Què podem fer quan la colitis ulcerosa crònica contínua se'ns resisteix? I què podrem fer?

Ingrid Ordás
Hospital Clínic Barcelona

XXIII Congrés de la SCD

INTRODUCTION

- **Chronic active** UC is associated with:
  - significant **morbidity**
  - increased **CCR risk**
  - **disability**, loss of **productivity** and increased **cost**
- Up to **18%** of patients suffer **chronic active** disease
- **30%** requiring **colectomy** at 10 years
- Management of these patients is **challenging**

Optimize Management

- ✧ Ensure maximal dose and correct topical formulation
- ✧ Combine oral and topical 5-ASA
- ✧ Appropriate CS tapering regime (prevent relapse)
- ✧ Adequate weight-based dose thiopurines
- ✧ Is there a role for methotrexate / leukocytapheresis?
- ✧ Anti-TNF Therapy: Drug Levels | Antidrug Antibodies

Principle of managing chronic unremitting UC

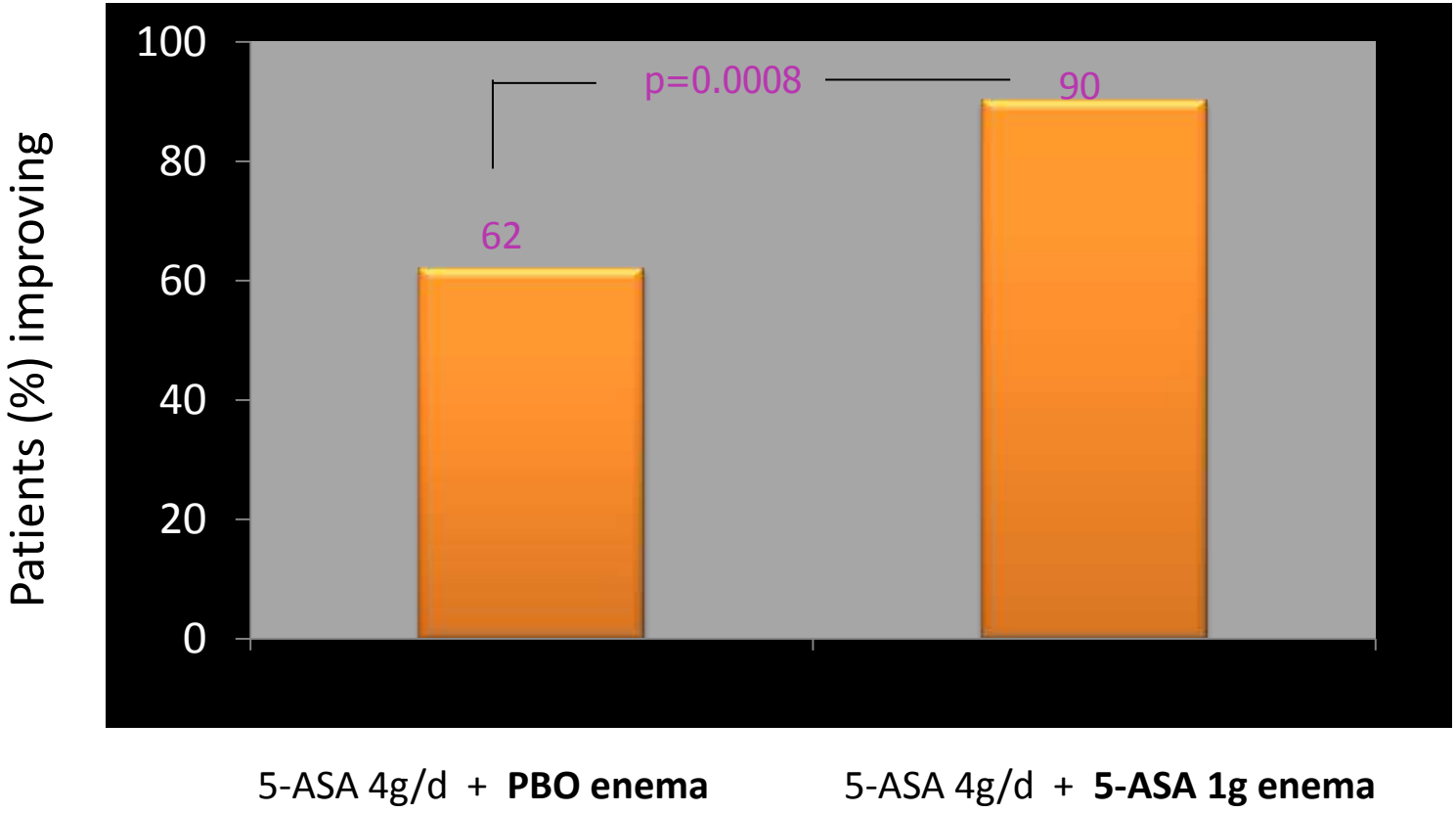
It should be standard practice to **confirm** disease activity **endoscopically before** considering **treatment escalation**

Adherence

- Adherence rates to mesalazine 60-70%
- Non-adherence is associated with
  - increased **risk of relapse**
  - **reduced quality of life**
- **Risk factors** for non-adherence
  - **male** (67%*vs* 52%, $p < 0.05$)
  - **single** (68%*vs* 53%, $p = 0.04$)
  - disease limited to the **left side** *vs* pancolitis (83%*vs* 51%, $p < 0.01$)

