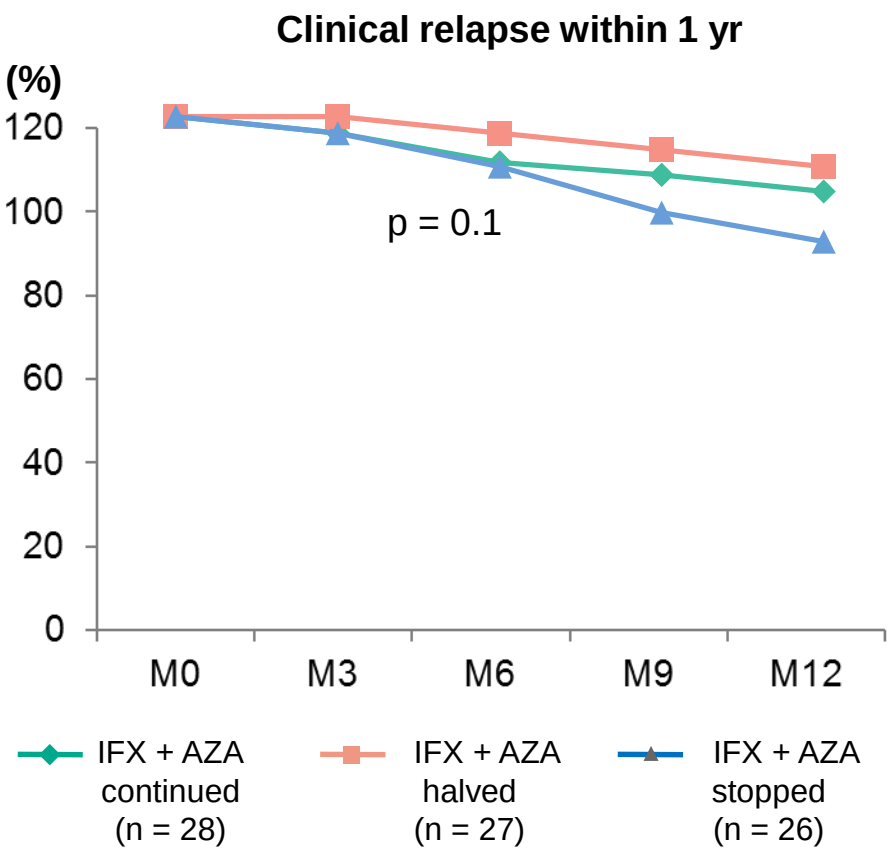
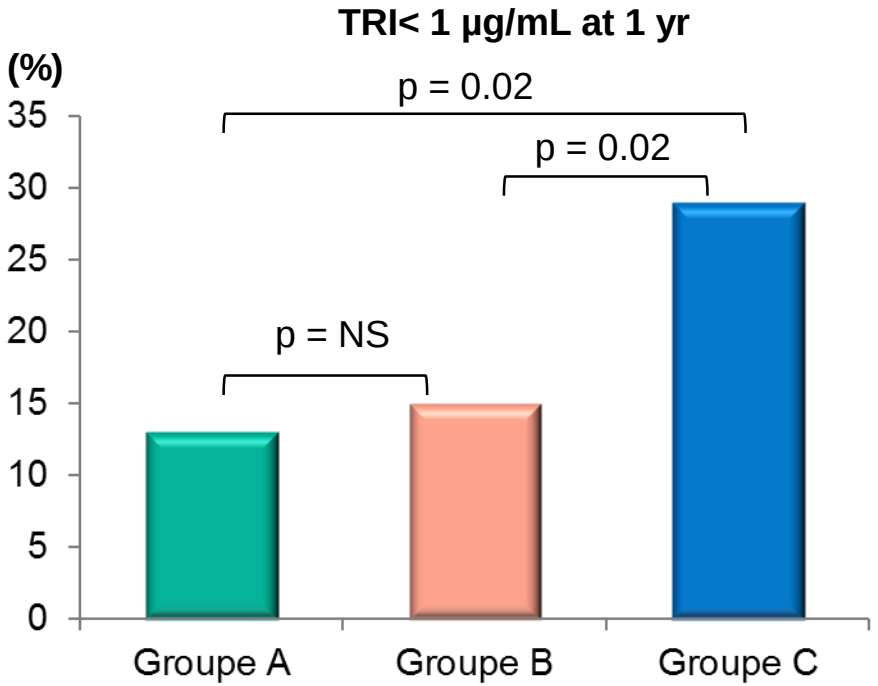
Azathioprine dose reduction in patients in deep remission receiving combination therapy (IFX + AZA)

