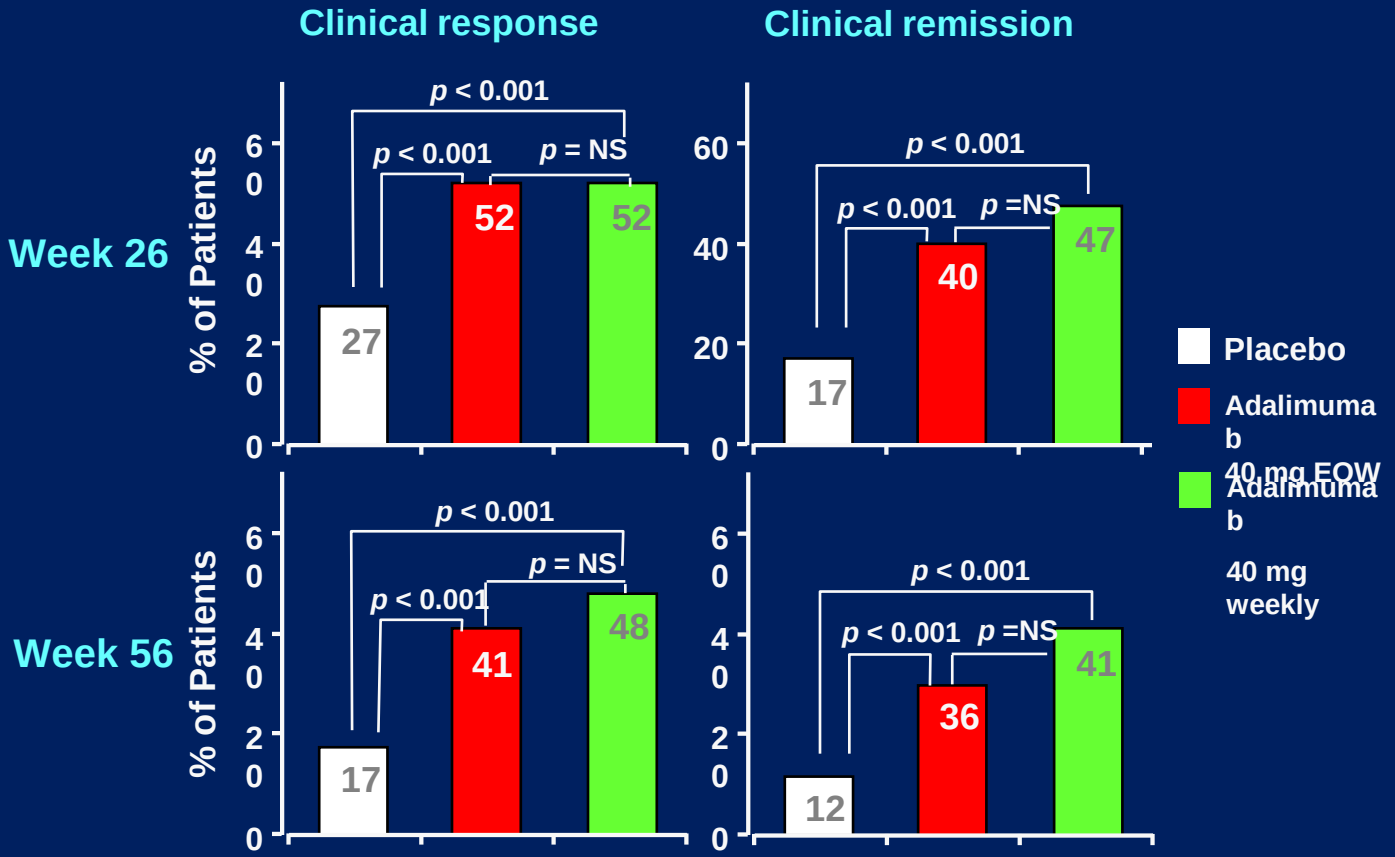
CLINICAL TRIALS robarts
A GLOBAL RESEARCH ORGANIZATION

Optimizing Biologic Therapy in IBD
The Role of Therapeutic Drug Monitoring:

Brian G. Feagan MD

Tuesday, August 2, 2016

Monoclonal Antibody Therapy: We Have Evolved - But we are a long way from perfect……



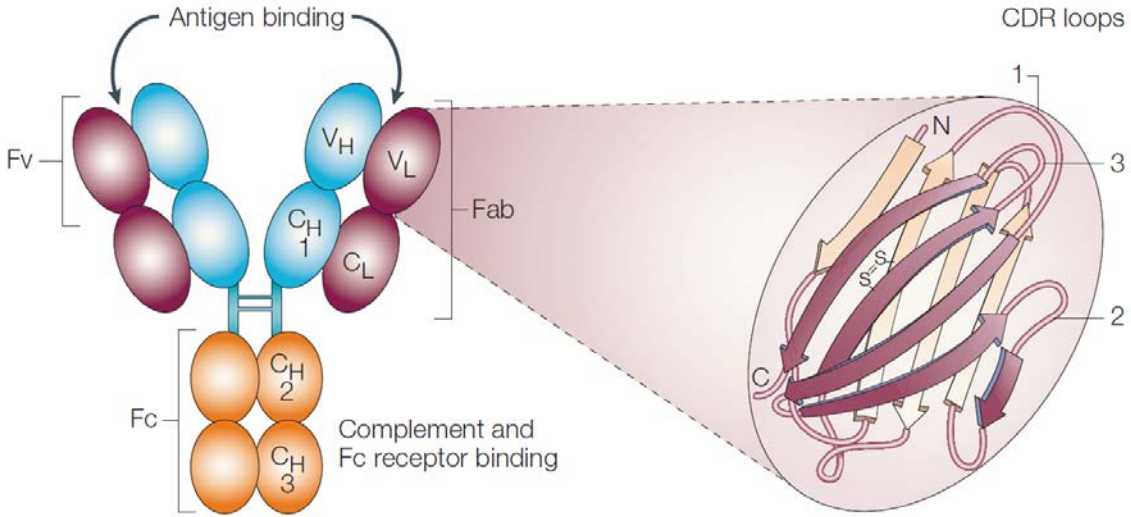
EOW = every other week.

Colombel JF, et al. Gastroenterology 2007

Optimizing Therapy
Some Facts\ Opinions

- Many misconceptions exist about the pharmacology of these agents
- Step – care is dead in CD
- Safety is not the issue

Antibody Structure \Function Relationships



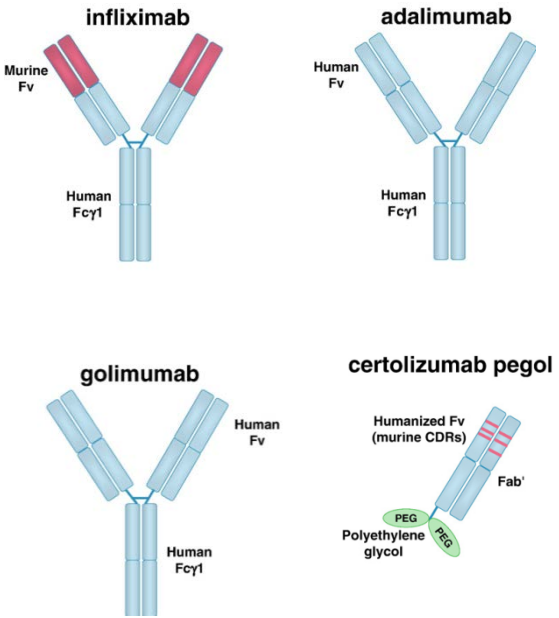
Effector functions

- ✓ Complement (C1)
- ✓ FcγR
  - Endocytosis
  - Phagocytosis
  - Antibody-dependent cytotoxicity (ADCC)
  - Cytokine release
- ✓ FcRn

Adapted from Brekke OH & Sandlie I. *Nat Rev Drug Discov* 2003;2(1):52-62

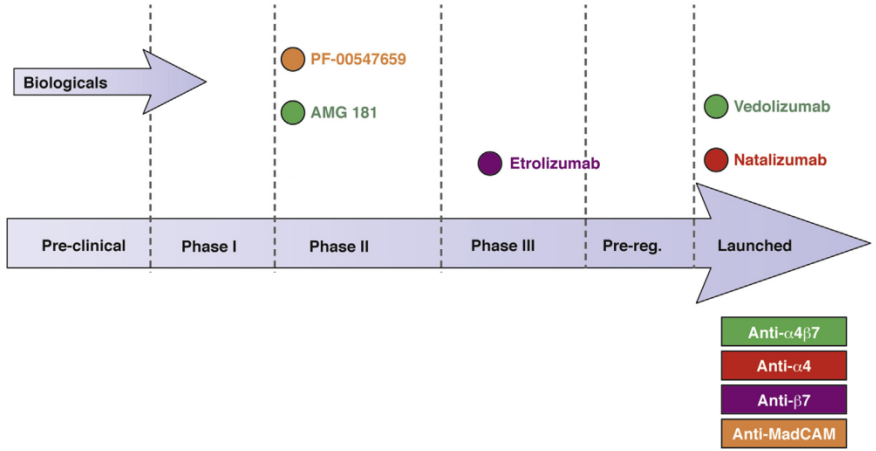
Monoclonals for IBD

TNF Antagonists



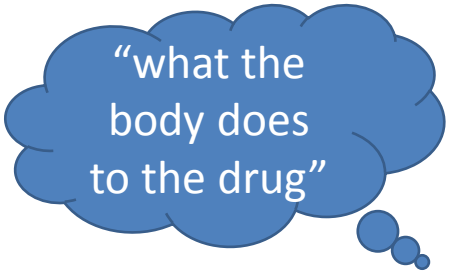
Adapted from Tracey D, *et al. Pharmacol Ther* 2008;117(2):244-79

