
Optimizacija terapije u lečenju inflamatornih bolesti creva
SIBDA - 4. – 5. novembar 2016. godine - Hotel „Izvor“ - Aranđelovac
Prof. Dr Dino Tarabar

Treatment Goals in IBD

1. Induce Remission
2. Maintain Remission
3. Maintain steroid-free remission
4. Mucosal healing
5. Prevent Complications
   - Disease Related
   - Therapy Related
5. Limit Surgery
6. Improve Quality of Life

Previous and Current Therapeutic Paradigms

Previous

- Fast Acting
- Bottom-up approach
- Conservative use of immunomodulators
- Goals
  - Induce remission
  - Maintain remission
  - Prevent complications
  - Optimize surgical outcomes

Current

- Early aggressive approach
- Earlier use of immunomodulators
- Additional goals
  - Disease modification
  - Mucosal healing
  - Pharmacoeconomics
- Disease prevention!

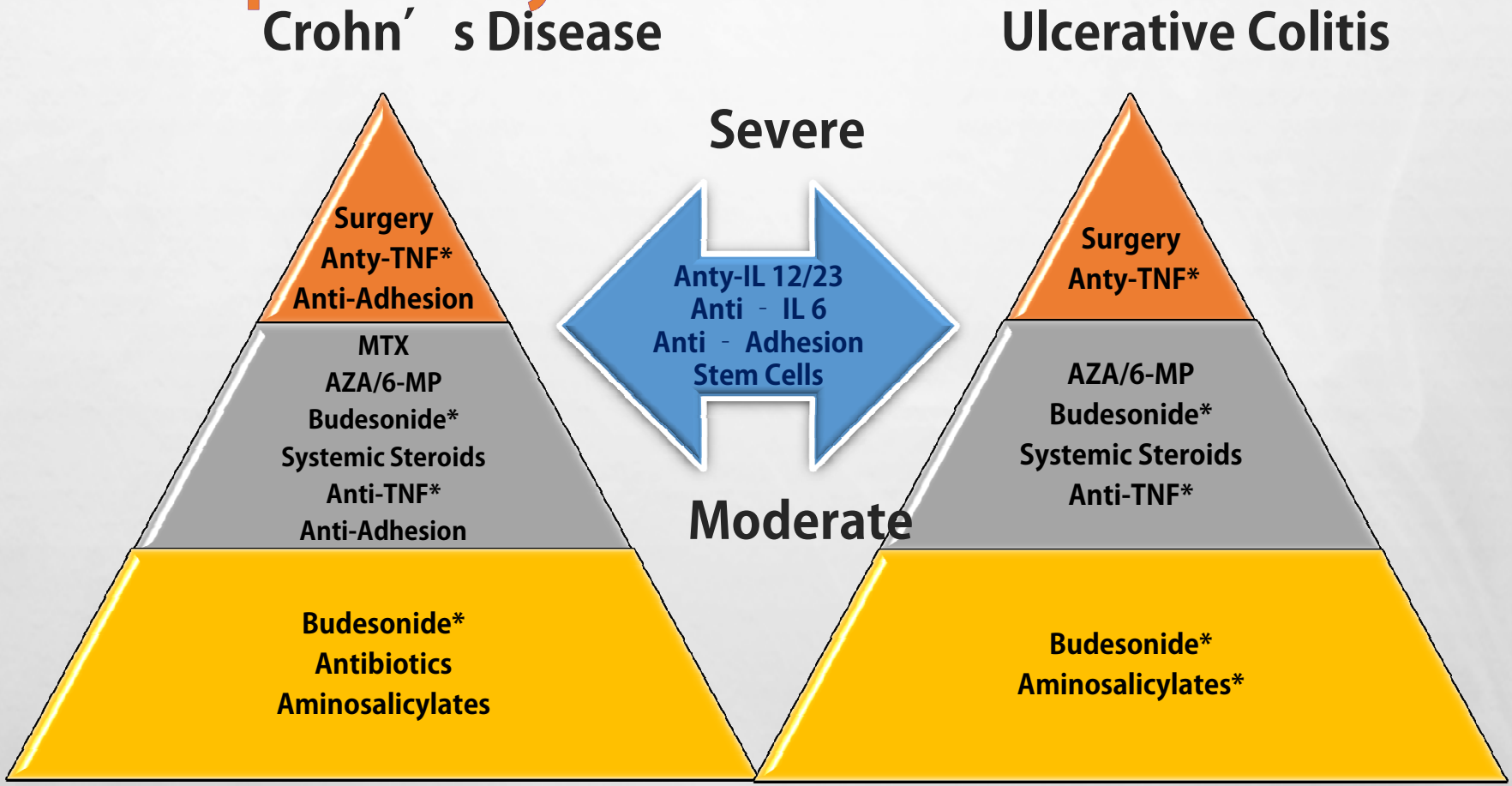
Another definition:

"Remission"

- The absence of disease or the impact upon disease upon the patient.
- Expectations change as therapies improve!

Remission = Perfection
(to the extent that non-perfection is due to active disease!)

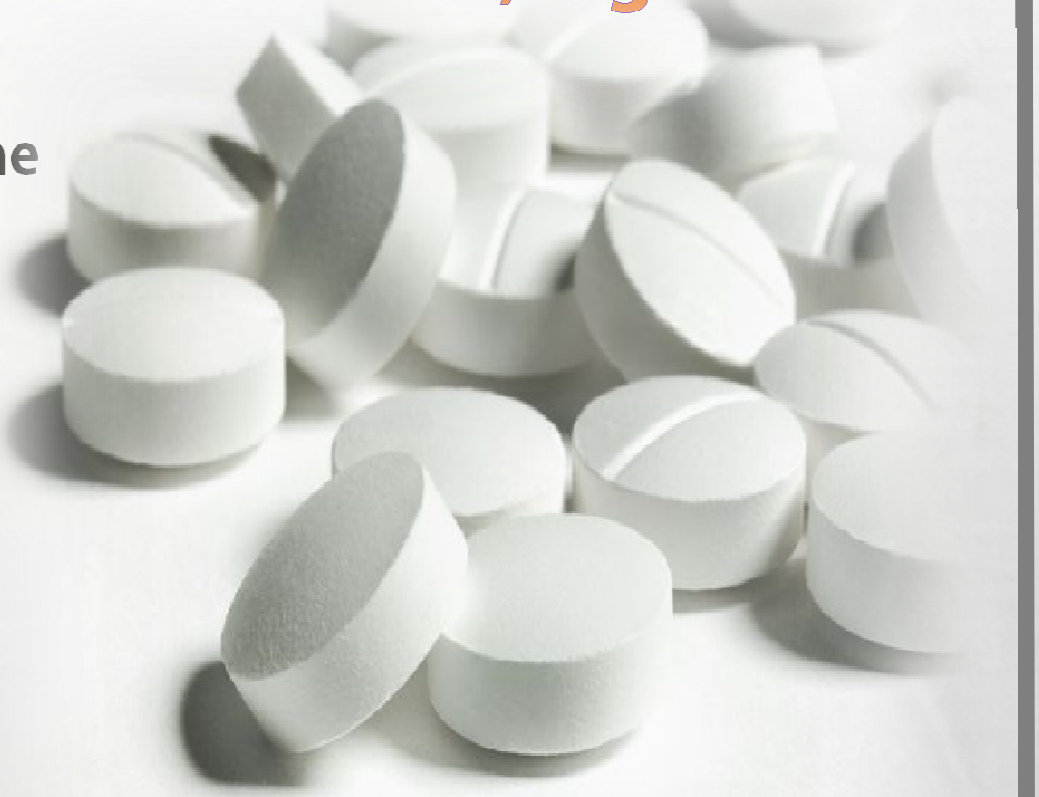
2 - 4 Years From Now: Potential Therapeutic Pyramids