Kane S et al. Am J Gastro 2001

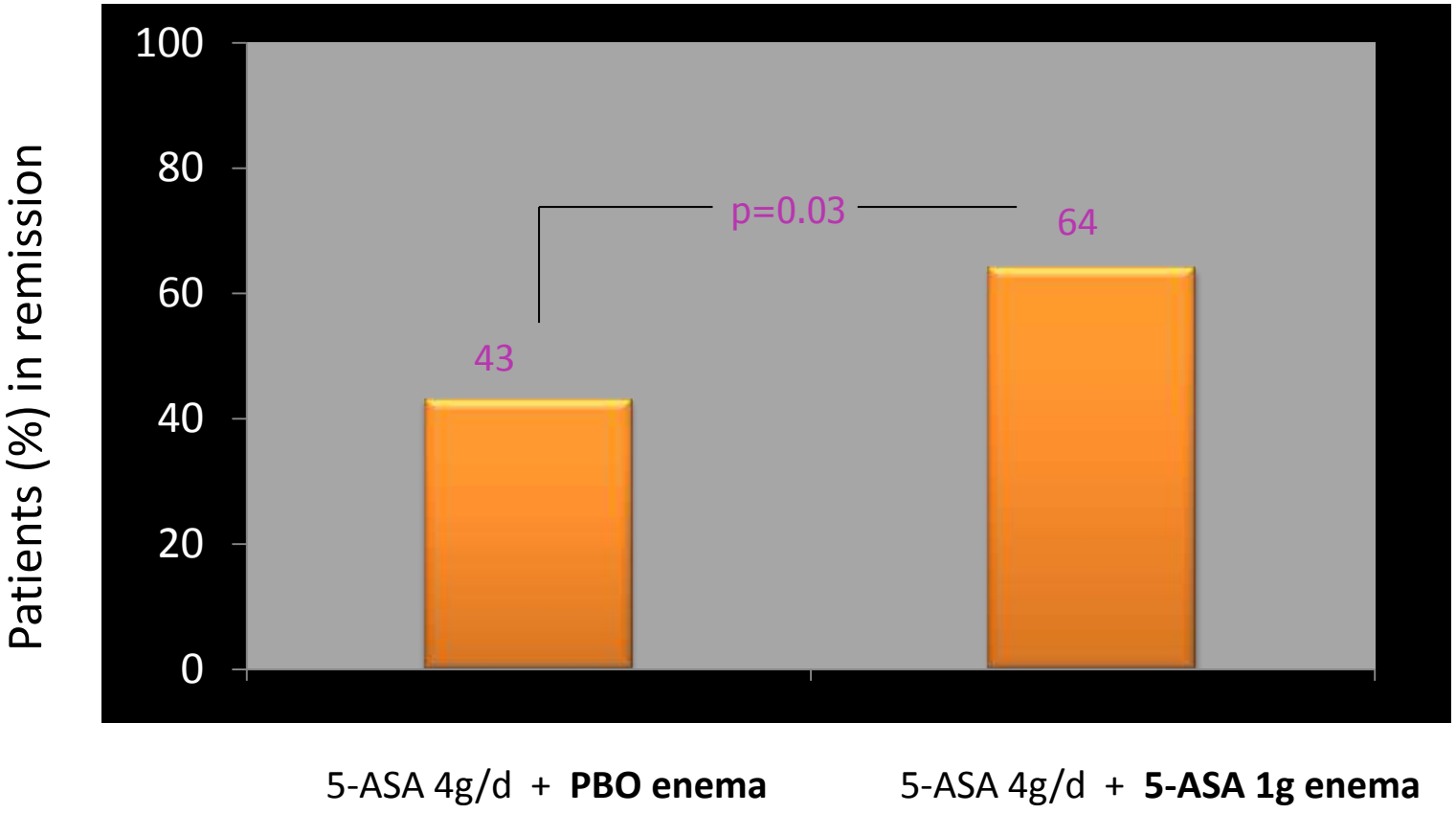
Optimizing Therapy in **Extensive** Mild/Moderate UC
Benefit of **Combining Oral and Topical** 5-ASA



patients (%) with **clinical improvement** after 4 weeks of treatment

Marteau P et al. Gut 2005

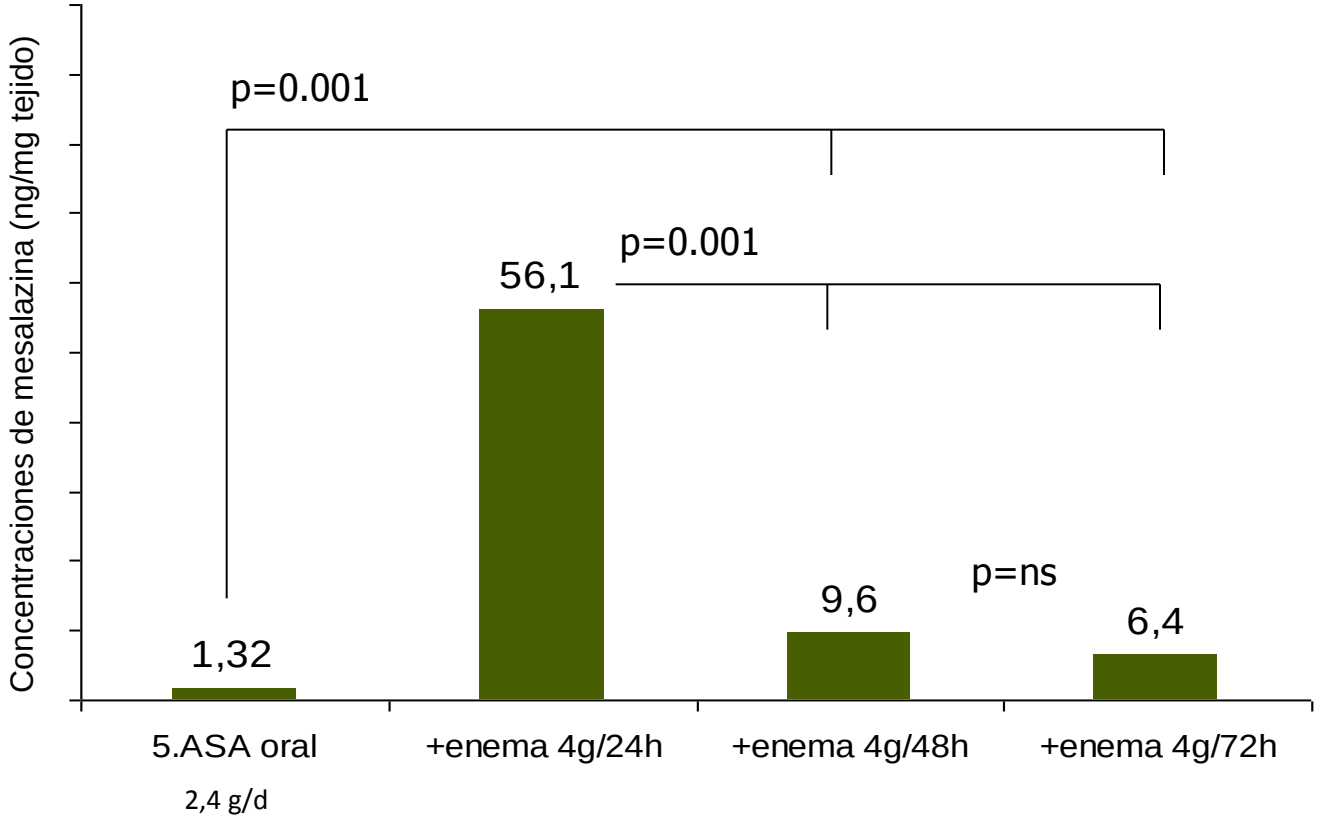
Optimizing Therapy in **Extensive** Mild/Moderate UC
Benefit of **Combining Oral and Topical** 5-ASA



patients (%) achieving **clinical remission** after 8 weeks of treatment

Marteau P et al. Gut 2005

[Mesalazine] in rectal mucosa in UC patients treated with 5-ASA oral monotherapy vs. combined with 5-ASA enema