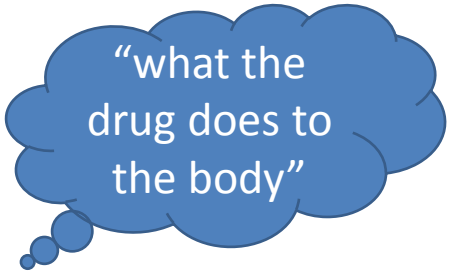
Anti-adhesion therapies



Adapted from Danese S & Panés J. *Gastroenterology* 2014 [Epub ahead of print]

PK/PD





Pharmacokinetics

- Study of the time course of drug in the body
  - **A**bsorption
  - **D**istribution
  - **M**etabolism
  - **E**xcretion

Pharmacodynamics

- Study of the time course of drug action (= effect)
  - Therapeutic
  - Toxicologic
- Mechanism of action
- Intimately linked to PK

Multiple Factors Affect the PK of Monoclonals[1]

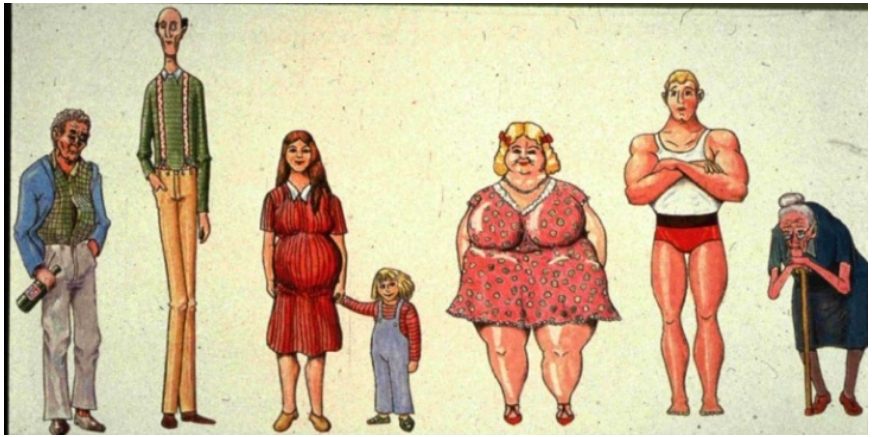
- BMI
- Inflammatory burden
- ADAs
- Serum albumin
- Concomitant antimetabolite administration
- Disease type (UC vs CD)
- Interactions?
- Others?

1. Khanna R et al Aliment Pharm and Therapeutics.

Inter- and intra-individual differences

- Different factors can influence the PK of a drug
  - Patient related factors (e.g. gender and BMI)
  - Disease related factors(e.g. type, location and severity)
  - Drug related factors (e.g. dosing schedule, synergism and immunogenicity)

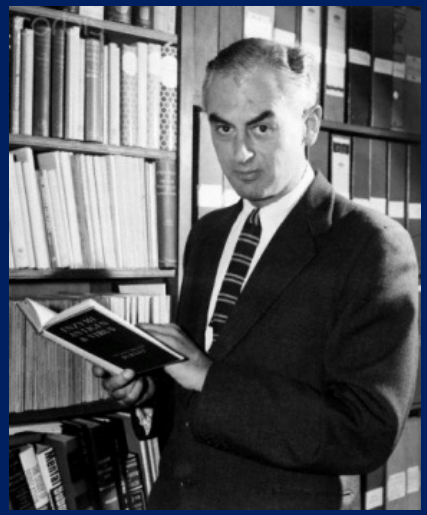
→ affect overall drug exposure



Lobo ED, et al. *J Pharm Sci* 2004;93(11):2645-68

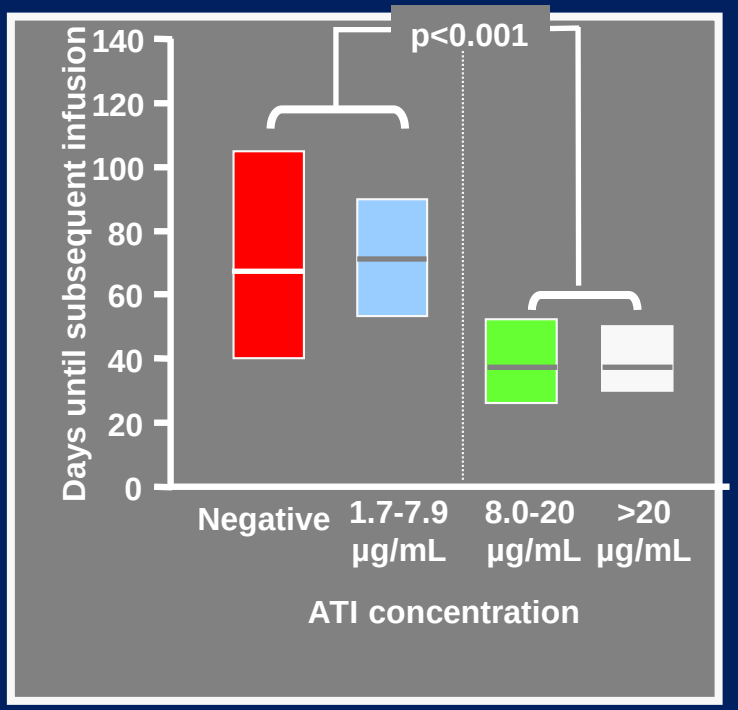
Sir Peter Medewar: Tolerance vs Sensitization

- Foreign proteins are immunogenic
- T cells recognize the three dimensional shape of foreign antigens
- Multiple determinants are present: genetics, route of administration, disease state, MW, concomitant treatment, exposure schedule, antigen dose
- There are no “murine” amino acids
- Cell line of origin is not a principal determinant

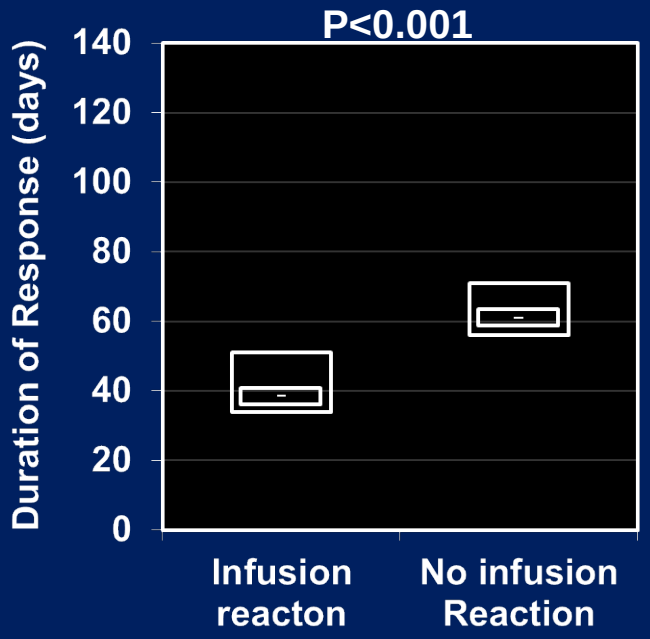


Effect of ATI Concentration and Infusion Reactions of Duration of Response During *Episodic* Dosing

ATI titre before an infusion



Infusion reaction

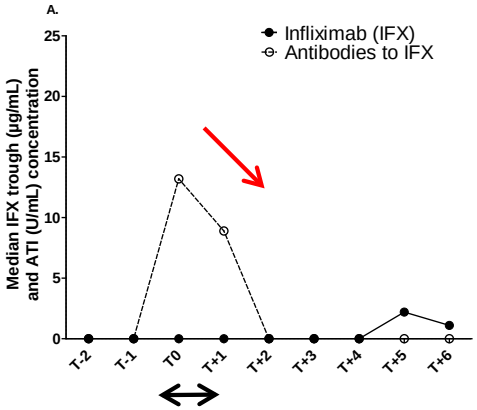


Baert F *et al.* N Engl J Med 2003;348:601-8.