* FDA Approved

Dino Tip #1 Right mesalamine, right dose

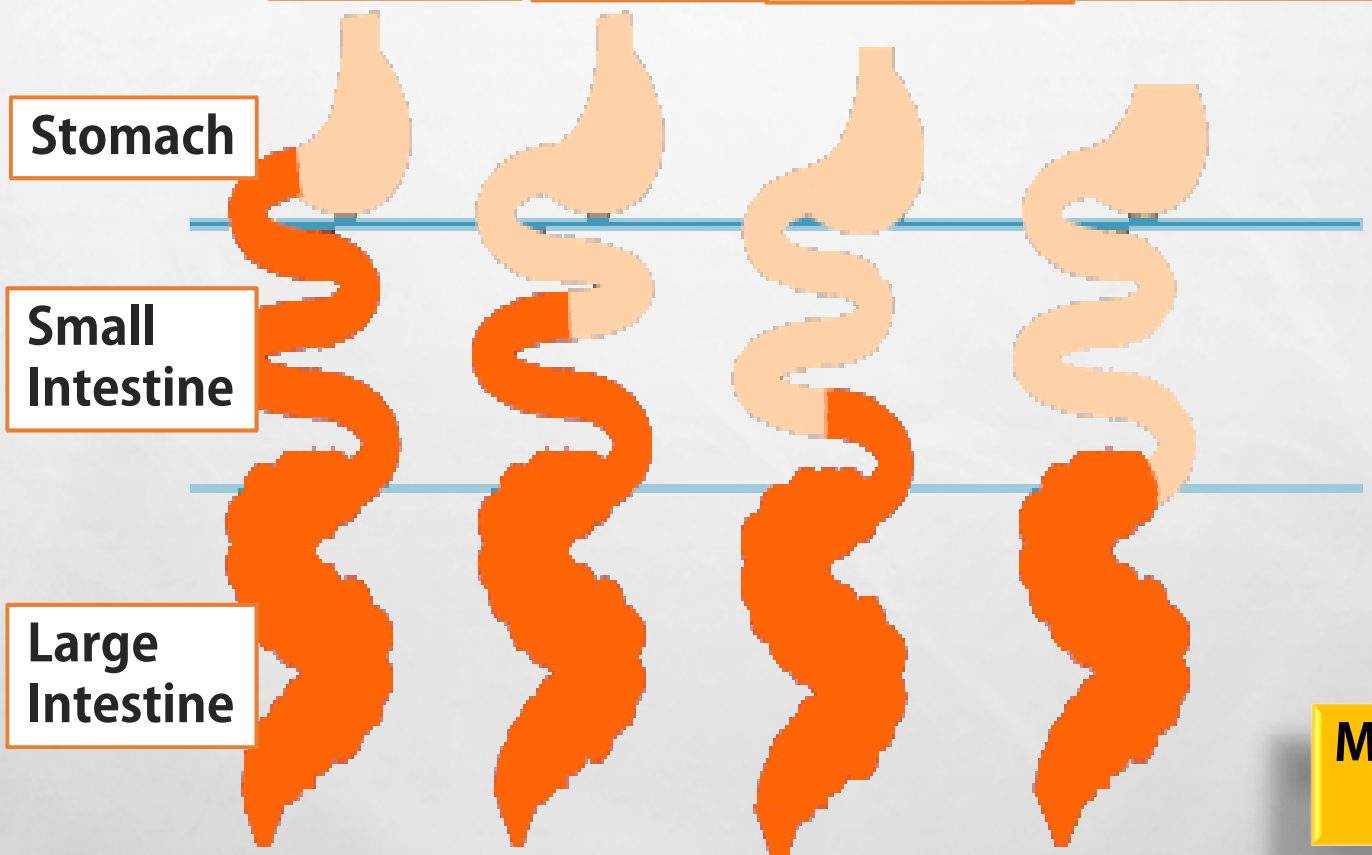
Use the Correct Mesalamine



Optimizing Mesalamine

- Works topically
  - By contact with the mucosa of the bowel wall.
  - Not intended to be absorbed.
- Need to match the location of disease to
- The specific release mechanism of the various agents
- DO NOT lower the dose if patients is doing fine
- Use combined therapy
- Disclaimer : Brand names listed on next slide to avoid confusion.

Optimizing Mesalamine



Sources: FDA package inserts / company websites.

Dino Tip #2 Antibiotics - When and how ??

- Crohn Disease: Use Antibiotics in
  - Perianal disease
  - Penetrating disease
  - ? Stricturing
- Ulcerative Colitis
  - Limited to "Pouchitis"

May Need To Use Long-Term

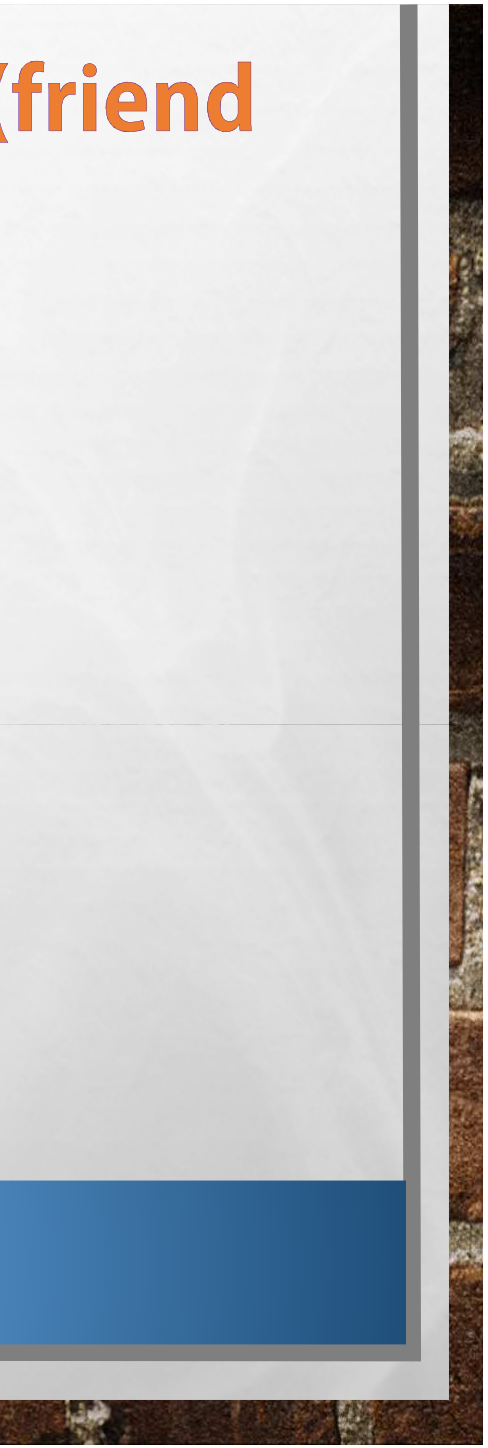
as in: Not Stop

Rationale for Antibiotic Therapy in IBD

- ↓ Luminal bacterial concentrations
- Selectively eliminate bacterial subsets
- ↓ Tissue invasion, microabscesses
- ↓ Bacterial translocation, systemic dissemination

Dino Tip #3 Less Corticosteroids (friend and enemy)

A. Don′ t Use Corticosteroids
B. You Will Need to Use Corticosteroids
C. When You Have a Patient on Corticosteroids, see “A” above.



Corticosteroid Therapies

- Oral, Parenteral, Topical (recta
- Effective in INDUCING REMISS
- Ineffective in MAINTAINING R
- Prohibitive Side Effect Profile

Risk of CIS

- Adverse effects specific to each individual therapy
- Increased risk of serious infection
- Increased risk of opportunistic infection
- Increased risk of non-melanoma skin cancer (NMSC)
- Increased risk of lymphoma
  - increased risk of hepatosplenic T-cell lymphoma

McLean&Cross, Expert Rev Gastroenterol Hepatol 2014; 8:223-40

Budesonide (MMX)

- High Potency
- Targeted Delivery To Bowel
- Extensive Hepatic First-Pass Metabolism
  - Fewer Steroid-Related Side Effects

"Customized" Budesonide For Crohns and now one also for Ulcerative Colitis

Dino Tip #4 More MTX to be used

- Do not Forget About Methotrexate !!

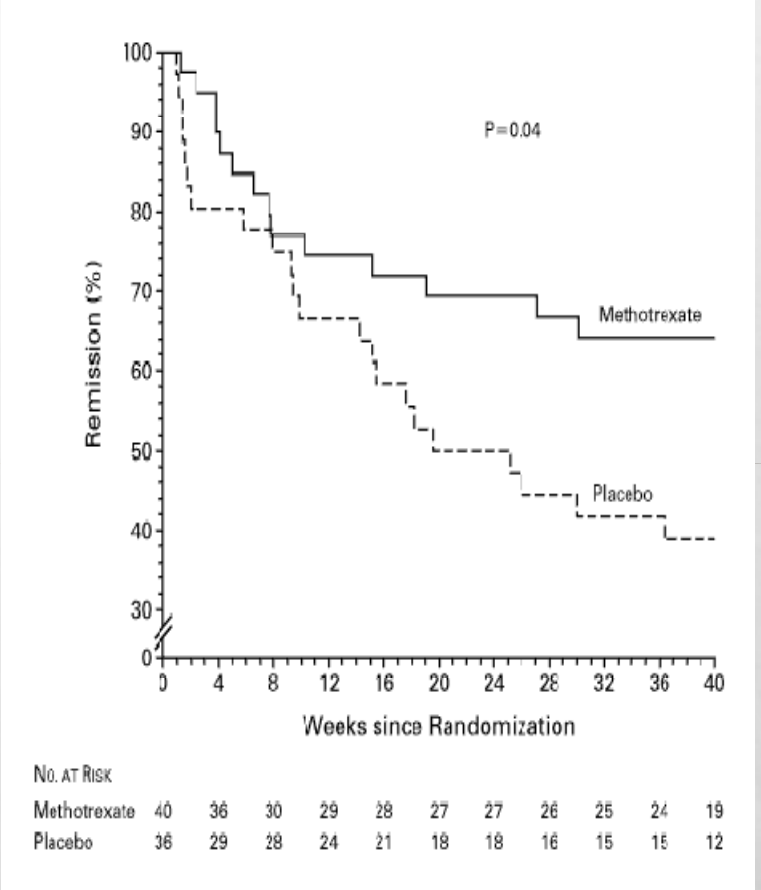
  (Crohns Disease).

MTX for Maintenance of Crohns

- Remission induced with MTX 25mg IM q week.
- Maintained with MTX 15mg IM q week vs. placebo.
- Week 40 Remission:
  - 65 % MTX
  - 39 % Placebo

  (p = 0.04)
- • Prednisone for relapse:
  - 28% MTX
  - 58% Placebo

  (p = 0.01)



Feagan et al. N Engl J Med 2000;342(22)1627-32.