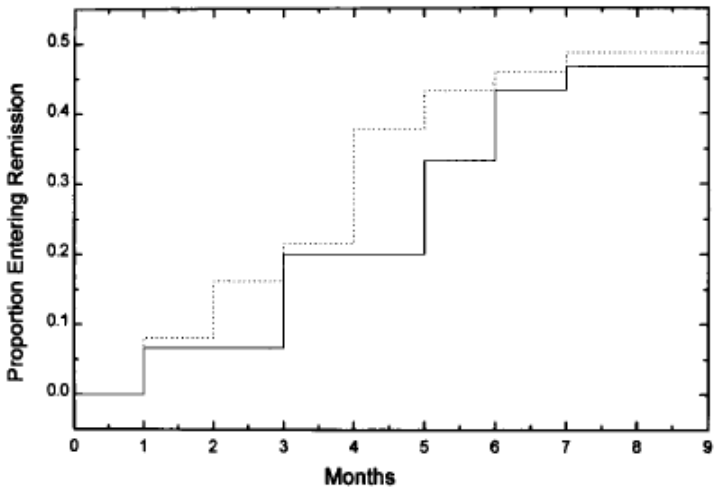
Pimpo MT et al. JCC 2010

Methotrexate in UC

- MTX proved efficacy in CD (25 mg/week i.m.)
- Data in UC is scarce
- One RCT has been negative with **oral** MTX
  - MTX 12,5 mg/week (N=30)
  - PBO (N=37)

Oren R et al. Gastroenterology 1996

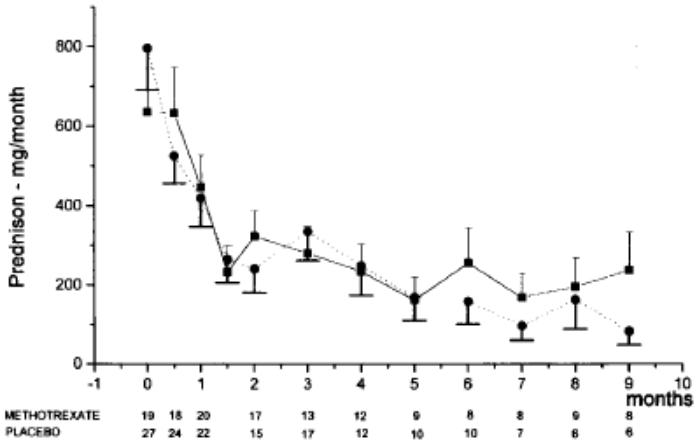
Methotrexate in UC



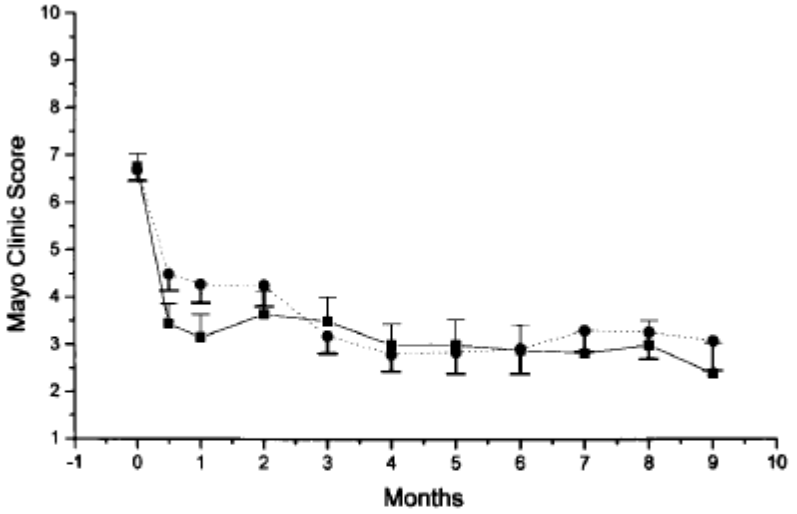
Cumulative proportion of patients entering remission in both groups; MTX group (….), PBO (---)

Table 2. Follow-up During Study

	Placebo group	Methotrexate group	*P* value
Completed the 9 months of study	25	23	0.411
Dropouts	9 (0.5, 1, 2, 2, 2, 3, 3, 5, 6)	2 (1, 7)	0.052
Treatment failure	2 (3, 3)	3 (3, 5, 8)	0.476
Withdrawal because of side effects	1 (0.5)	2 (2, 5)	0.465
Total	37	30	



Monthly steroid dose throughout the study (■MTX •PBO)