Antibodies to infliximab (ATI)

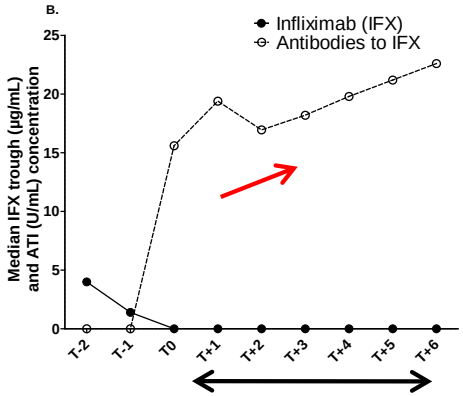
1,232 serum samples / 90 IBD patients

Transient ATI (N=15)



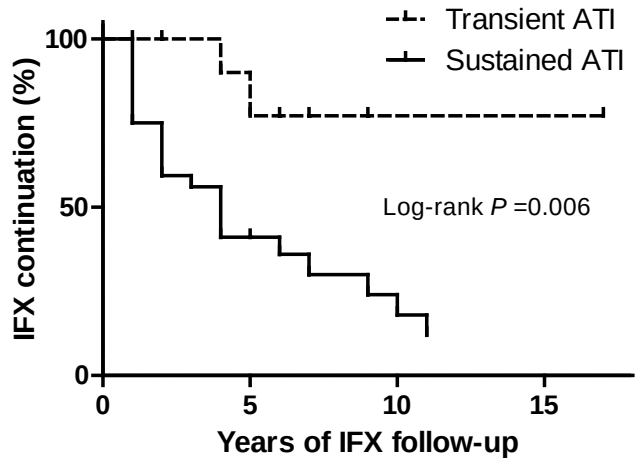
17 weeks [9-60]

Sustained ATI (N=38)



45 weeks [20-115]

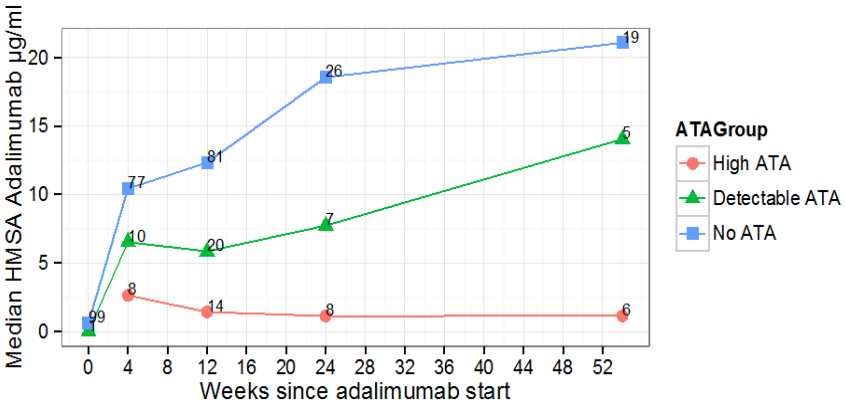
Loss of response and/or hypersensitivity



Vande Casteele N, *et al. Am J Gastroenterol* 2013;108(6),962-71

Antibodies to adalimumab (ATA)

536 serum samples / 148 CD patients



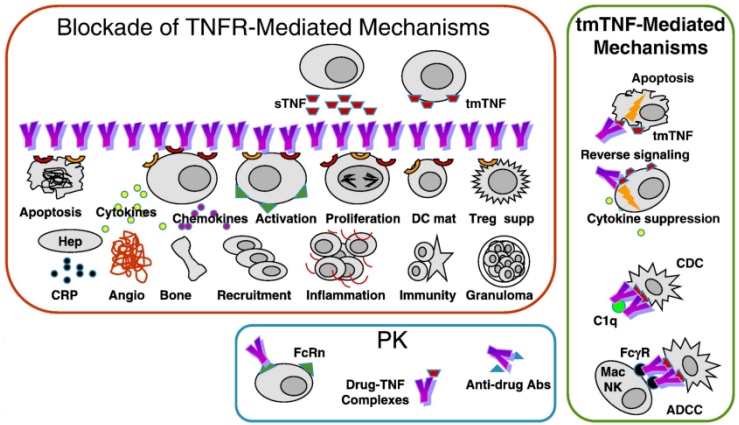
- ATA detected in 20% of patients
- Loss of response in ATA+ patients (OR 3.1 95% CI 1.0 – 9.1)
- Risk factors for ATA formation:
  - Week 4 adalimumab <5 µg/mL
  - No concomitant IMM

Baert F, *et al. Gut* 2016

Pharmacodynamics of anti-TNF's

Concentration of drug at proximity of the biological receptor determines the magnitude of the pharmacological response

Anti-TNF therapies



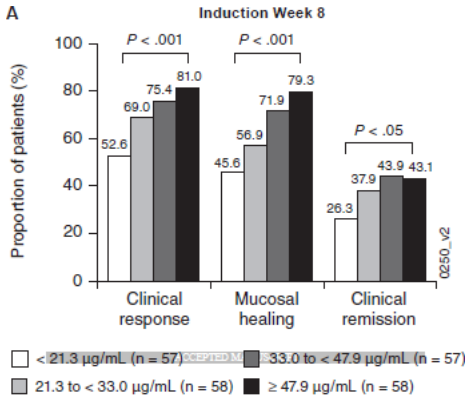
Adapted from Tracey D, *et al. Pharmacol Ther* 2008;117(2):244-79

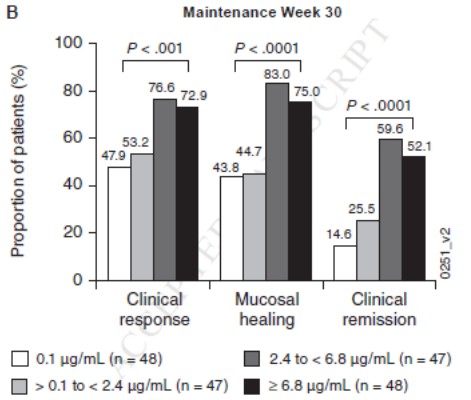
Exposure-response relationship (IFX-UC)

Post hoc analysis ACT 1 & 2

- 242 patients with UC
- IFX 5 mg/kg at weeks 0-2-6
  - 5 mg/kg every 8 weeks

- IFX trough concentration quartile analysis





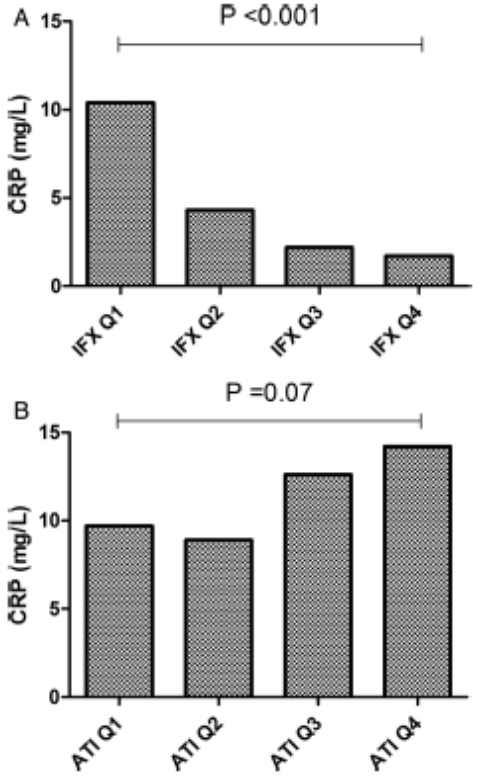
Adedokun OJ, *et al. Gastroenterology* 2014 [Epub ahead of print]

Exposure-response relationship (IFX-CD)

COMBINED study

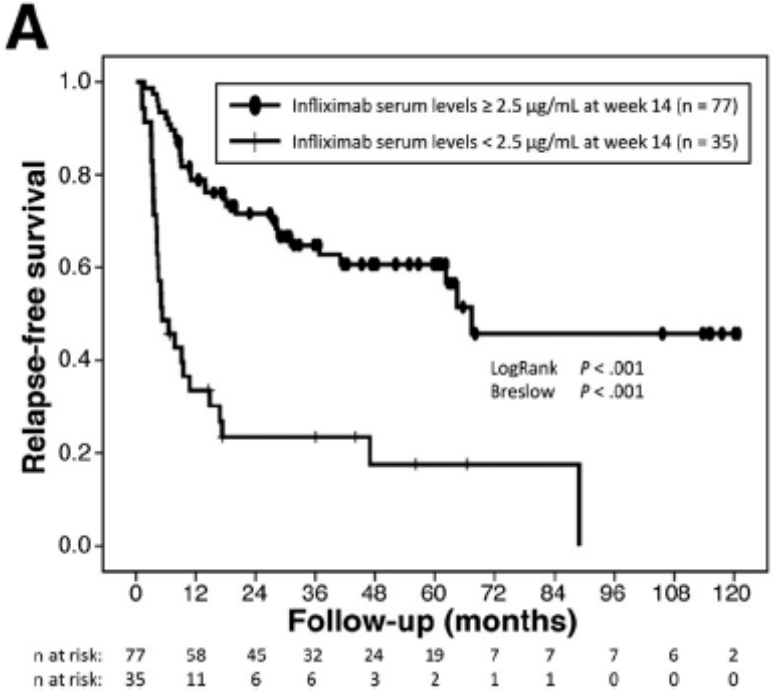
- 483 patients with CD
- 4 trials – 1487 samples
- Maintenance IFX

- Quartile analysis
  - IFX
  - ATI
- Remission (CRP ≤5 mg/L)
  - ROC analysis IFX >2.79 µg/mL