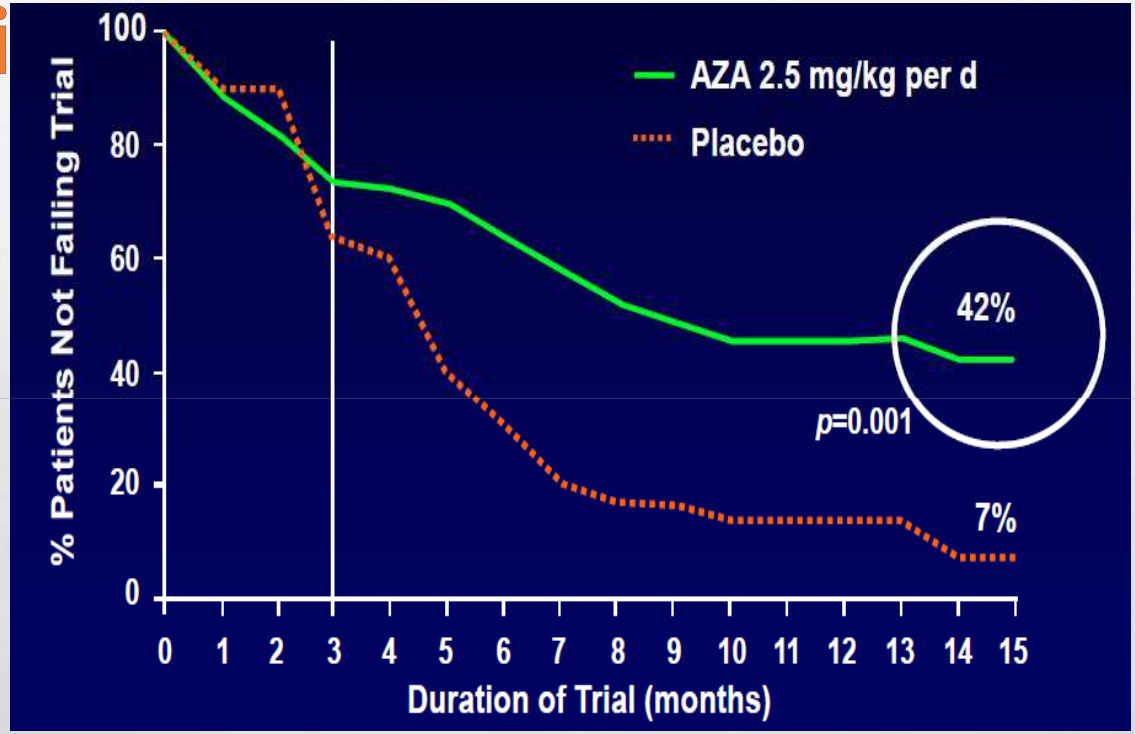
Dino Tip #5 Purine Analogs use earlier and properly

- The Purine Analogues Are Reliable, Safe Long-Term Choices.
  - They are typically under-dosed.
  - They are should not be stopped if working.
  - You should use them more.

Purine Analogues

- 6 - mercaptopurine
- Azathioprine
- Work SLOWLY
- Wear off SLOWLY
- Be Patient
- Also should be used with anti-TNF as combined therapy

Efficacy of AZA as Crohn's Disease, Maintenance Therapy After Steroi

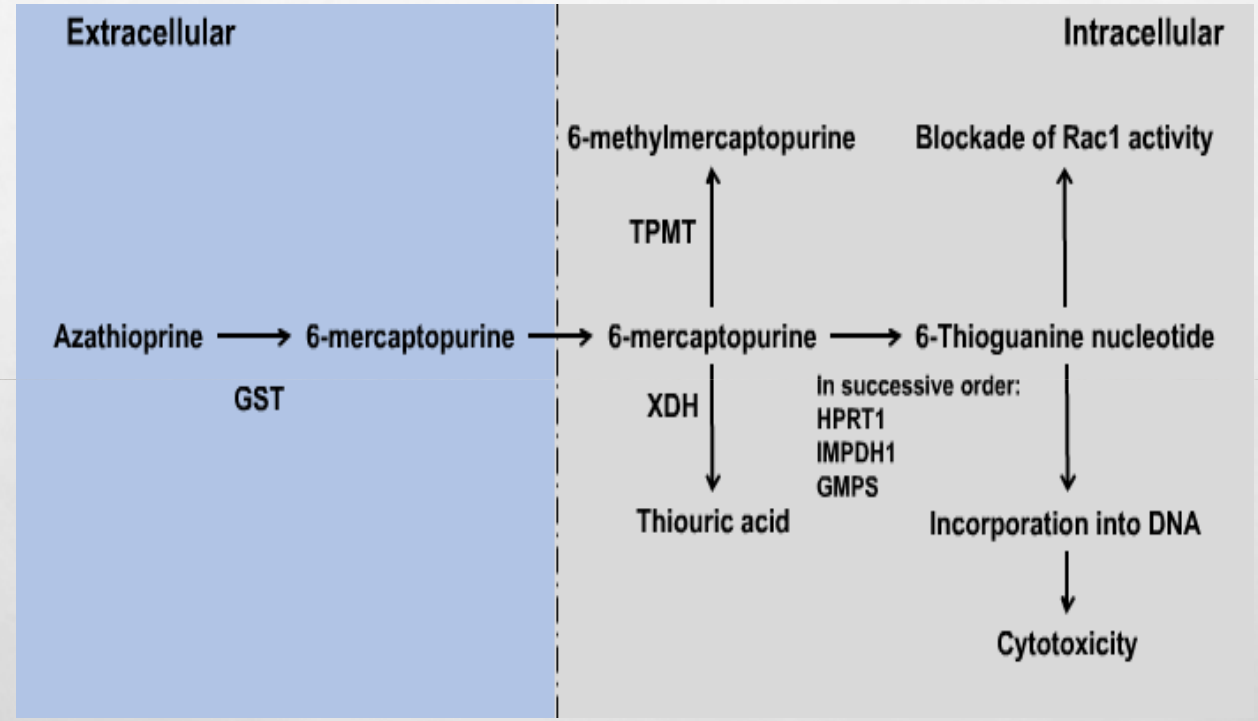


* Remission induced by prednisolone tapered over 12 wk
Inclusion: Patients were not steroid dependent

Candy S, et al. Gut. 1995;37(4):674-678.

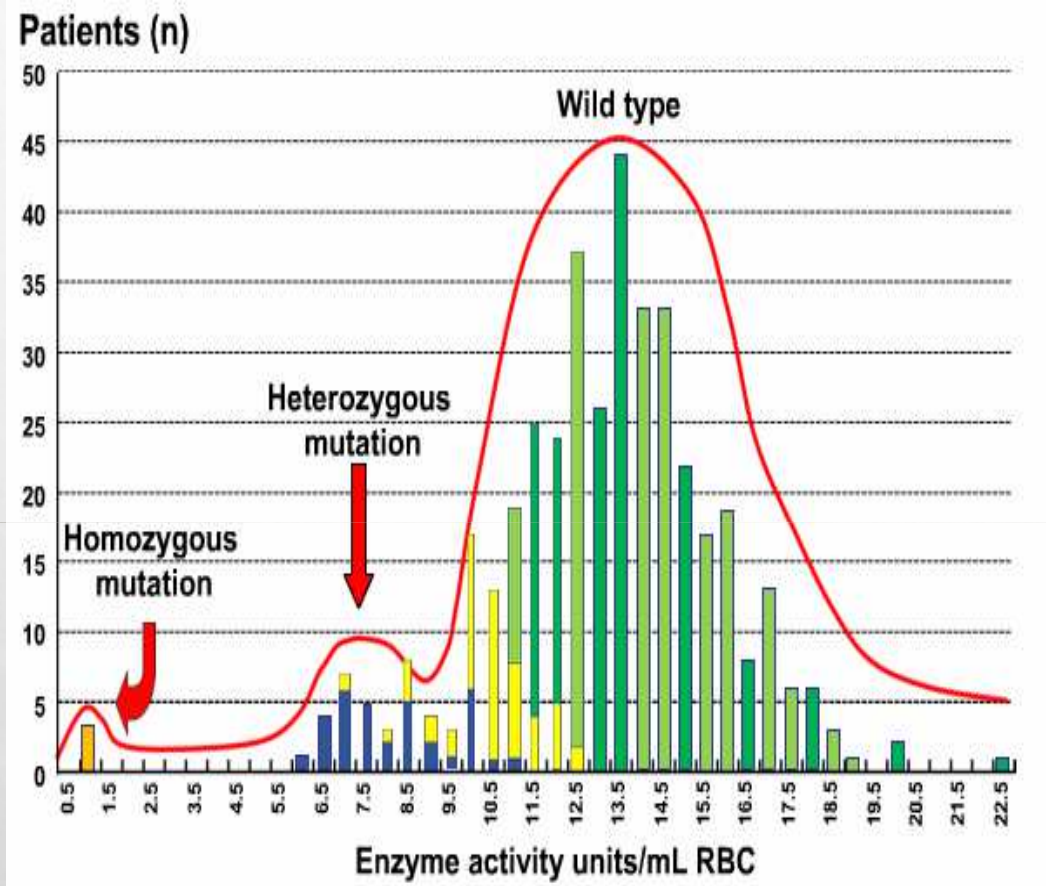
Thiopurine metabolism

A simplified representation of major thiopurine metabolic pathways



Chua et al, Pharmacogenomics J 2015; 15: 414-21

TPMT activity distribution



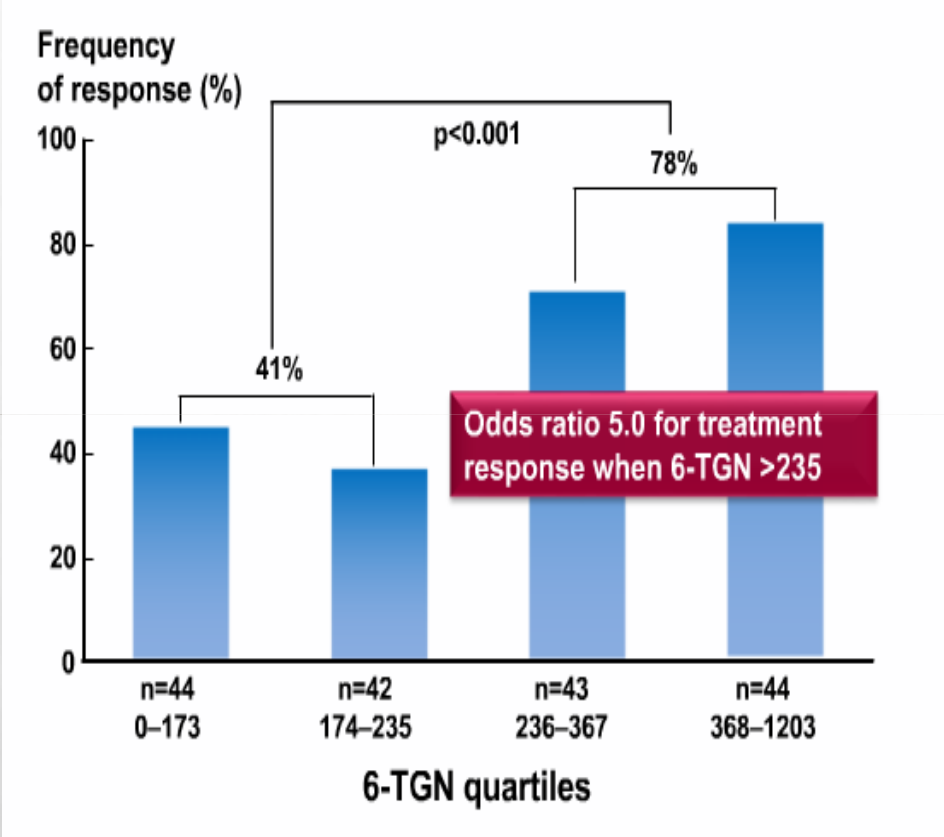
www.nzma.org.nz/ journal/118-1210/1324/

TMPT testing: What do we know

- TMPT recommended for ali patients initiating thiopurines
- **Normal TPMT activity:** Can use standard dosing of 2.5-3 mg/kg/day azathioprine or 1-1.5 mg/kg/day 6-MP
- **High TPMT activity:** Associated with high 6-MMP, low 6-TGN
- **Low or intermediate TPMT activity:** Associated with leukopenia
- Leukopenia not always associated with low TPMT