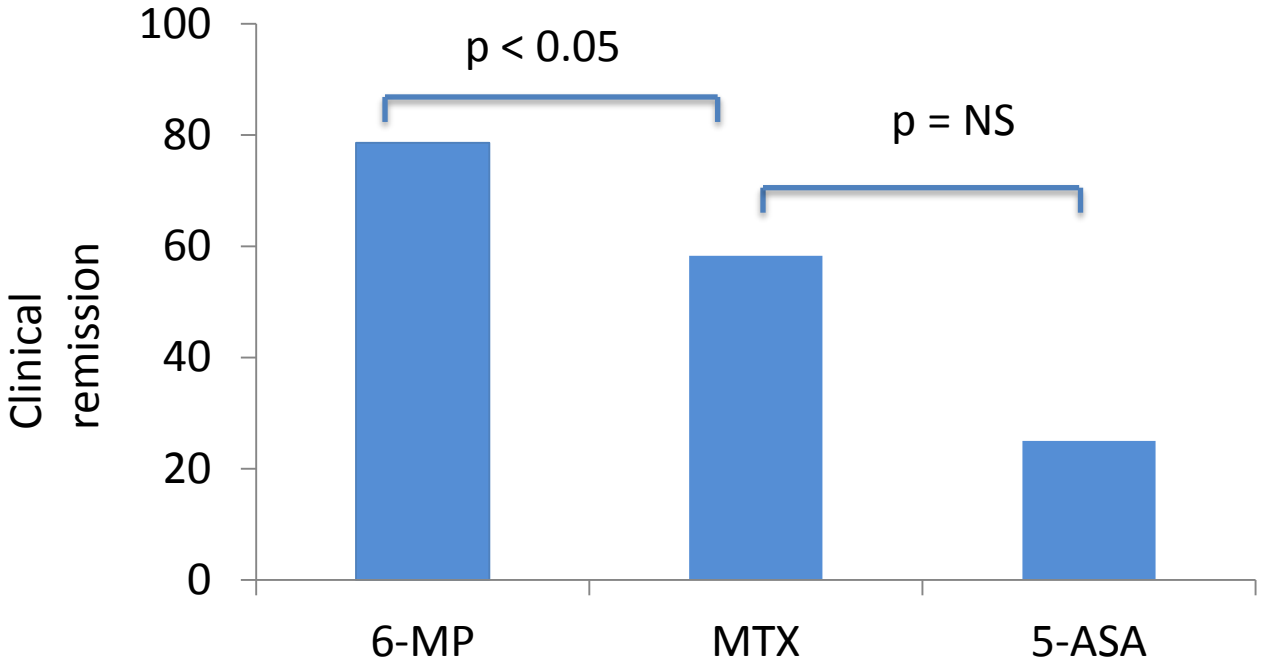


Monthly clinical disease activity (Mayo clinical score)
■MTX •PBO

Oren R et al. Gastroenterology 1996

Methotrexate in UC

34 UC patients receiving treatment with PDN
Randomly assigned (2:2:1) to additionally receive, orally (30 weeks):
6-MP [1.5 mg/kg/day] vs. MTX [15 mg/week] vs. 5-ASA [3 g/day]



Mate-Jimenez et al. Eur J Gastroenterol and Hepatol 2010

Spanish Multicentric Study on Clinical Use and Efficacy of MTX in UC

- **AIM:** To evaluate the efficacy and safety of MTX in UC patients.

- **PATIENTS AND METHODS:** 40 patients (70% steroid-dependency, 27% steroid refractoriness) Therapeutic success was defined as the **absence** of UC-related **symptoms**, **steroid withdrawal** and **no** requirement of **rescue therapies** within the first **6 months after** starting MTX

- **RESULTS:**
  - Previously treated with Thiopurines 87,5%
  - Median dose for induction 25mg/wk parenterally
  - **45%** met criteria for **therapeutic success**
  - Cumulative probability of maintaining **steroid-free** clinical **remission**
    - **60%** (6 months), **48%** (12 months), **35%** (24 months) after starting MTX
  - 27.5% experienced adverse events (MTX discontinuation in only 8)

- **CONCLUSIONS:** MTX appears to be **effective to maintain clinical remission in UC** (at least in the short-term) with an acceptable safety profile.

Mañosa M et al. JCC 2011

Controlled, Randomised, Double-Blind, Multicenter Study, Comparing **Methotrexate vs Placebo** in Steroid-Dependent UC (METEOR)

- **PHASE II** | Multicenter, **randomized**, double-**blind** study
- **INCLUSION** CRITERIA: Steroid-dependent ulcerative colitis
- **OBJECTIVES**: To show superiority of MTX vs PBO in inducing steroid-free remission in steroid-dependent UC
- **STUDY TREATMENTS**: **MTX 25 mg i.m./week** vs PBO 1 i.m./week
- **NUMBER** of patients: 55 patients in each group, i.e. a total of 110 patients
- **EVALUATION CRITERIA**: Remission without steroids at 16 and 24 weeks of ttx

http://clinicaltrials.gov/ct2/show/study/NCT00498589 GETAID

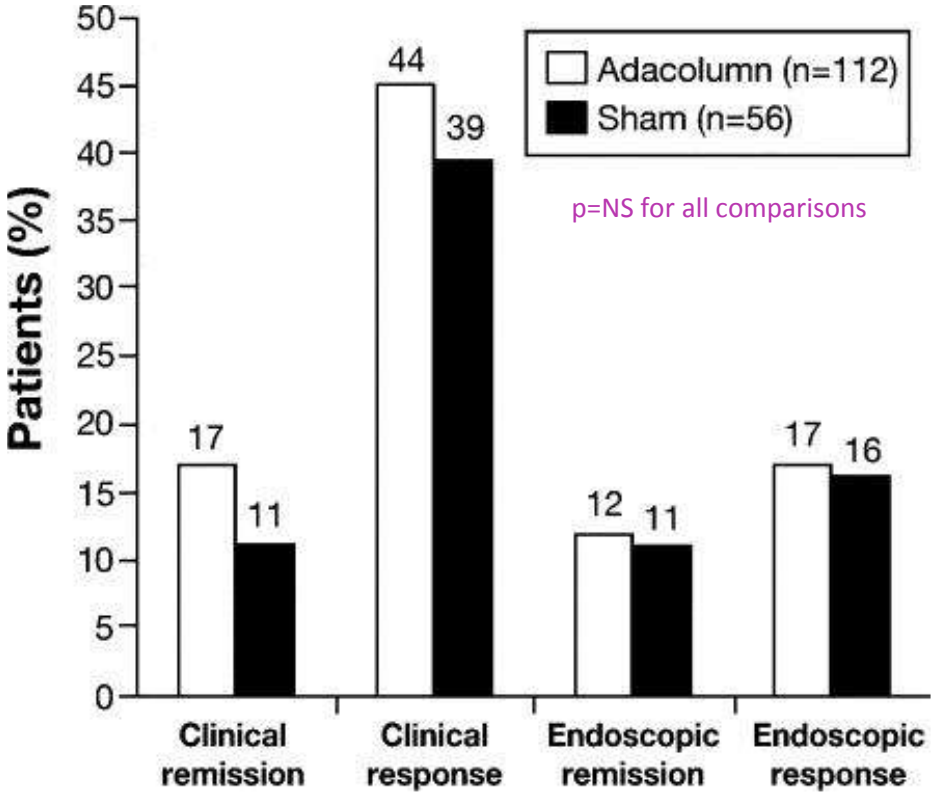
A randomized, double-blind, sham-controlled study of **granulocyte/monocyte apheresis** for active ulcerative colitis

- **BACKGROUND & AIMS:** To evaluate the efficacy of granulocyte/monocyte apheresis in patients with active moderate-to-severe UC