Vande Casteele N, *et al. Gut* 2015

Infliximab TC - induction

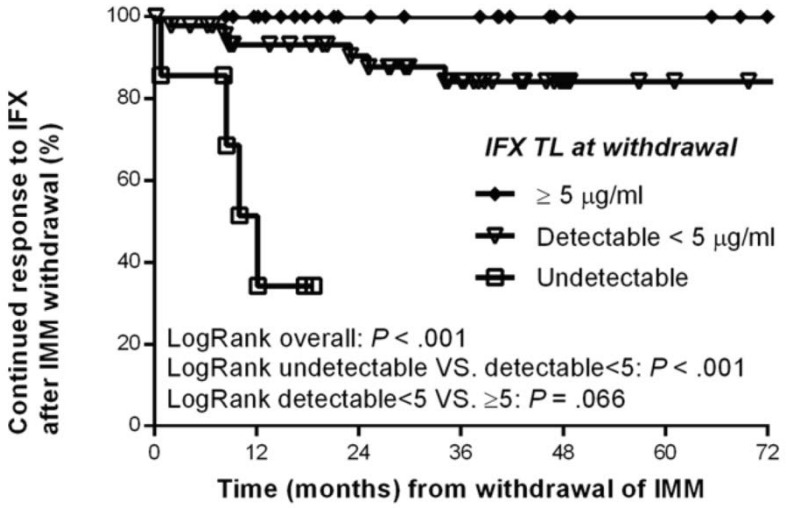


- 285 patients with UC on maintenance IFX
- Median follow-up of 5 yrs
- IFX trough concentration at week 14 associated with
  - Relapse-free survival
  - Colectomy-free survival

Arias M, *et al. Clin Gastroenterol Hepatol* 2015;13:531-538

Infliximab TC - maintenance

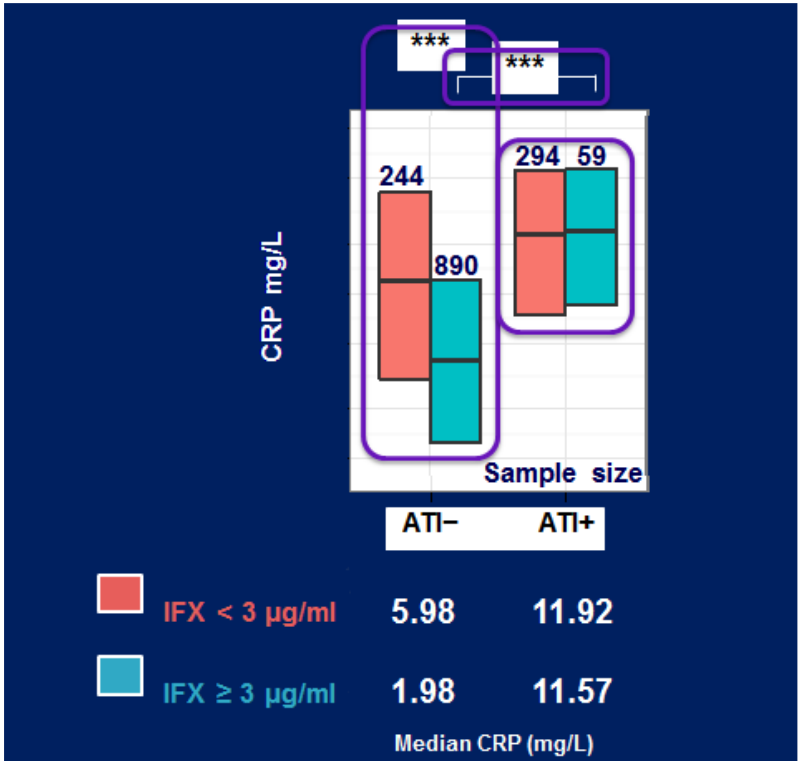
- 223 CD patients on maintenance IFX
  - 158 on combo treatment
  - 65 on monotherapy
- IFX trough concentration at time of IMM withdrawal predicted clinical outcome



Adapted from Drobne D., *et al.* Clin Gastroenterol Hepatol 2015

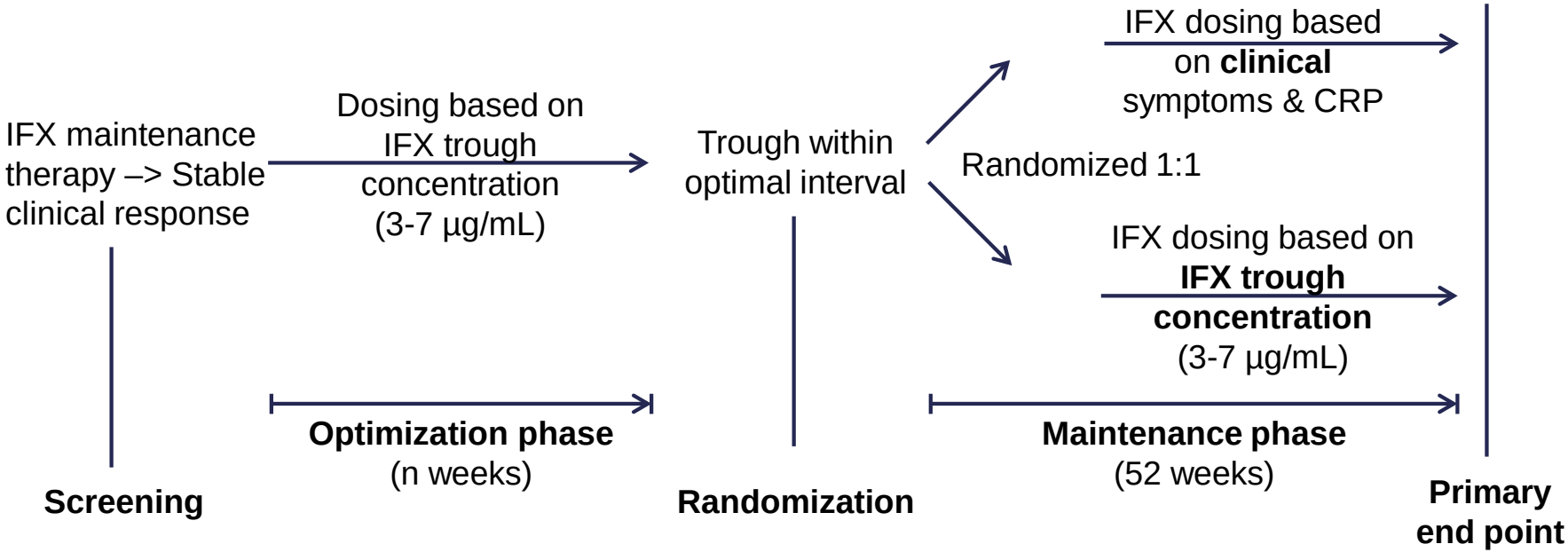
Univariate IFX, ATI & CRP Analyses

- Median CRP significantly lower in ATI− serum samples with IFX ≥3 µg/ml
  - *P*<0.0001
- ATI+ serum samples: High median CRP independent of IFX
- Even for high IFX, median CRP significantly higher in ATI+ vs. ATI−
  - *P*=0.0002



Vande Castlile N et al Gut 2015

Study outline TAXIT

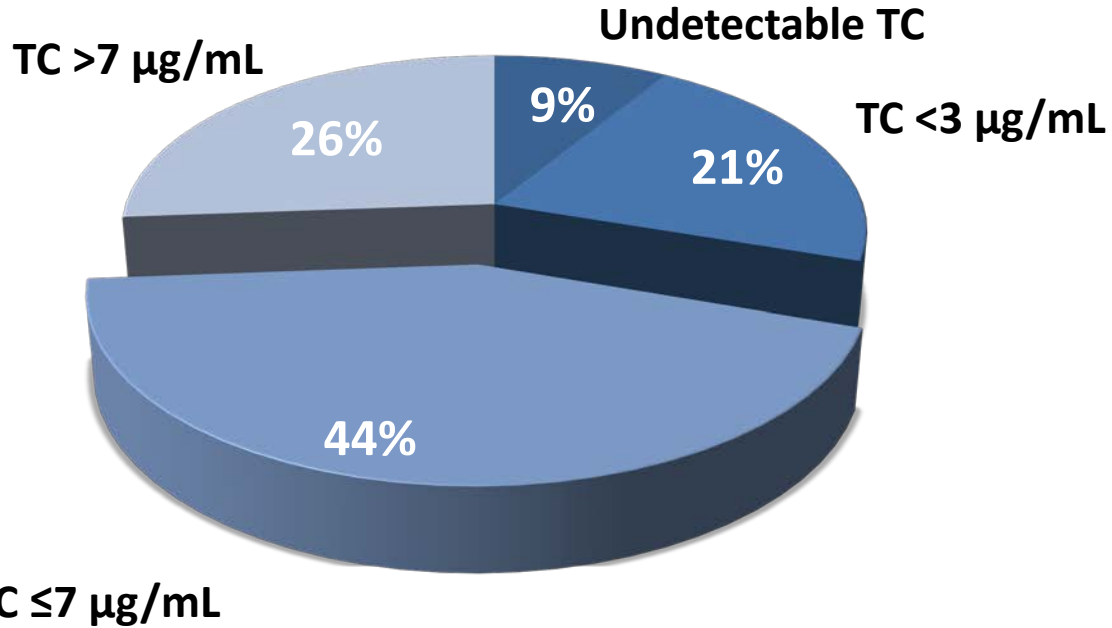


Primary endpoint = rate of clinical (Harvey-Bradshaw or Partial Mayo score) **and biological**
(C-reactive protein ≤5 mg/l) **remission one year after randomization in each group**

Vande Casteele N, *et al. Gastroenterology* 2015; 148(7):1320-1329.e3.