Target 6-TGN level to optimize efficacy: >235

Frequency of response (%) 100



Dubinsky et al, Gastroenterology 2000; 118: 705-13

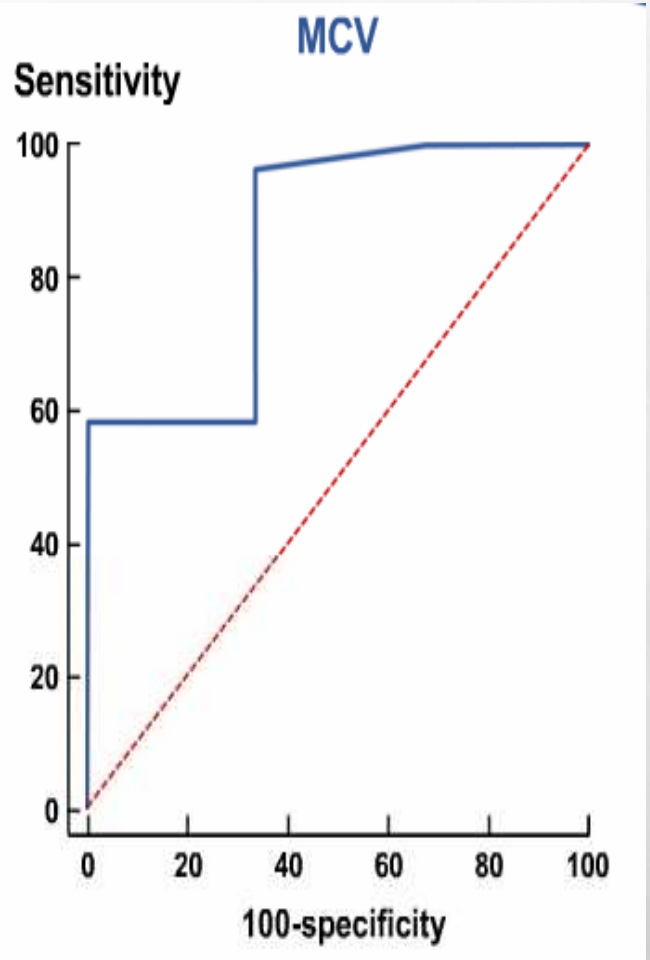
MCV and lymphopenia: Predicting 6-TGN >235

	Sensitivity	Specificity	PPV	NPV
Macrocytosis	35	96	92	53
Lymphopenia	50	70	67	54

Heerasing et al, Intern Med J 2015;

MCV>101 is predictive of 6-TGN >235

- Cut-off MCV value 101 fL
  - sensitivity: 35%
  - specificity: 96%
  - area under curve (AUC): 0.85; p=0.01

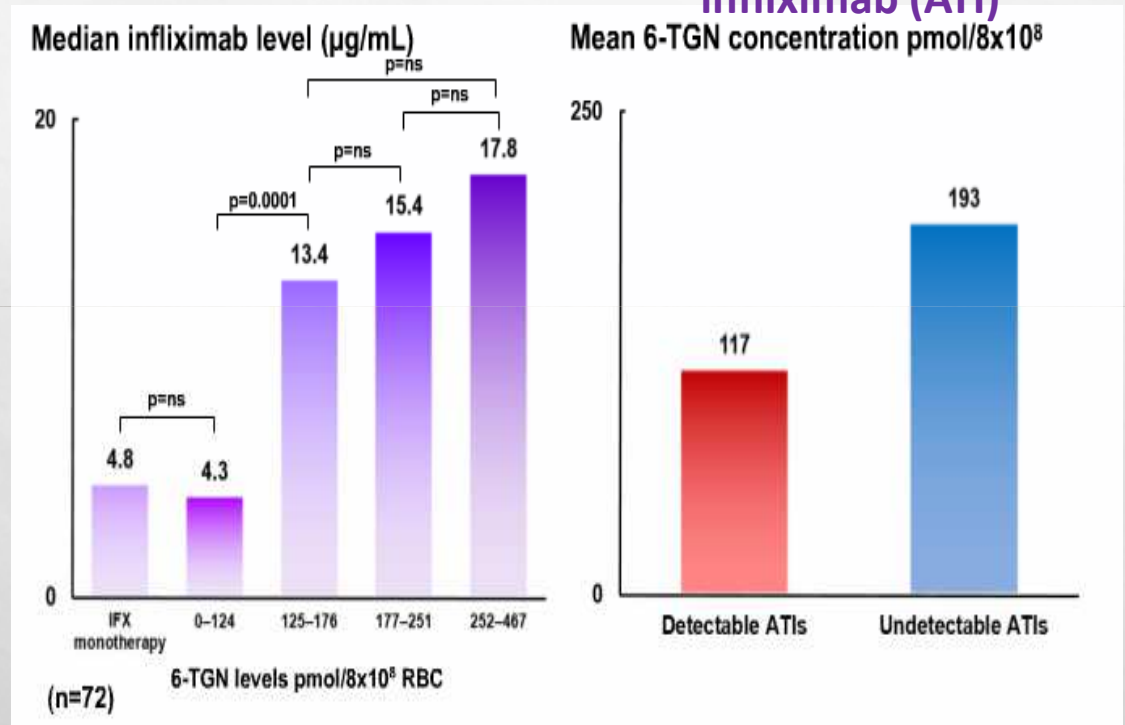


Heerasing et al, Intern Med J 2015;

6-TGN level >125 associated with higher infliximab levels

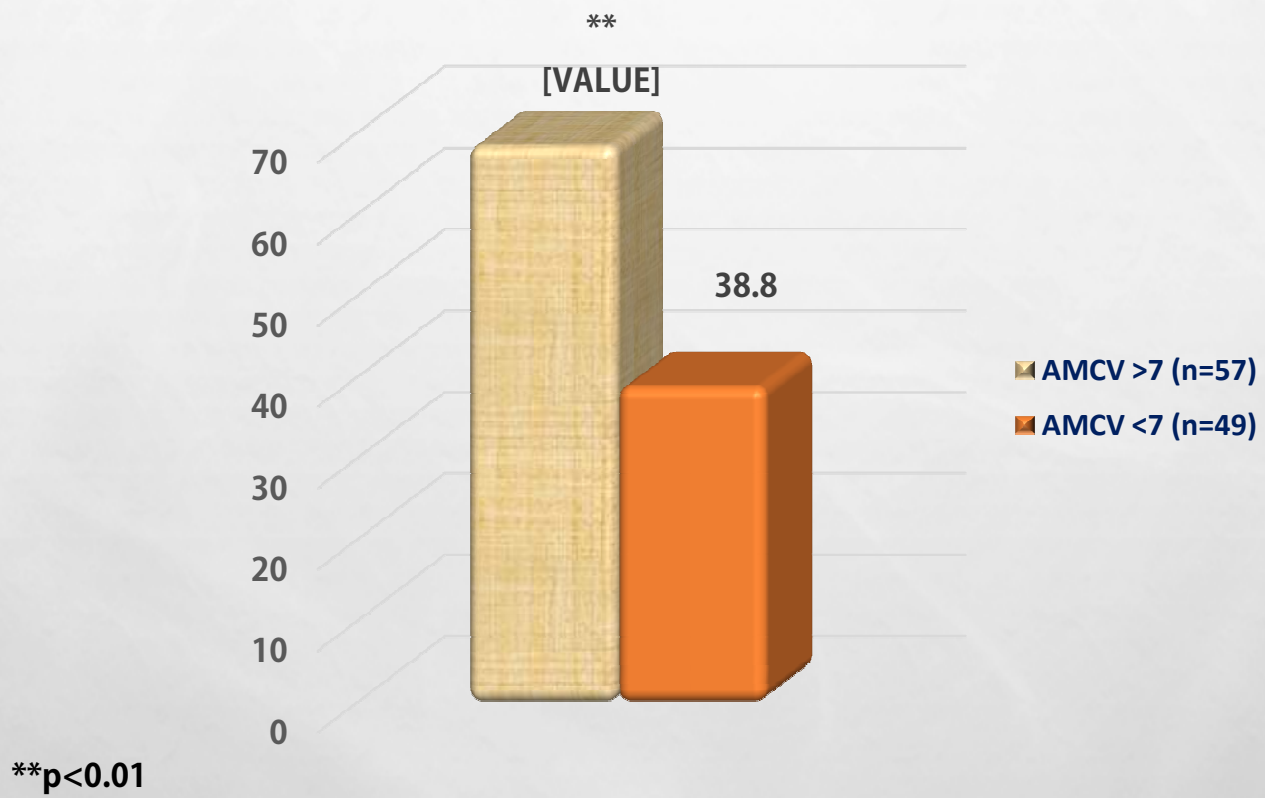
Correlation between 6-TGN and infliximab concentrations

Comparison between groups with and without detectable antibodies to infliximab (ATI)