Prospective monocentric study (Saint-Etienne)

n = 81 IBD on combotherapy and in deep remission for at least 6 months

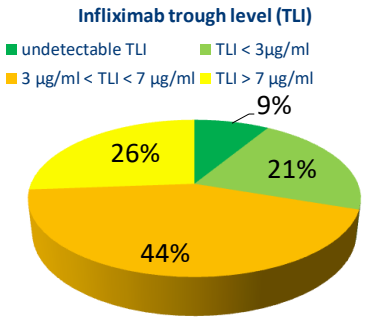




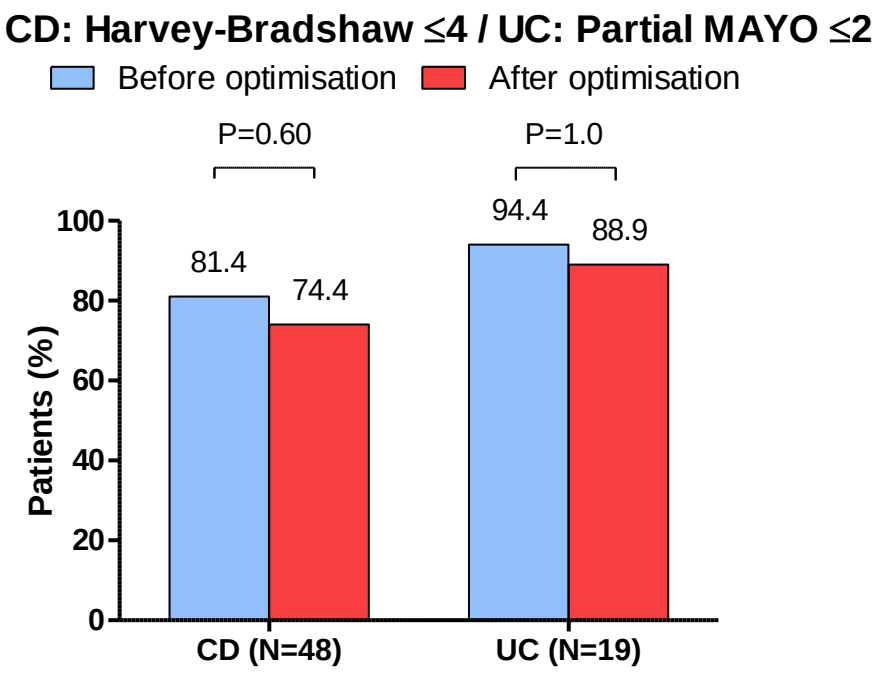
ROC analysis (AUROC: O.93), a threshold of **6-TGN < 105 pmoles** was associated with unfavourable pharmacokinetic (sensitivity, 67%; specificity, 92%; likelihood ratio, 7.67).

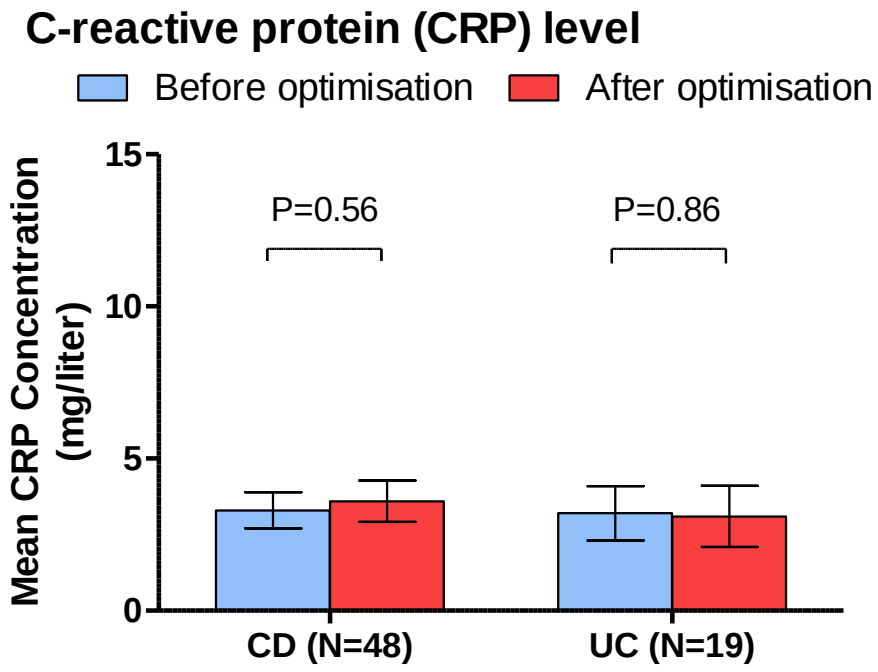
Del Tedesco E, APT 2017

TAXIT: optimisation phase



IFX Dose de-escalation in patients with high levels (n=67, 26%: TL>7ug/ml)