Proactive TDM – TAXIT trial

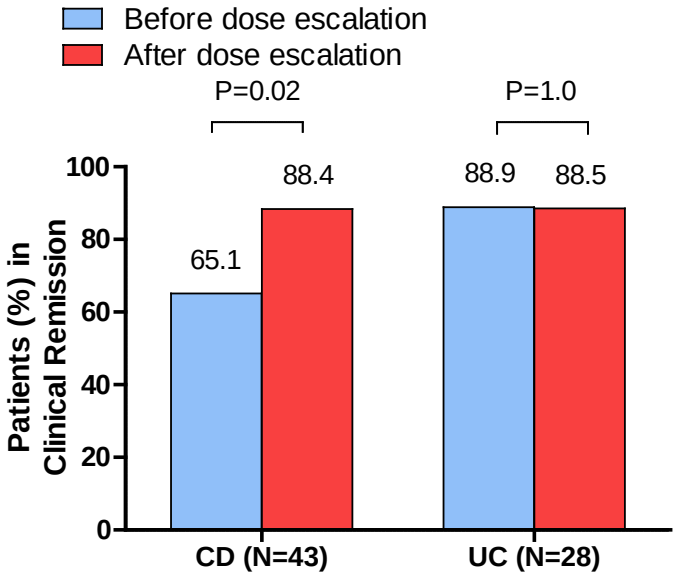
Infliximab trough concentration (TC) **at screening** (N=275)

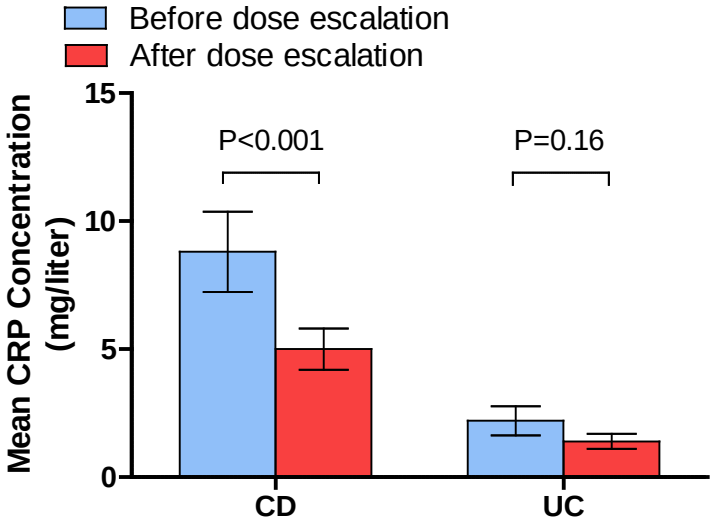


Vande Casteele N, *et al. Gastroenterology* 2015; 148(7):1320-1329.e3.

Optimization phase

Dose escalation



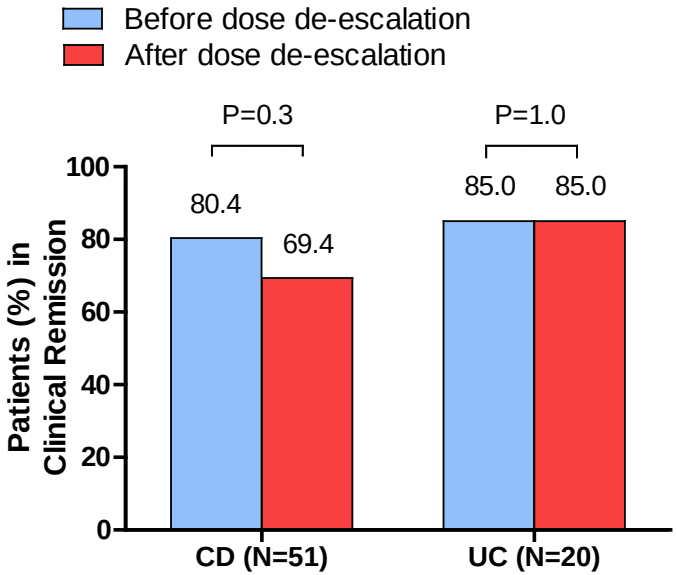


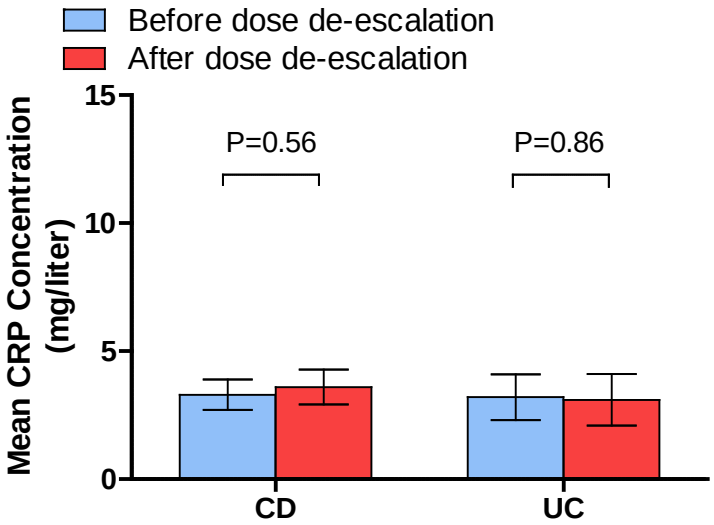
Dose escalation in Crohn's disease patients with subtherapeutic levels results in better disease control

Vande Casteele N, *et al. Gastroenterology* 2015; 148(7):1320-1329.e3.

Optimization phase

Dose reduction





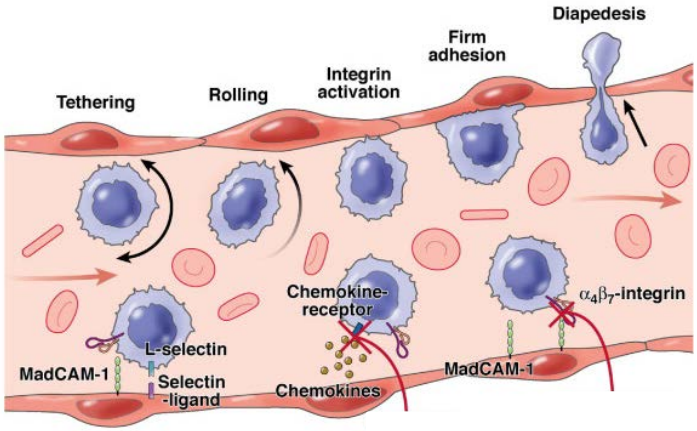
Succesful dose reduction of patients with supra-therapeutic levels whilst retaining disease control results in 28% decreased drug cost

Vande Casteele N, *et al. Gastroenterology* 2015; 148(7):1320-1329.e3.

Pharmacodynamics of anti-integrins

Concentration of drug at proximity of the biological receptor determines the magnitude of the pharmacological response

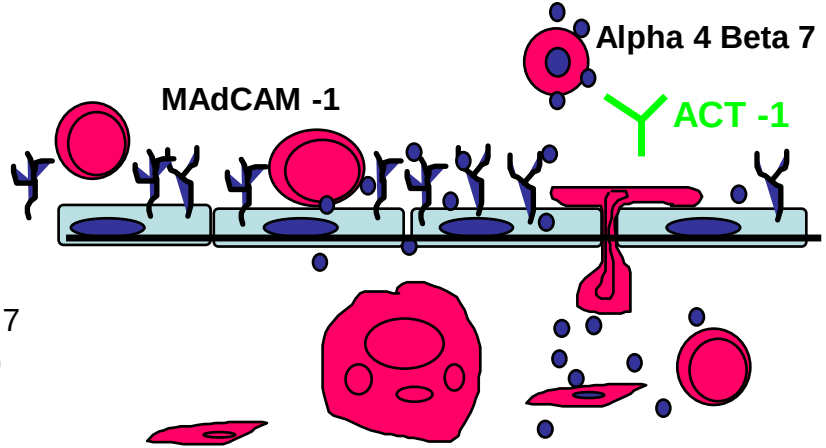
Anti-adhesion therapies

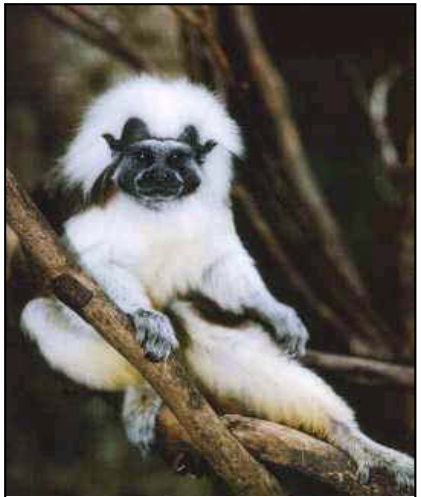


Adapted from Rutgeerts P, *et al. Gastroenterology* 2009;136:1182-97

Background

- Ligand for $\alpha_4\beta_7$ is MAdCAM
- Animal models show that ACT-1 selectively blocks trafficking of $\alpha_4\beta_7$ positive lymphocytes to the gut
- Raises possibility of gut specific immune modulation
- Striking benefit in cotton-top tamarin model