Yaruretal, Clin Gastroenterol Hepatol 2015; 13: 1113-24

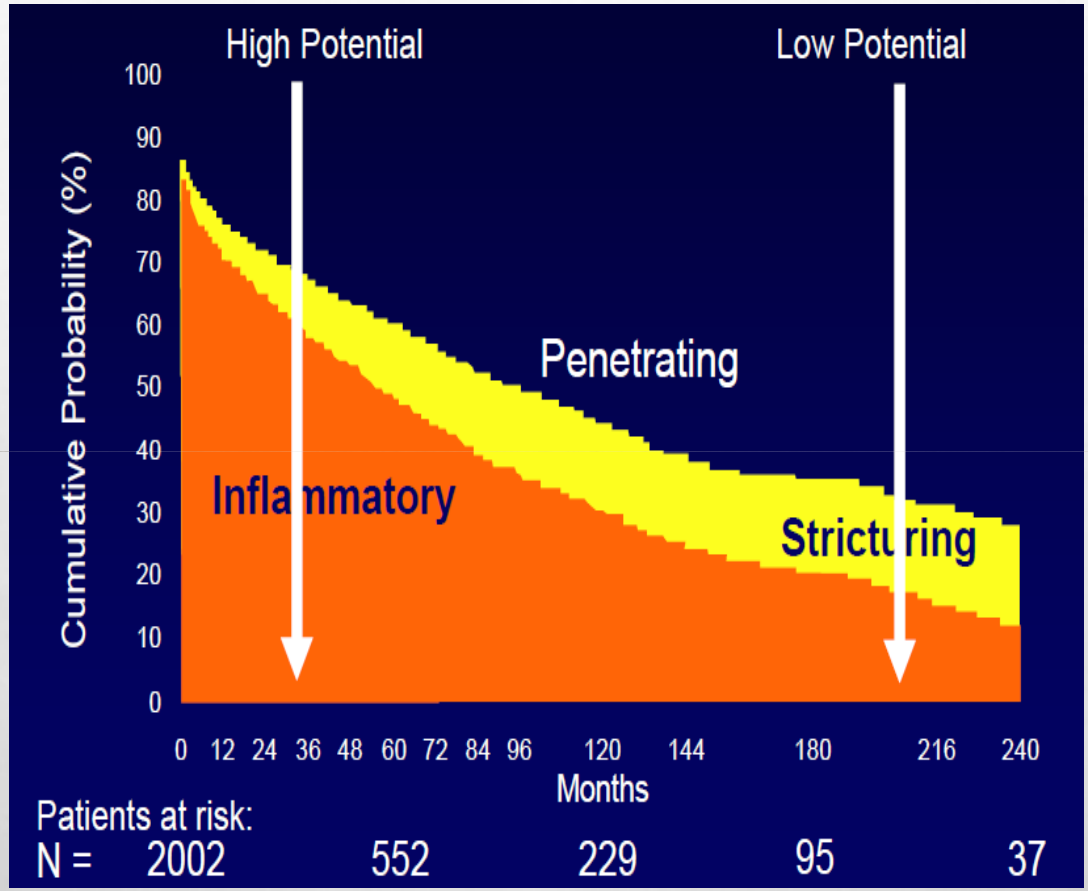
MCV and infliximab trough levels



**p<0.01

Bouguen et al. Inflamm Bowel Dis 2015; 21: 606-14

Impact of Therapy will Depend on Degree of Structural Damage & Velocity of Progression



Cosnes J et al. Inflamm Bowel Dis. 2002;8:244.

Dino Tip #6 Early Intervention

- Response rates highest if start medications early in disease course.

Crohn's disease:

  - BEFORE stricturing / penetrating occurs

Ulcerative colitis:

  - BEFORE chronic inflammation, "tubular colon"

- FDA indications are for moderate to severe disease.

Currently FDA approved for Crohn's Disease

Biologics in IBD

The Promise

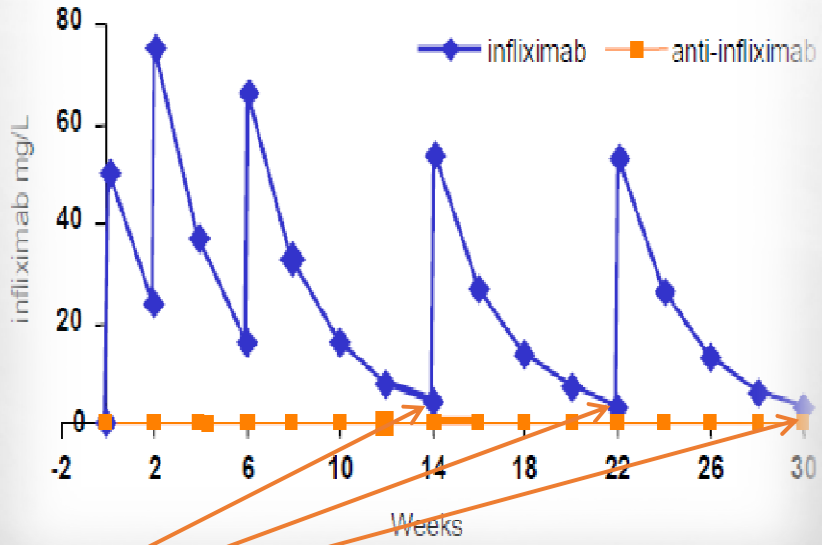
- Fast Acting
- Efficacious
- Induction
- Maintenance
- Steroid Sparing
- Hospitalization Sparing
- Surgery Sparing

The Threat

- Infection Risk
- Neoplasm Risk
- Cost
- Running out of Options

Trough Level vs Drug Level

PK model no anti-infliximab detected



Trough level

infliximab

Trough level = TL

CASE 1

- 34-y female, UC, 48 kg
- CS-resistant
- Infliximab 300 mg 0-2-6
- Week12:
  - 8 bloody BM/day
  - CRP 66, Calprotectin >1800
  - Rectosigmoidoscopy: Mayo 3

CASE 2

- 28-y male, UC, 68 kg
- CS-dependent, AZA resistant
- Infliximab 400 mg 0-2-6
- Week 14:
  - 10 bloody Bm/day
  - CRP 24, Calprotection 588
  - Rectosigmoidoscopy: Mayo 3

Primary non-response to infliximab diagnosed

„non TNF-alpha mechanism " ? → colectomy?

Drug level w12/w14

CASE 1

infliximab trough level < 0.3

anti-infliximab antibody <0.3
infliximab antibody > 20

CASE 2

infliximab trough level < 0.

anti-

blem

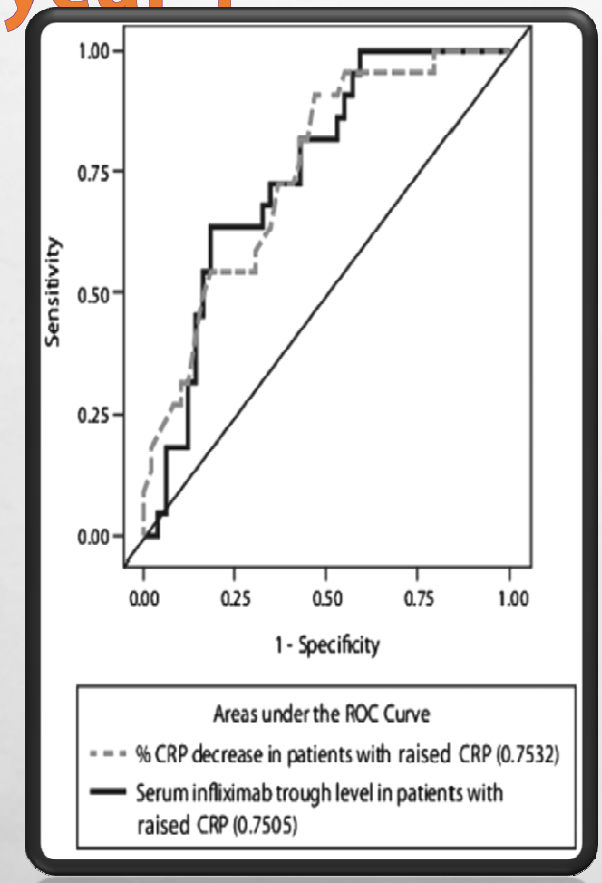
40/40...

TDM prevented wrong conclusion „primary non-response“
TDM guided correct decision dose opt/switch during induction

After 2 years in clinical and biochemical remission (calprotectin

After 1.5 years in clinical and biochemical remission (calprotectin <

Crohn ‘s disease: predicitive value of week 14 trough level for response at year 1



Week 14 infliximab trough level > 3,5 µg/m

Table 3 Accuracy of week 14 infliximab trough levels ≥3.5 µg/mL and CRP decrease ≥60% from baseline at week 14 in predicting sustained response in patients with raised baseline CRP >8 µg/mL given infliximab 5 mg/kg every 8 weeks without dose escalation (n=71)