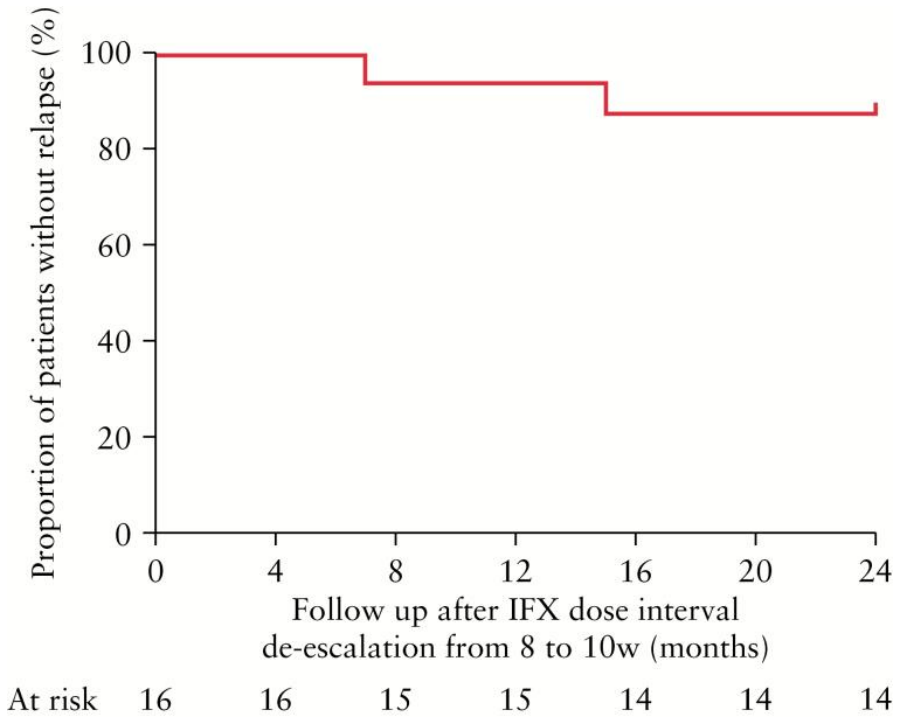


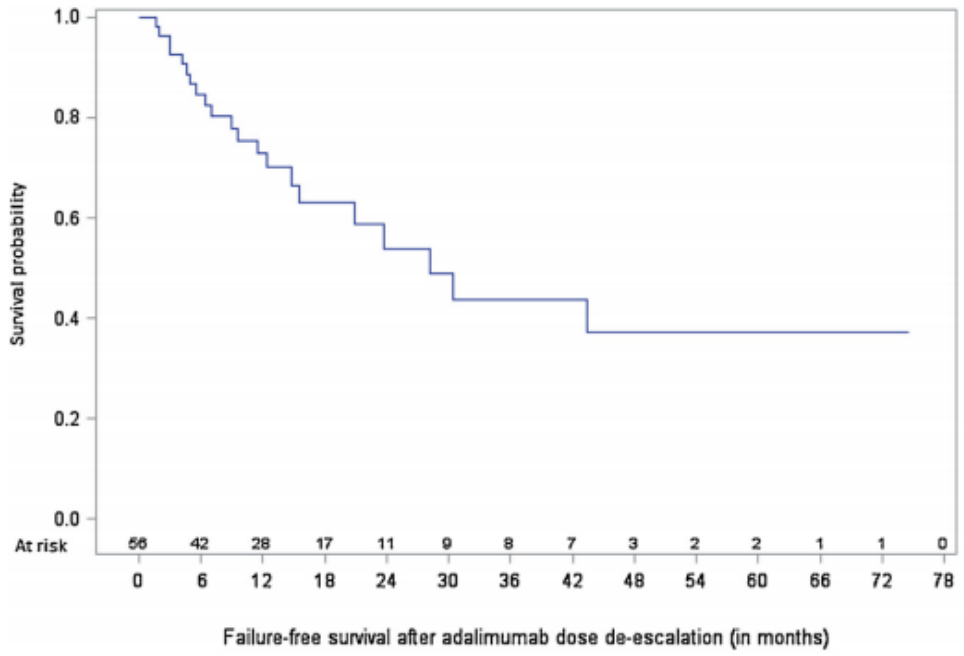


Successful dose de-escalation of patients with supra-therapeutic levels whilst retaining disease control