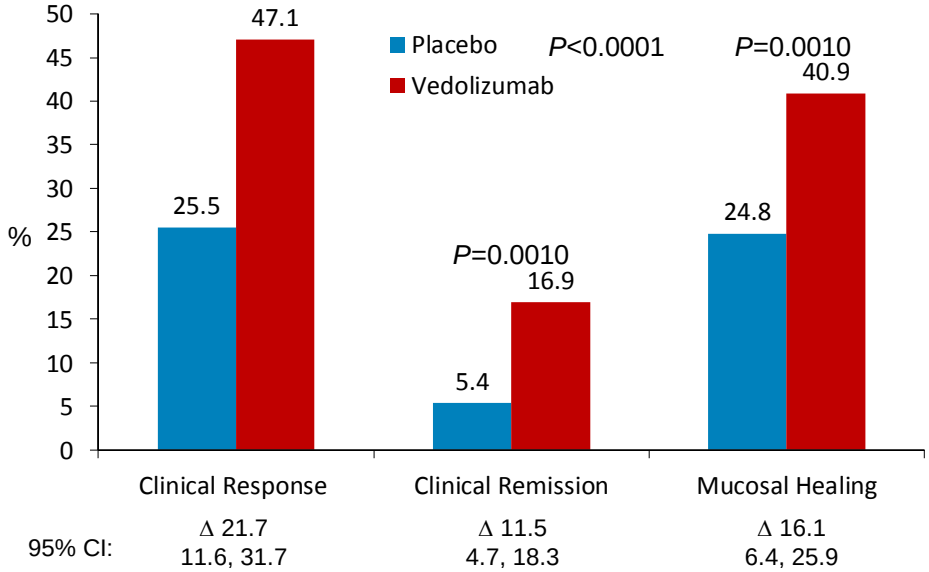




Hesterberg PE et al. *Gastroenterology* 1996;111:1373-80

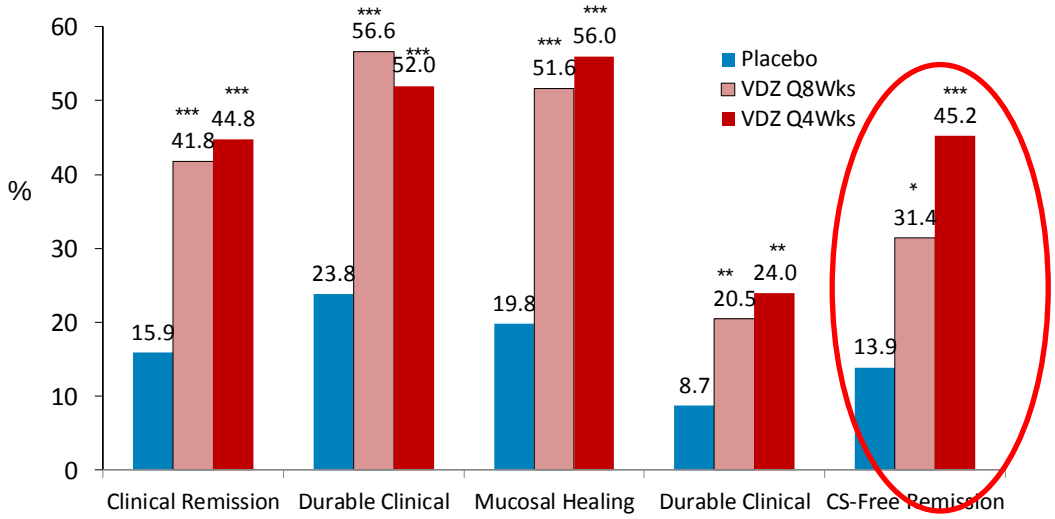
Podolsky et al. *JCI* 1993;92:372-80

GEMINI: Outcomes for Induction (Week 6)



Feagan BG et al. N Engl J Med. **2013** Aug 22;369(8):699-710

GEMINI: Maintenance Therapy



*P<0.05. **P<0.01. ***P<0.0001

Δ26.1
Δ29.1

Δ32.8
Δ28.5

Δ32.0
Δ36.3

Δ11.8
Δ15.3

Δ17.6
Δ31.4

Feagan BG et al. N Engl J Med. **2013** Aug 22;369(8):699-710

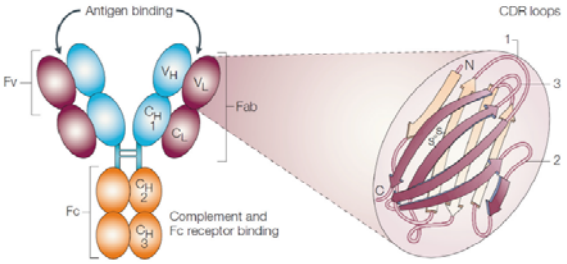
Primary and Secondary properties

Optimized amino acid sequence (Fc)

- ✓ Point mutations in FcγR motif at Leu^{239} and Gly^{241} by Ala
- ✓ Reduces binding of VDZ to FcγR

Half-life infliximab ≈ 8 to 9.5 days
Half-life adalimumab ≈ 14 days
Half-life vedolizumab ≈ 25.5 days

Monoclonal antibodies



Adapted from Brekke OH & Sandlie I. *Nat Rev Drug Discov* 2003;2(1):52-62

Effector functions

- ✓ Complement (C1)
- ✓ FcγR
  - Phagocytosis
  - Endocytosis
  - Antibody-dependent cytotoxicity (ADCC)
  - Cytokine release
- ✓ FcRn

Wyant T, *et al. mAbs* 2013;5(6):842-50

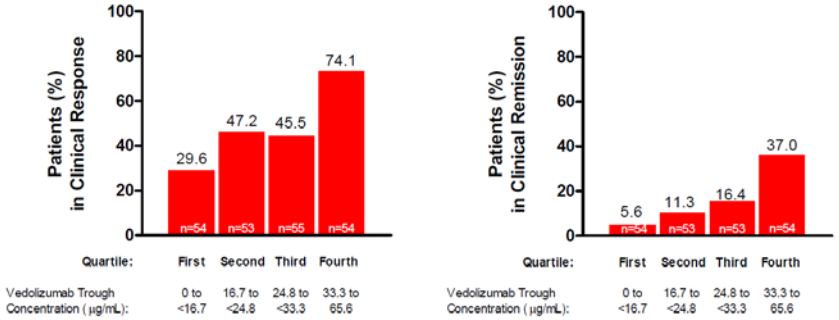
Exposure-response relationship (VDZ-UC)

GEMINI 1

- 225 patients with UC
- VDZ 300 mg IV at week 0-2

- VDZ trough concentration quartile analysis at <u>week 6</u>

Induction trial – week 6



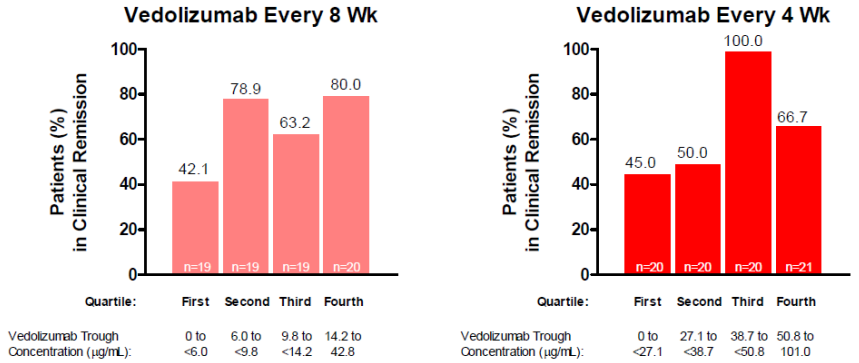
Feagan BG, *et al. N Engl J Med* 2013;369(8):699-710

Exposure-response relationship (VDZ-UC)

GEMINI 1

- 247 patients with UC
- VDZ 300 mg IV
  - q8 weeks (N=122)
  - q4 weeks (N=125)
- VDZ trough concentration quartile analysis at week 46
- Clinical remission week 52
- **95% saturation of $\alpha_4\beta_7$**

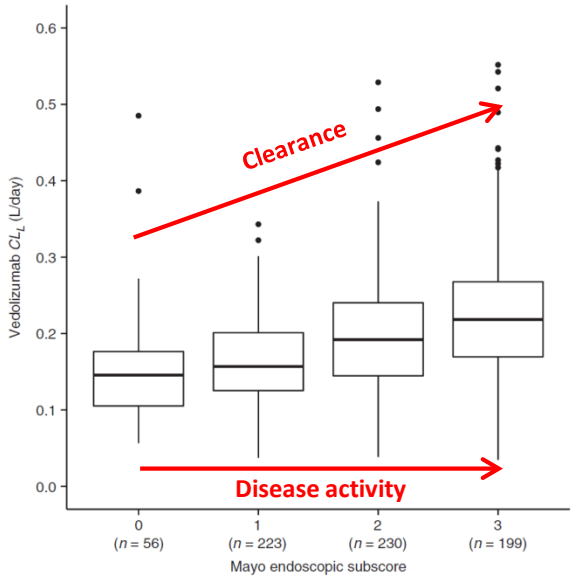
Maintenance trial



Feagan BG, *et al. N Engl J Med* 2013;369(8):699-710

PK-PD analysis VDZ in UC

Week 6

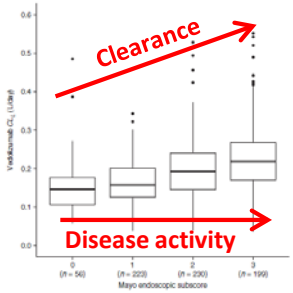


- VDZ CL_L estimates by Mayo endoscopic subscore
- CL_L 25% higher for patients with endoscopic subscore of 3 *vs.* 0[1]
- Potentially influenced by protein losing enteropathy[2]

[1] Rosario M., *et al. Aliment Pharmacol Ther* 2015 [Epub ahead of print]; [2] Beeken WL, *et al. Gastroenterology* 1972;62(2):207-15

Adapted from [1] Rosario M., *et al. Aliment Pharmacol Ther* 2015 [Epub ahead of print]:

In Summary



CL of MA increased during high inflammatory state:
- Catabolic pathway upregulated (RES)
- Target mediated degradation upragulated (membrane bound antigen)

Also **Ka** and **V** can be influenced by inflammatory state

Measure for disease activity:
- Direct
  - Endoscopic activity
  - Disease questionnaire
- Indirect
  - C-reactive protein
  - Fecal calprotectin

PD
(disease state)

PK
(exposure)

Measure for drug exposure:
- Serum drug concentration
  - Peak
  - Intermediate
  - Trough
  - Area under curve
- Tissue drug concentration

✓ **Anti-TNF: concentration – effect relationship** [2]

? **Anti-integrin: minimal effective concentration** [1]

Receptor saturation when vedolizumab > 1µg/mL[1]

Depending on mechanism of action:
- Measure receptor occupancy

[2] Vande Casteele N, *et al. Gastroenterology* 2015; 148(7):1320-1329.e3.