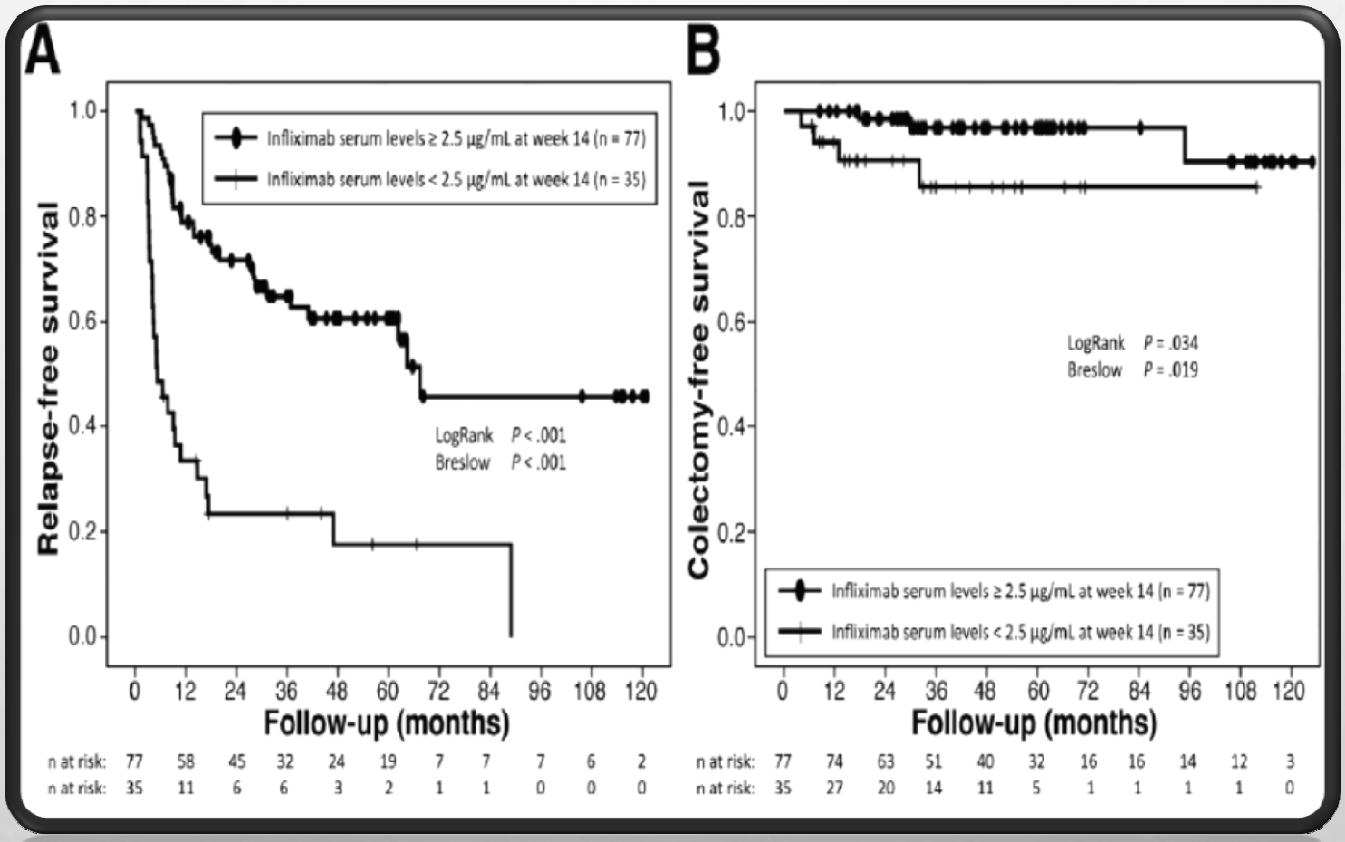
	IFX level	CRP change from baseline	IFX level *and* CRP change from baseline	IFX level *or* CRP change from baseline
Optimal cut-off point	3.5 µg/mL	60%	3.5 µg/mL and 60%	3.5 µg/mL or 60%
Sensitivity	0.64	0.91	0.59	0.95
Specificity	0.78	0.53	0.82	0.49
PPV	0.56	0.47	0.59	0.46
NPV	0.83	0.93	0.82	0.96

CRP, C reactive protein; IFX, infliximab; NPV, negative predictive value; PPV, positive predictive value.

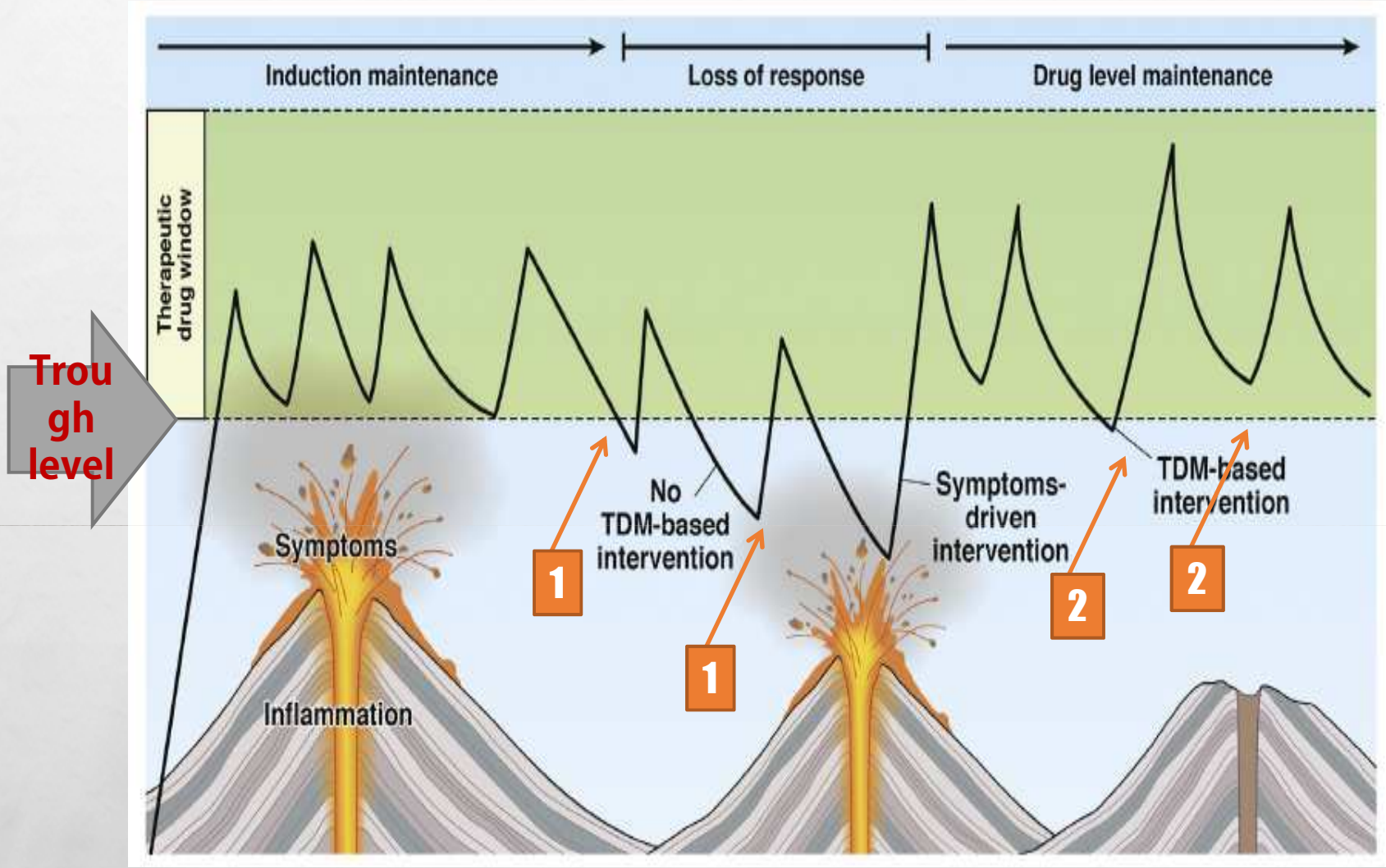
Cornillie. GUT 2014

Ulcerative colitis: predicitive value of week 14 trough level for response at year 1

Week 14 infliximab trough level > 2,5 µg

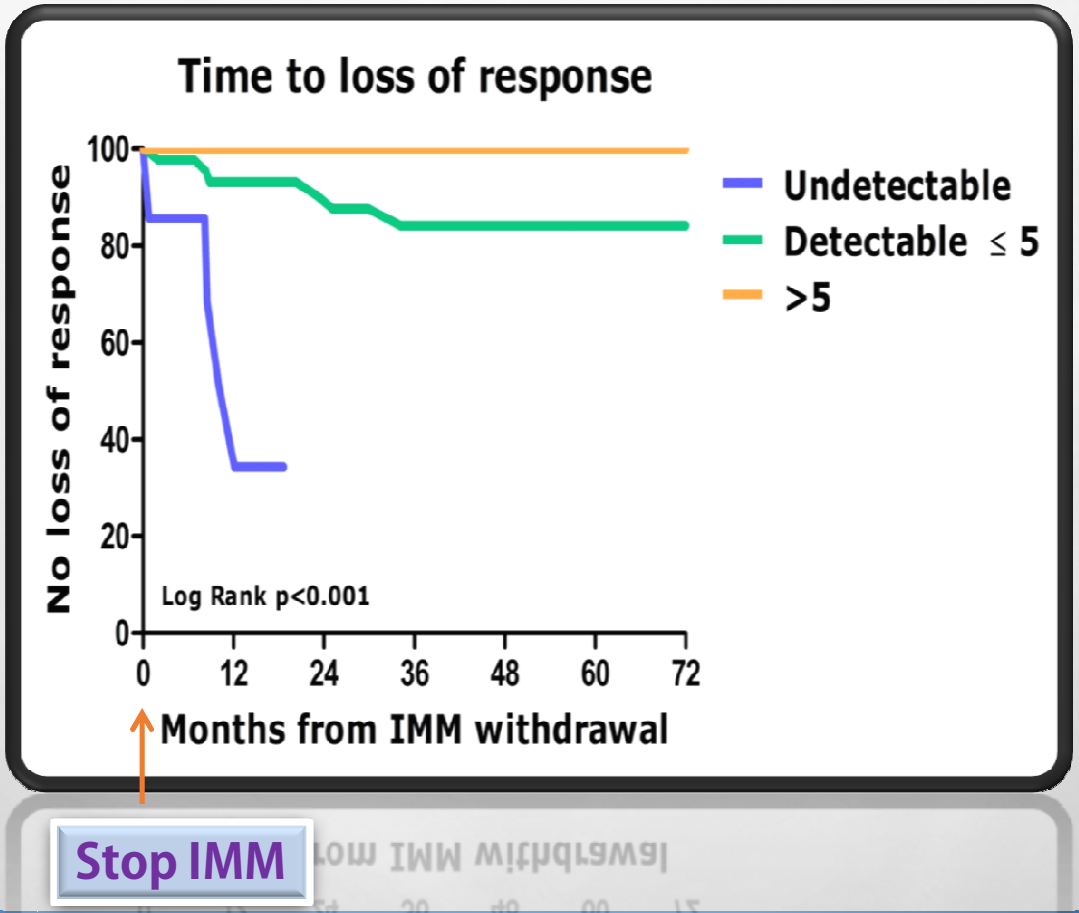


Arias. Clinical Gastroenterology and Hepatology 2015



Ben-Horin. GUT 2015

Infliximab trough levels predict outcome
+
COMBO → MONO IFX



Drobne. Clinical Gastroenterology and Hepatology 2015

Target infliximab trough level ?