- **METHODS:**
  - Randomized, double-blind, sham-controlled trial
  - Community-based and tertiary care centers.
  - Granulocyte/monocyte apheresis (Adacolumn Apheresis System) vs. sham apheresis
  - 2:1 ratio for 9 weeks of treatment
  - North American pivotal study (N = 168)
  - Smaller study of identical design conducted in Europe and Japan (N = 47)

Sands BE et al. Gastroenterology 2008

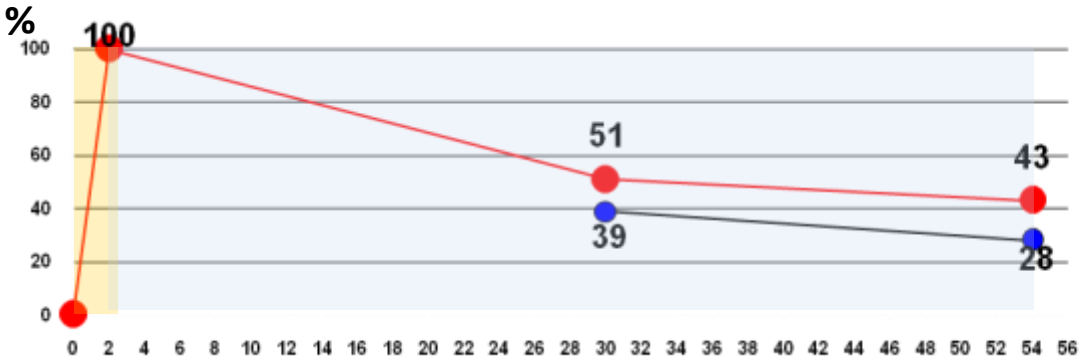
A randomized, double-blind, sham-controlled study of granulocyte/monocyte apheresis for active ulcerative colitis



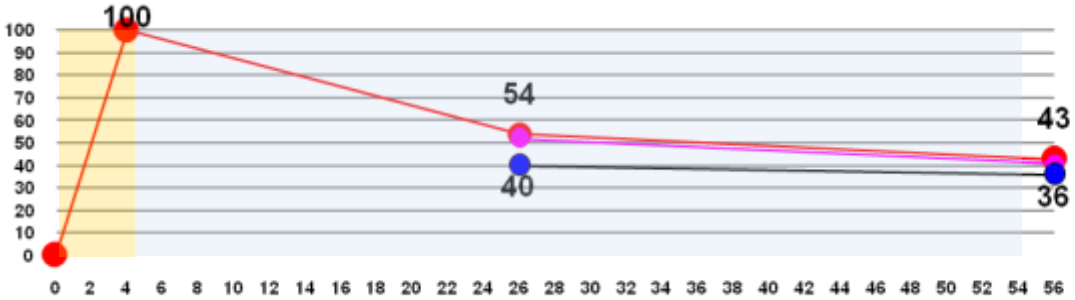
CONCLUSIONS: granulocyte/monocyte apheresis was well tolerated but **did not demonstrate efficacy** for induction of clinical remission or response in patients with moderate-to-severe UC.

Sands BE et al. Gastroenterology 2008

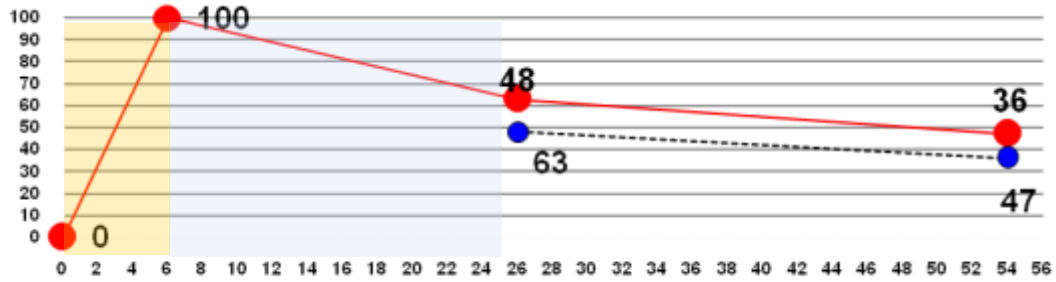
Anti-TNFs: High Rates of Loss of Response



Infliximab
ACCENT 1
(5 mg/kg/8s)



Adalimumab
CHARM*
(40 mg/2s)



Certolizumab
PRECISE 2
(400 mg/4s)

Hanauer et al., Lancet 2002

Colombel JF et al., Gastroenterology 2007

Schreiber S et al., NEJM 2007

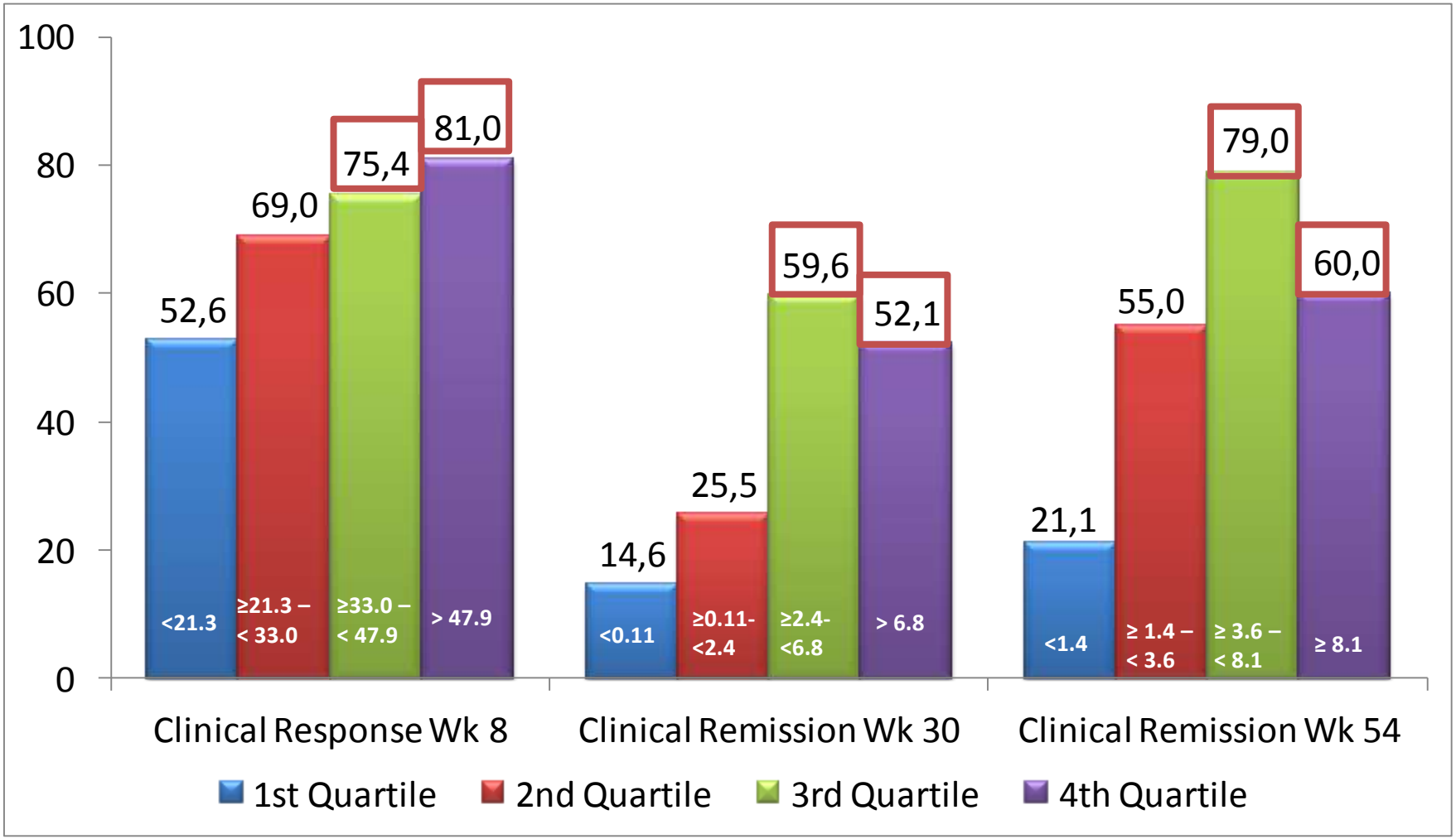
Factors Affecting the PK of TNF-antagonists