So How Do I Apply this Clinically?

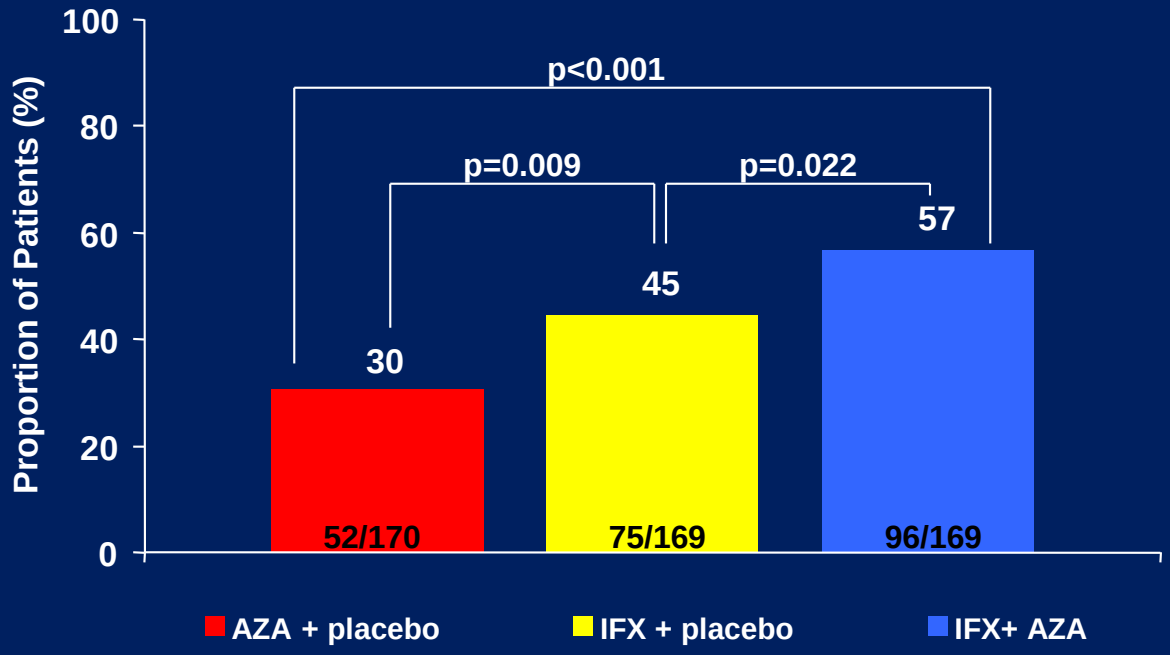
- Therapeutic drug monitoring in non- responders
- Combination therapy
- Dose intensification in severe UC

Feagan BG, *et al. N Engl J Med* 2013;369(8):699-710

High Risk Patients Should be Considered for Early Treatment with Combined Therapy

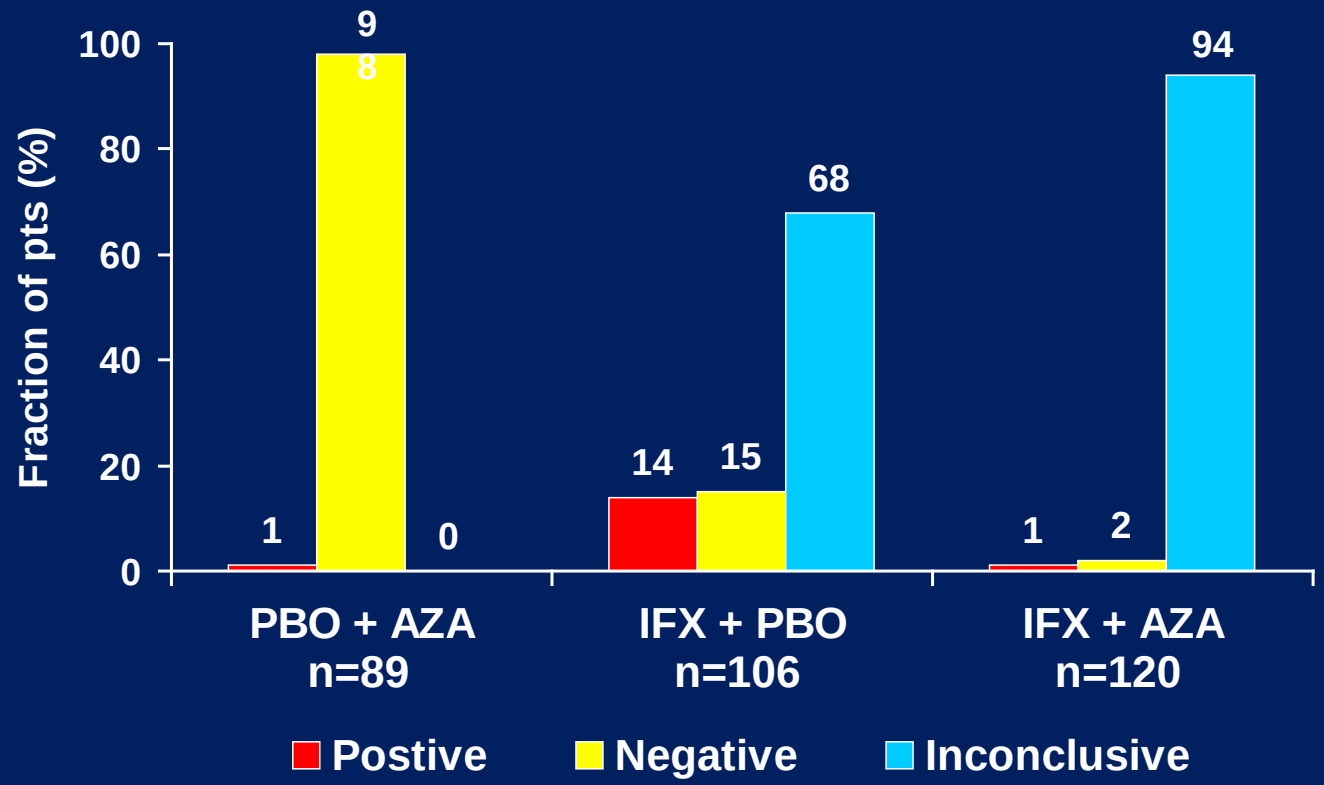
- Complex fistula
- Deep ulceration on endoscopy
- Young age
- Steroid-dependence\resistance
- High risk anatomy (foregut disease, extensive disease, perianal disease)
- Severe disease activity (weight loss, low albumin, Hgb)

SONIC



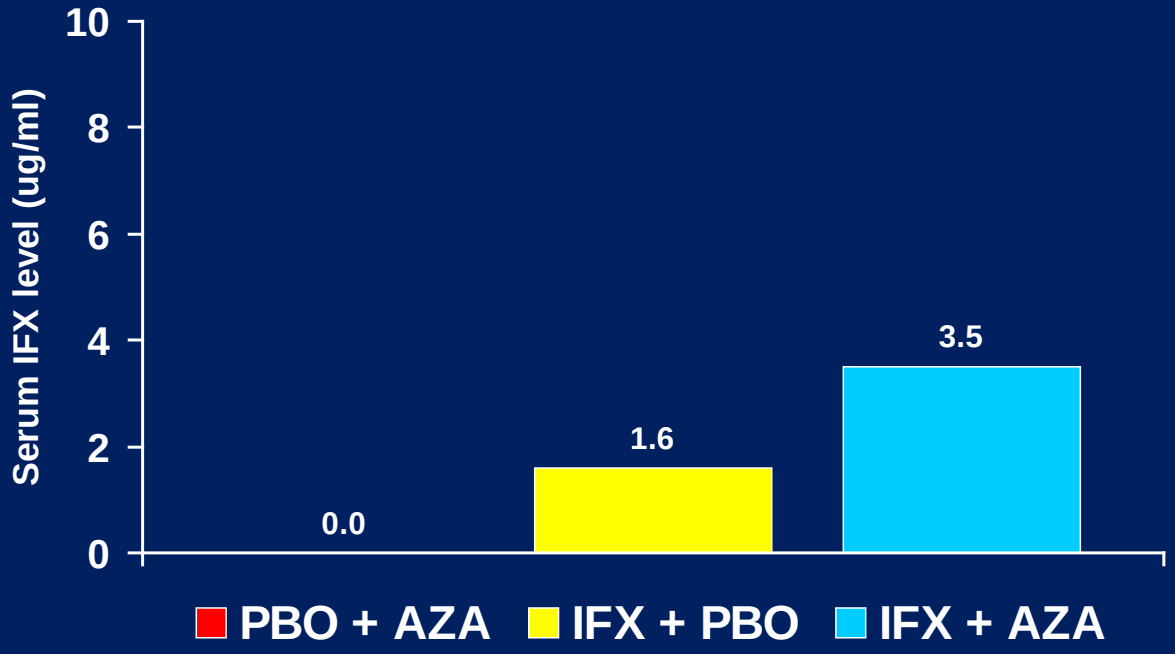
Colombel JF. et al.; . N Engl J Med. 2010 Apr 15;362(15):1383-95.