...depends on the efficacy criterion chosen in IBD patients

mean infliximab trough level

Pts in clinical remission: 2.6 µg/ml

↓

Pts in clinical remission + normalisation of C

↓

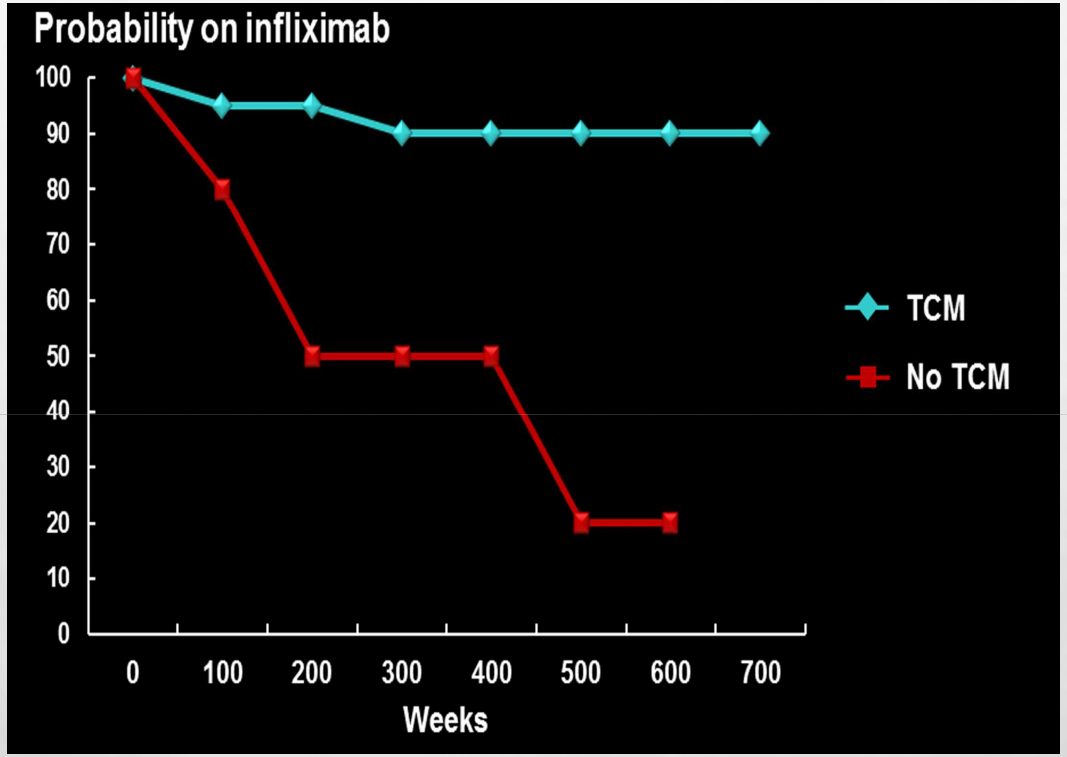
Pts in clinical remission + calprotection<250: 4.9 µg/ml

Our data on UC:
TL<0.3 → calpo 745
TL 1-3 → calpo 542
TL 3-5 → calpo 410
TL 5-7 → calpo 412
TL >7 → calpo 260

Higher infliximab trough level → better disease control

Roblin. OP005. ECCO 2015

Proactive therapeutic drug monitoring (TDM) improves persistence with infliximab



n=78

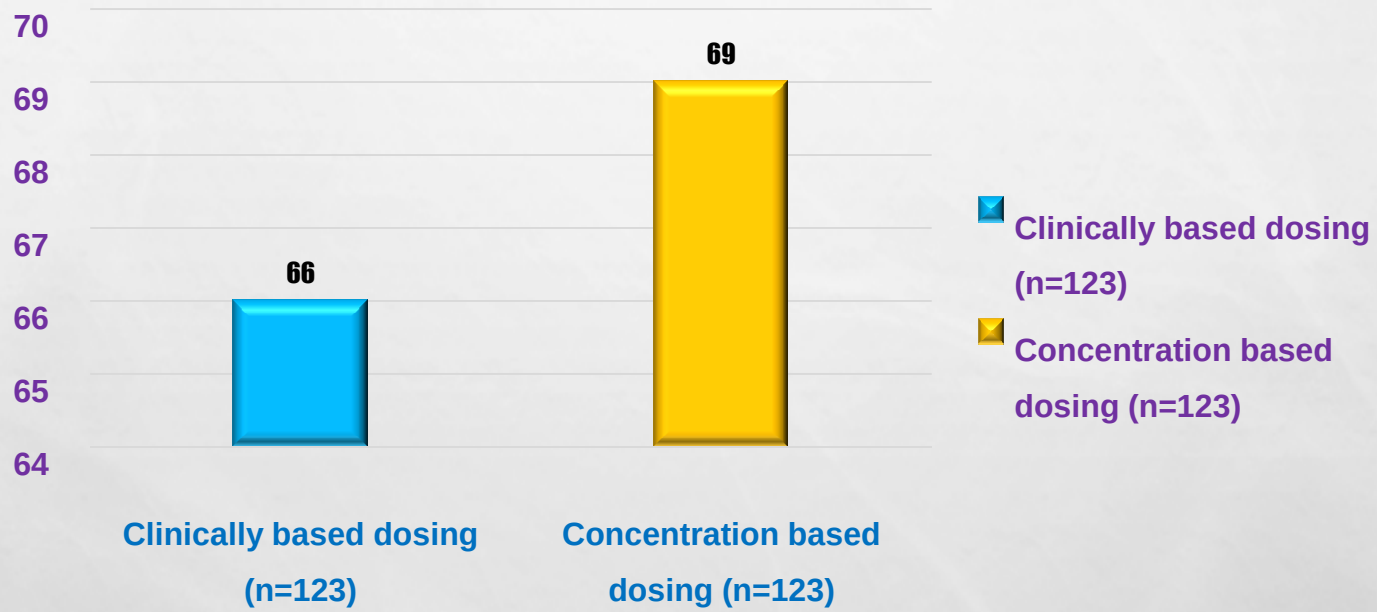
p=0.009

TCM: Therapeutic concentrationmonitoring

Adapted from Vaughn et al, Inflamm Bowel Dis 2014; 20:1996-2003

Infliximab dosing based on infliximab levels vs , clinically based dosing of infliximab: TAXIT* trial

Clinical and biological remission at one year (%)



29% of patients had an infliximab level below 3 pg/mL at baseline; remission rate increased from 65 to 88% (p=0.020) after one time dose optimization

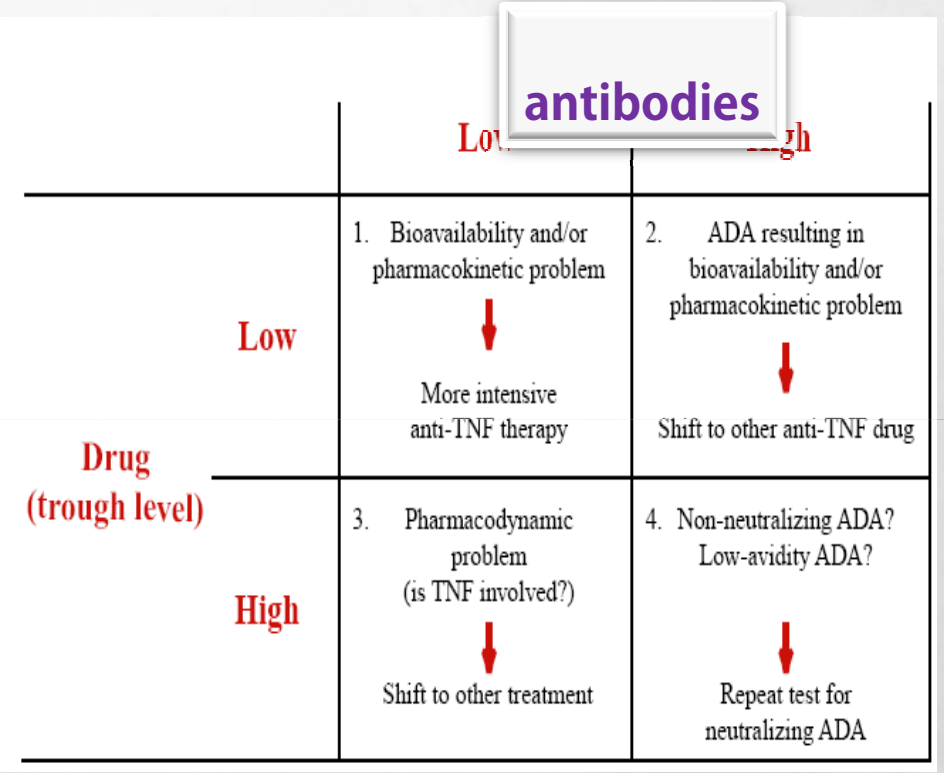
*Trough level Adapted infliXimab Treatment (TAXIT) trial

Vande Casteele et al, Gastroenterology 2015; 148:1320-9

At disease flare

Adalimumab > 4.5 or infliximab > 3.8
→ 90 % specificity for NO response to dose escalation or switch to another anti-TNF

Anti-adalimumab antibodies > 4 or anti-infliximab ATI > 9
→ 90% specificity for NO response to dose escalation of current TNFi