	IMPACT on PK
Presence of ADAs	Decreases serum [mAbs] Three fold-increased clearance Worse clinical outcomes
Concomitant use of IS	Reduces ADAs Increases serum [mAbs] Decreases mAbs clearance Better clinical outcomes
High Baseline [TNF-α]	May decrease [mAbs] by increasing clearance
Low Albumin	Increases clearance Worse clinical outcomes
High Baseline CRP	Increases clearance
Body size	High BMI may increase clearance
Gender	Males have higher clearance

ADAs: Anti-drug antibodies

Ordas I, et al Clin Pharmacol Ther 2012

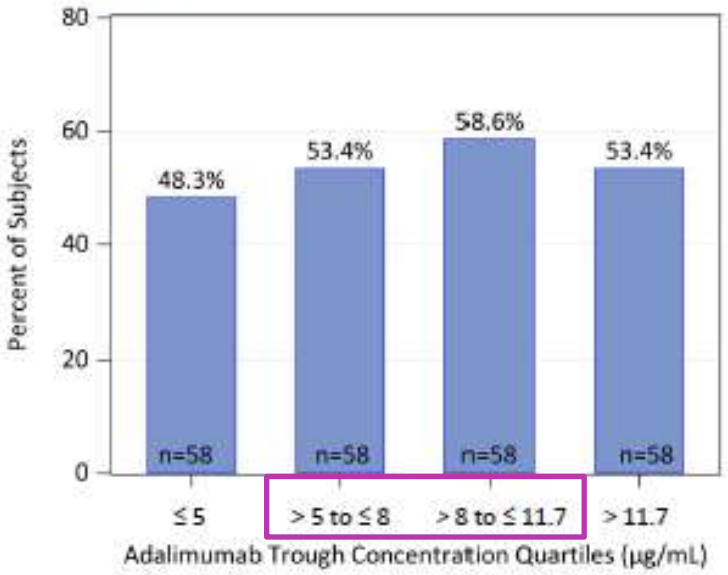
Proportions of Patients with Ulcerative Colitis Achieving Efficacy Endpoints by Serum Infliximab Concentrations (ACT1/ACT2)



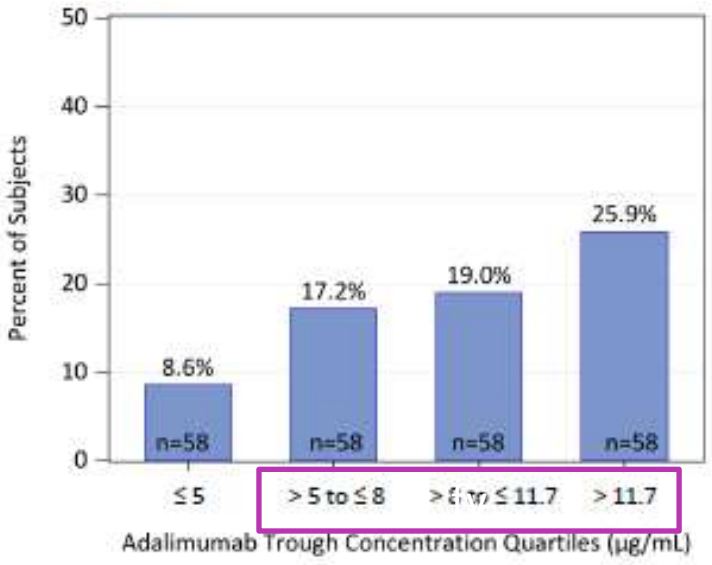
Reinisch W, et al., Digestive Disease Week 2012; Abstract # 566

Exposure-Efficacy Relationship for Adalimumab during Induction Phase of Treatment of Patients with Moderate to Severe UC

- **Aim**: to characterize the **relationship** between **trough [ADA]** and clinical **remission** and **response** per Full Mayo Score (n=258) at induction (160-80 mg)



Exposure-Efficacy Relationship for Response at week 8



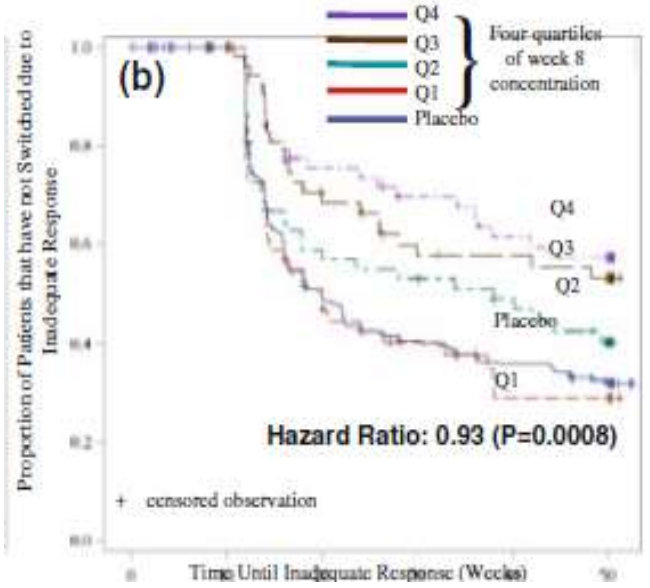
Exposure-Efficacy Relationship for Remission at week 8