Immunogenicity Status at Week 30



Colombel JF. et al.; . N Engl J Med. 2010 Apr 15;362(15):1383-95.

SONIC:Trough Levels at Week 30



Colombel JF. et al.; . N Engl J Med. 2010 Apr 15;362(15):1383-95.

Value of Measuring Infliximab Drug Concentrations and Antibodies[1]

- Retrospective review Mayo Clinic 2005-2008 in 155 patients
- Indication
  - Loss of response (50.3%)
  - Partial response after initiation (22.6%)
  - Adverse event (14.8%)
- Results changed treatment in 73.4%
- ATIs in 22.6%
- ATIs present - change to another TNF agent- complete or partial response - 91.6%
- Sub-therapeutic level -increased dose vs. change to another anti-TNF- 86.2% vs. 40% (P<0.048)
- Patients with clinical symptoms and therapeutic infliximab levels were: continued at the same dose 70.8% of the time (95%CI:49-87%) and had no evidence of active inflammation by endoscopic/radiographic assessment 61.9% of the time (95%CI:38-82%)

1. Afif et al American J Gastro 2010.

Conclusions

- Benefits of such anti-TNF monitoring to asymptomatic patients requires further study
- Treatment paradigms in symptomatic patients:

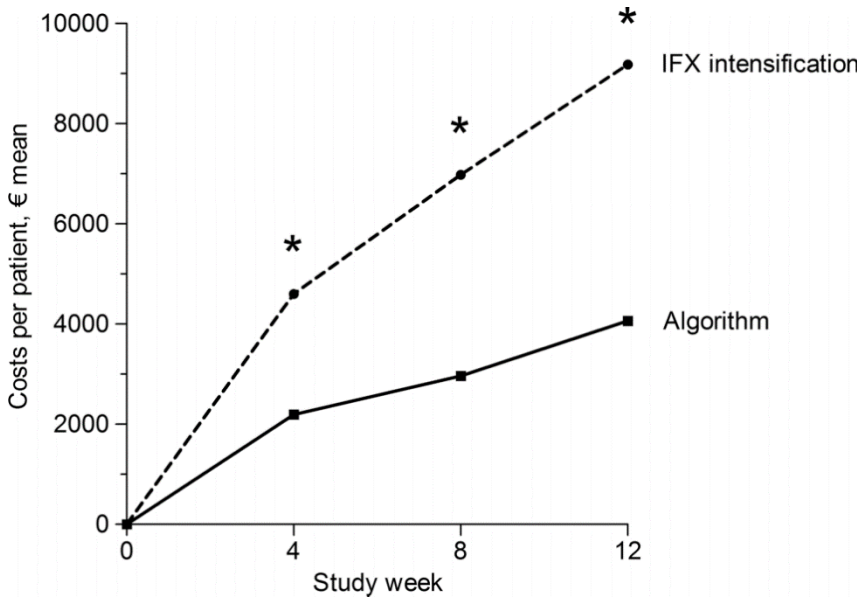
	ATI−	**ATI+**
IFX < threshold	Increase dose	Switch (high ATI) or Dose optimize (low ATI)
IFX ≥ threshold	Check endoscopy or Switch	Switch (high activity) or Monitor (low activity)

Reactive TDM: RCT

- ✓Response rates at week 12
  - Control group 53%
  - Algorithm group 58%

    P=0.81
- ✓Cumulative cost at week 12
  - Control group € 9,178
  - Algorithm group € 6,038

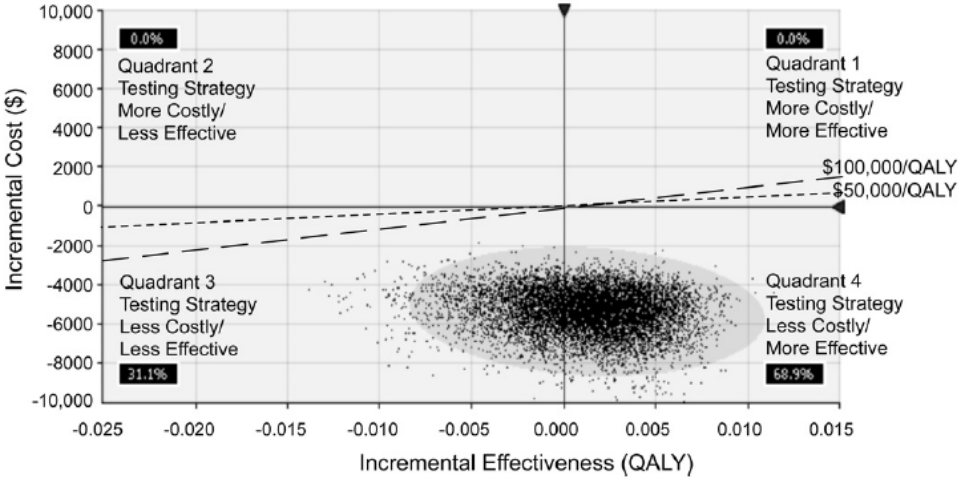
    P<0.001



Steenholdt C, *et al. Gut.* 2014;63(6):919-27

Reactive TDM: Decision analysis

- TDM-guided treatment strategy dominated empiric dose escalation (numerically lower costs, and similar but higher QALY)
- Similar rates of remission (63% vs 66%) and response (28% vs 26%) were achieved through differential use of available interventions
- The testing-based strategy resulted in a higher percentage of surgeries (48% vs 34%) and lower percentage use of high-dose biological therapy (41% vs 54%)
- Stable across multiple sensitivity analyses with variable model inputs



Velayos FS *et al. Clin Gastroenterol Hepatol.* 2013;11:654–666

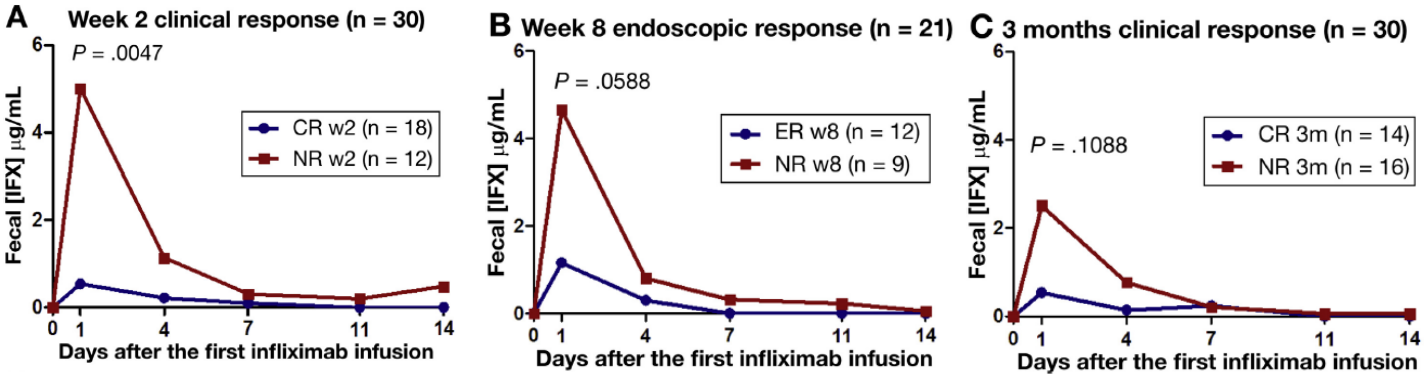
Dose Intensification in Severe UC?

- Severe UC is still associated with high colectomy rates in the modern era
- Low IFX drug concentrations are observed in these patients because of high drug clearance – associated with increased risk
- CRP reflects TNF burden – short half life
- Biomarker for drug effect
- Monitoring with dose intensification vs. Empiric high dose therapy ?

Feagan BG, *et al. N Engl J Med* 2013;369(8):699-710

Loss of Infliximab Into Feces Is Associated With Lack of Response to Therapy in Patients With Severe Ulcerative Colitis

Johannan F. Brandse,[1,2] Gijs R. van den Brink,[1,2] Manon E. Wildenberg,[2] Desiree van der Kleij,[3] Theo Rispens,[4] Jeroen M. Jansen,[5] Ron A. Mathôt,[6] Cyriel Y. Ponsioen,[1] Mark Löwenberg,[1] and Geert R. A. M. D'Haens[1]



Brandse J. et al, Gastroenterology 2015; 350-55

Conclusions

- PK\PD relations are important for monoclonal antibody therapy
- Multiple determinants of PK exist
- Immunogenicity is an important issue for most drugs
- TDM is an emerging technology that will likely facilitate precision medicine
- Clinical examples of the benefits of understanding PK\PD relationships include understanding the value of combination therapy, making informed decisions in patients with loss of response to TNF antagonists,and management of patients with severe colitis.