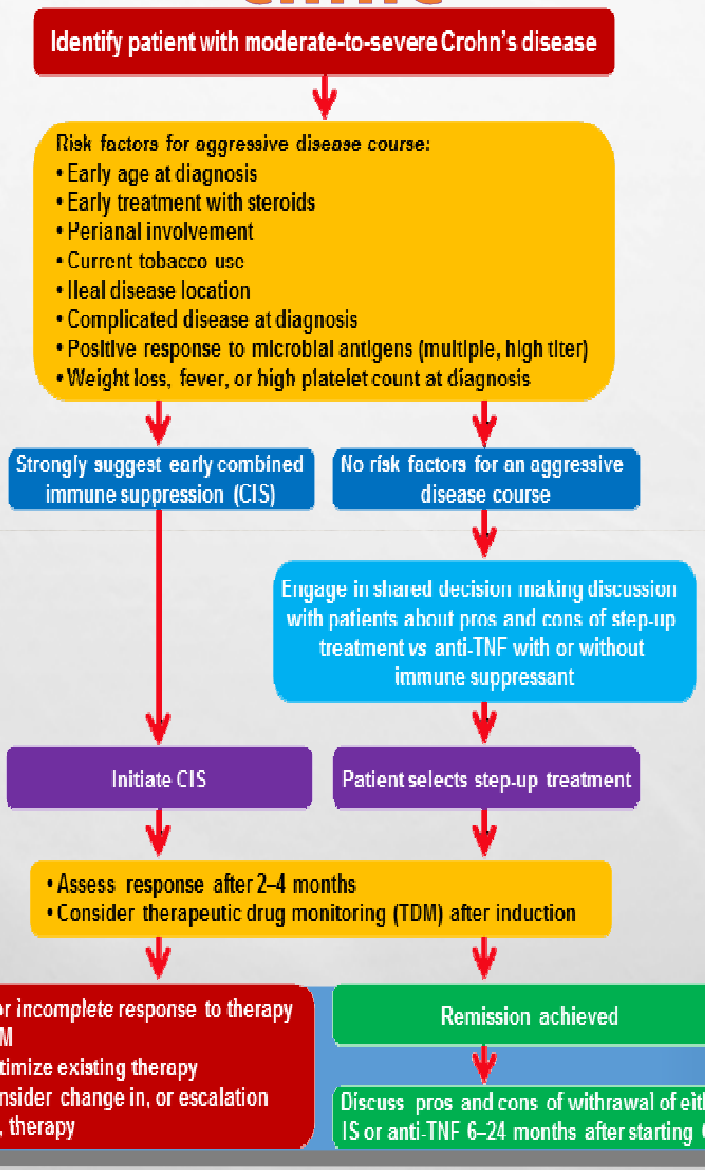


Bendtzen et al. ; Yanai. Clinical Gastroenterology and Hepatology 2015.; ADA: Anti-Drug Antibody = ATI,;
Bendtzen K et al. Scan J Gastroenterol 2009 epub 13JAN09

Time points for TDM

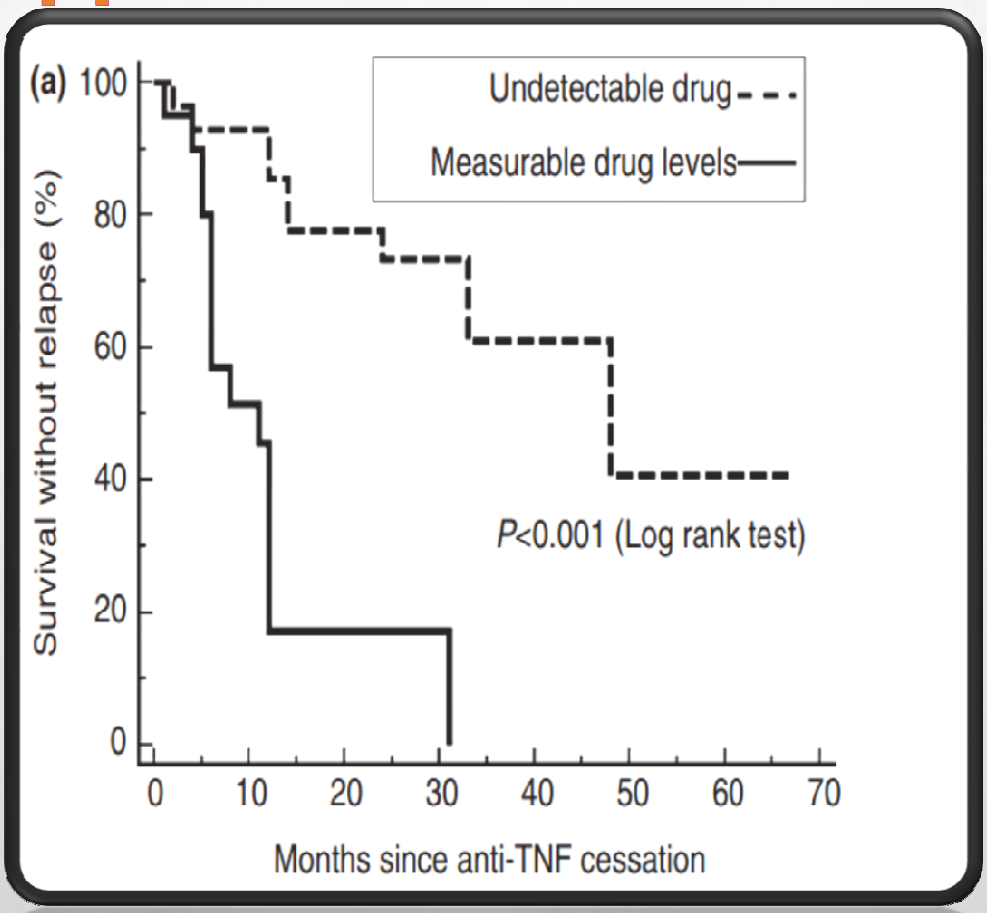
- During induction → To confirm primary non-response
- Shortly after induction → To predict year 1 outcome
- In remission → To detect undetectable TL and dose optimise to target TL
- At disease flare → To distinguish pharmacokinetic vs pharmacodynamic
- At de-escalation from combo to mono infliximab → To predict outcome after withdraw
- After drug holiday during re-start of infliximab → To predict success and safety
- Sc agents → To monitor adherence

Algorithm to optimize anti-TNF use in the clinic



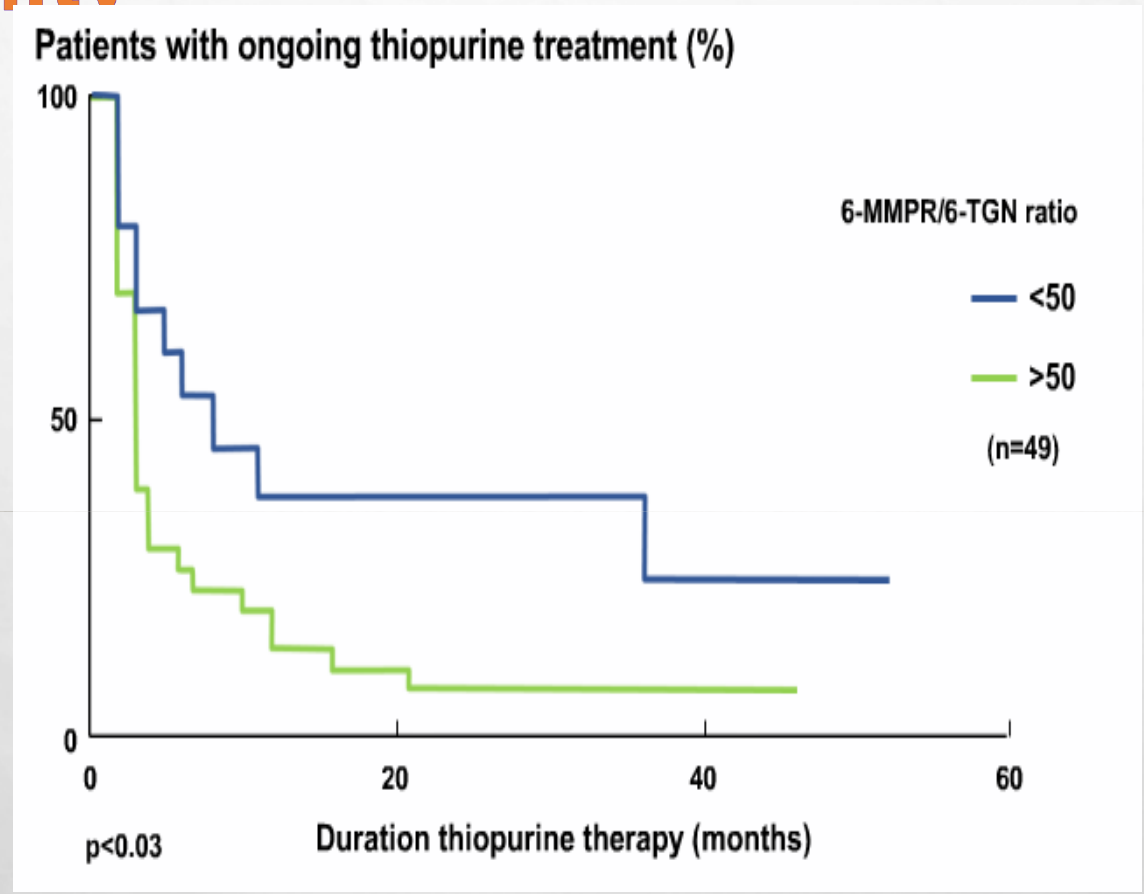
Thank you for your attention

Undetectable TL: 32% will flare in 1 year if TNF is stopped



Ben-Horin. Alimentary Pharmacology and Therapeutics 2015

6MMP: 6-TGN ratio predicts thiopurine durabilitv



Kreijne et al, Ther Drug Monit 2015; 37: 797-804

Time points for TDM

- During induction
- At de-escalation from combo to mono infliximab
- Shortly after induction
- After drug holiday during re-start of infliximab
- In remission
- To monitor adherence to sc agents
- At disease flare