Vande Casteele *et al*, Gastroenterology 2015

De-escalation strategies





Deep remission
Every 10-week FC assessment
Cumulative probability of relapse at 12 months
14%

Ada every 3 weeks, median FUP 15.9 months
Failure in 35.7%

Papamichael K,JCC 2016; Pouillon L, et al DLD 2018

Lots of strategies (?)

1. Assess the risk of relapse
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Treatment cycles in CD

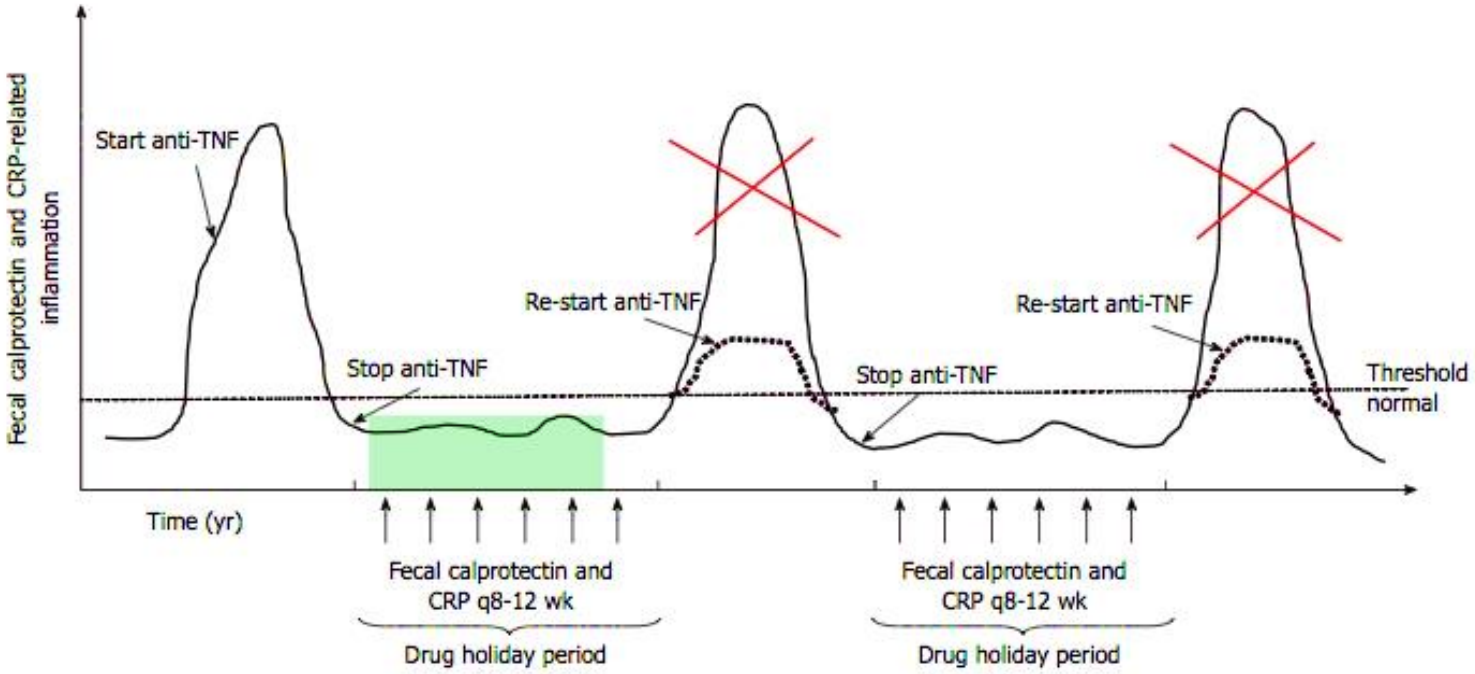
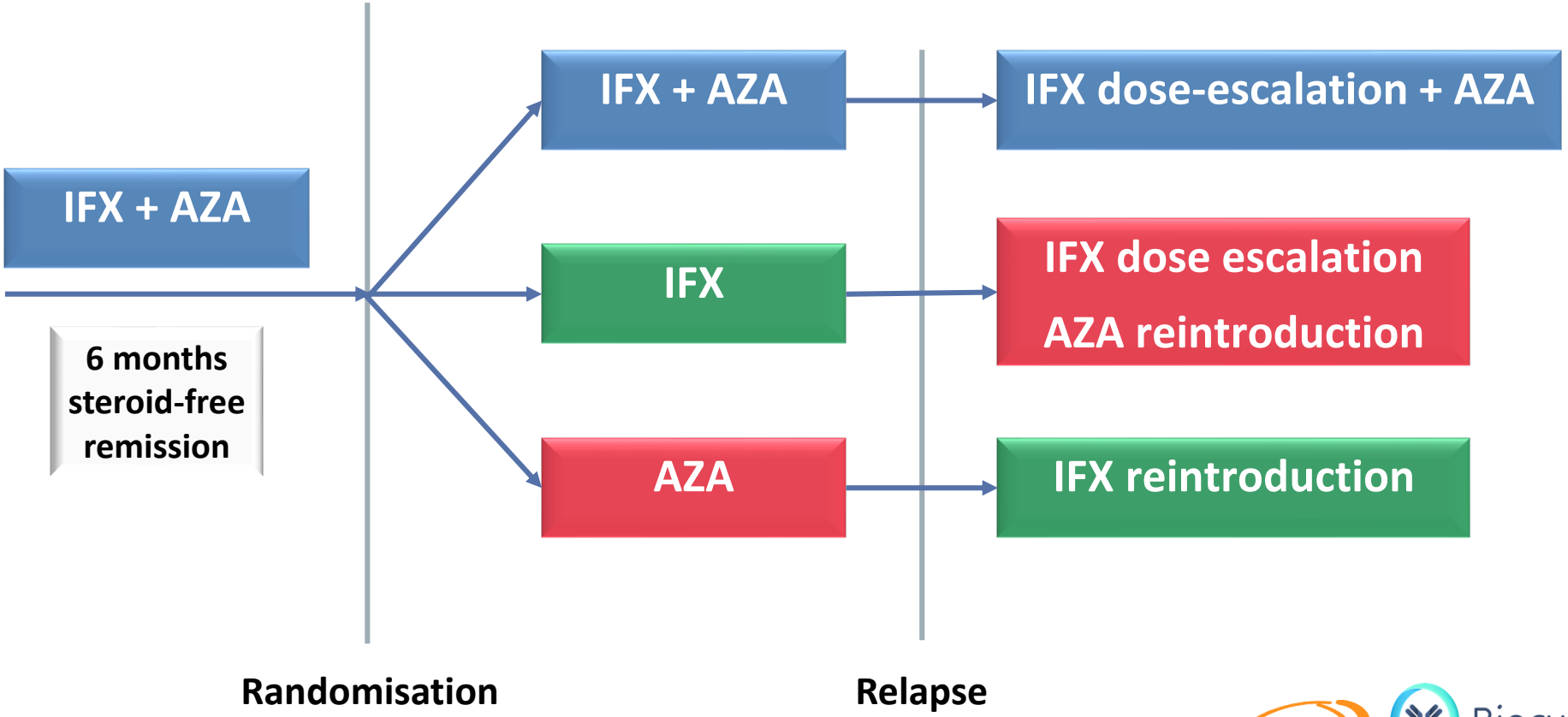


Figure 1 New concept of intermittent anti-tumor necrosis factor α therapy in inflammatory bowel disease. Stopping anti-TNFα agents after achieving a deep remission may result in prolonged clinical remission. Close monitoring of these patients with fecal calprotectin and CRP measurements (arrows) will allow early re-initiation of anti-TNFα therapy, when inflammation is starting to rise, which may result to a sustained clinical benefit (dotted line) preventing a disease flare (red cross). These patients may be considered as treated periodically and not episodically. TNF: Tumor necrosis factor; CRP: C-reactive protein.

Papamichael K, et al. WJG 2015

A pro**S**pective randomized controlled trial com**P**aring inflixim**A**b-antimetabolites combination therapy to anti-metabolites monothe**R**apy and infliximab monoth**E**rapy in patients with Crohn's disease in sustained steroid-free remission on combination therapy **(SPARE)**



Conclusions ?

- Drug withdrawal may be an option in select IBD patients
- There is a lack of consistency across the studies in terms of individual prognostic markers
- TDM can offer a promising strategy to indentify candidates for drug withdrawal