Mostafa N et al. Poster DDW 2013

Assessment of Adalimumab Dose Selection for Adult UC using Exposure-Response Analysis

- **Higher wk 8** trough **[adalimumab]** are associated with:
  (1) greater % patients achieving clinical remission at week 8
  (2) increased duration of clinical remission

- Given the modest effect size of ADA for induction of remission (ADA 16.5% vs. PBO 9.3%) a **higher dose** for the **induction** of remission may provide **greater benefit** to UC patients



Bewernitz M et al. J Pharmacokinet Pharmacodyn 2013

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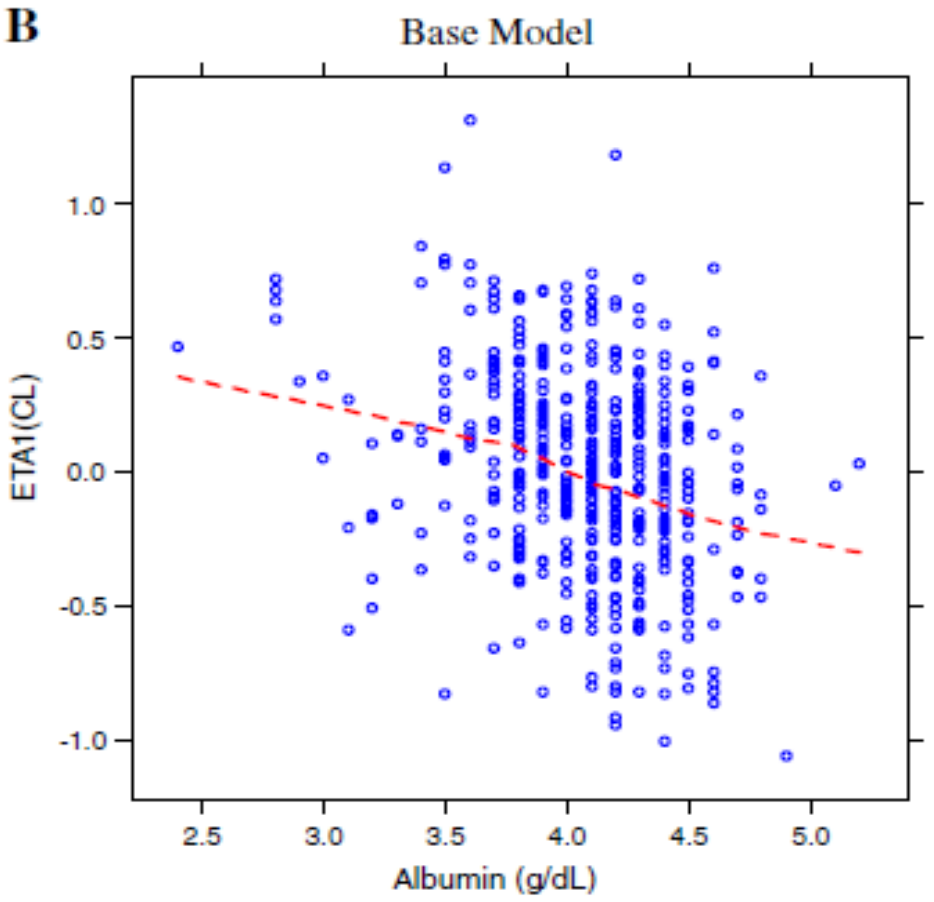
ADAs: Anti-drug antibodies

Ordas I, et al Clin Pharmacol Ther 2012

Population Kinetics of IFX from ACT 1 and ACT 2

- Albumin concentration was inversely proportional to the clearance of infliximab

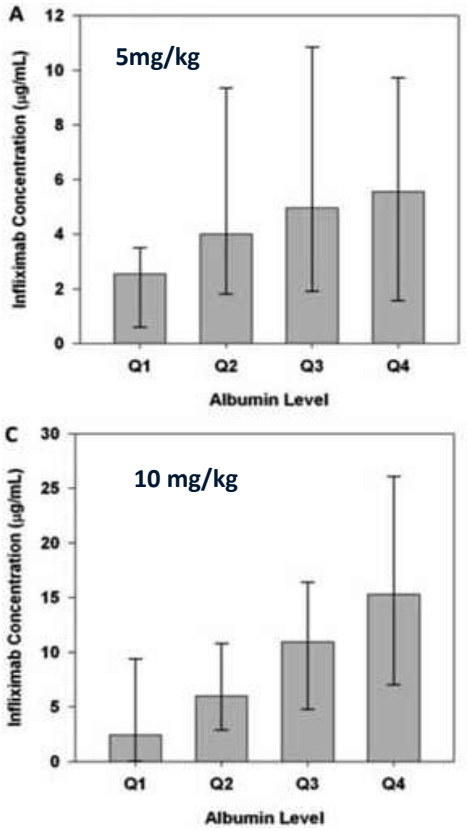


Fasanmade et al. Eu J Clin Pharmacol 2009

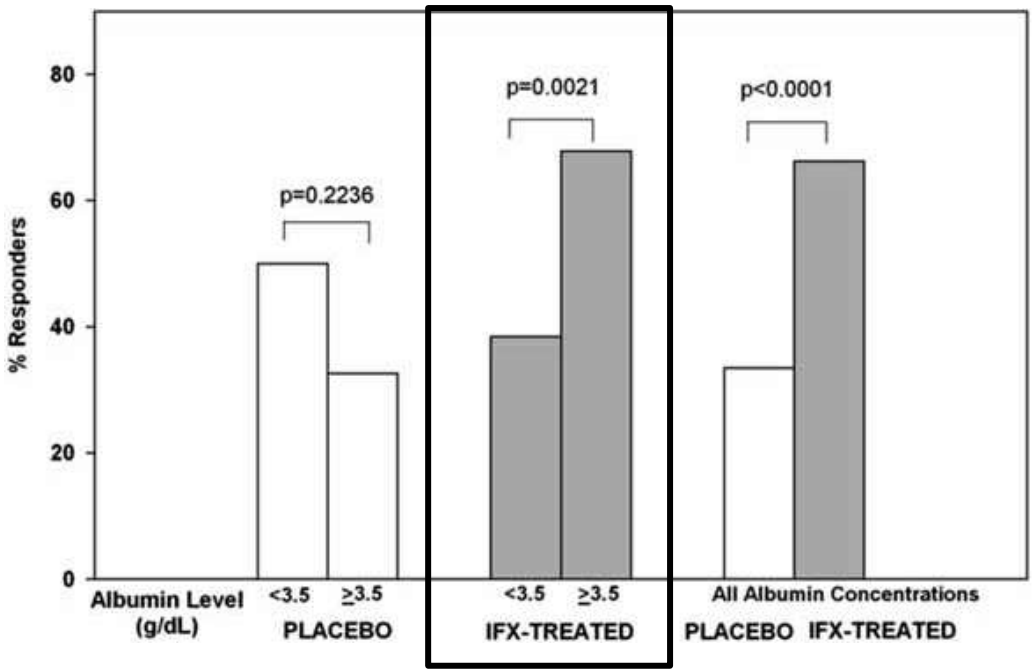
Serum Albumin Concentration Predicts PK and Clinical Response in Patients with Ulcerative Colitis

Higher SAC - Higher [IFX],

lower CL and longer $T_{1/2}$



Patients with **Albumin below normal** had a **lower response** rate



Fasanmade et al IJCPT. 2010

Pharmacokinetics of Adalimumab in Adult Patients with Moderately to Severely Active Ulcerative Colitis

Aim: to characterize the PK of ADA in moderate-to-severe UC

- Randomized, double blind, placebo-controlled, 52-week study
- Serum [ADA] trough at Weeks 0, 2, 4, 8, 32 and 52
- Serum Anti-Adalimumab Antibody (AAA) at Weeks 0, 8, 32 and 52
- Effect of Baseline covariates on ADA PK

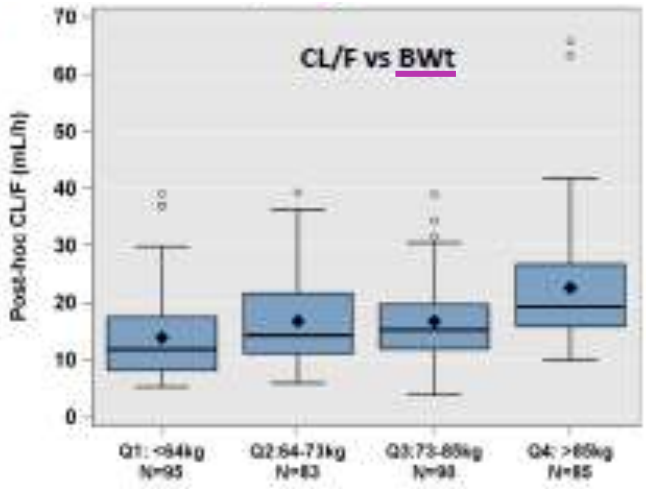
- Only **body weight** and plasma **albumin** were found to be statistically **significant covariates**; (explained 4.9% and 3.7% of the total PK variability, respectively)

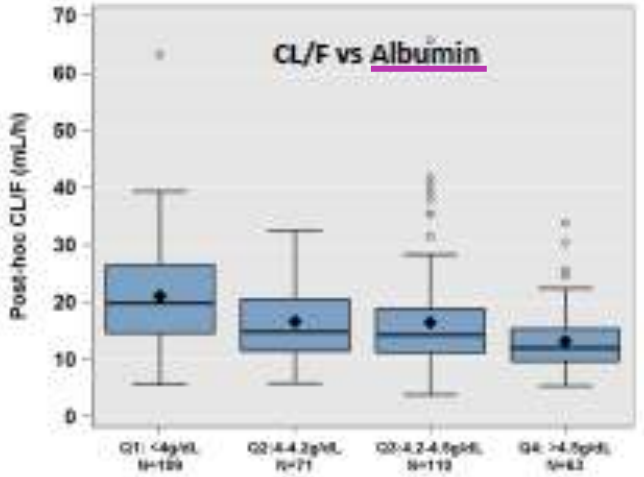
- A **combination** of **multiple covariates** (body weight, albumin, age, sex, CRP and concomitant IMM) explain 13% of the total variability in PK

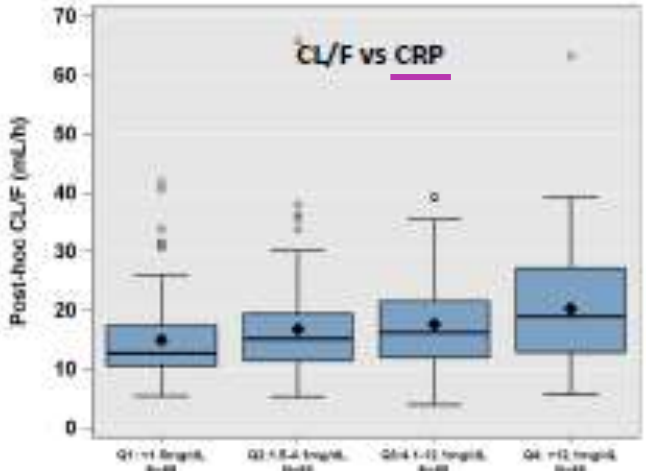
Awni W et al. Poster ECCO 2013

Pharmacokinetics of Adalimumab in Adult Patients with Moderately to Severely Active Ulcerative Colitis

Effect of **Body weight**, **Albumin** and **CRP** on Adalimumab **Clearance**







Mean ADA **Clearance** increased slightly **with**

- **increasing body weight and CRP**
- decreased with increasing albumin

(substantial overlap between quartiles)

Awni W et al. Poster ECCO 2013

Future

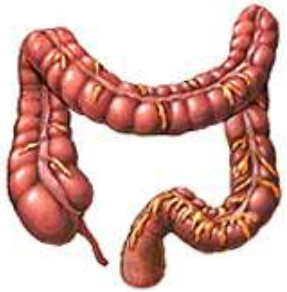
- **The light on the ….horizon…?**

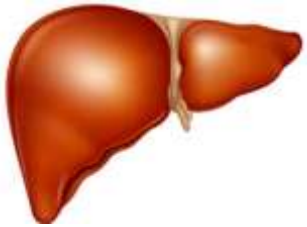
- Budesonide MMX
- Golimumab (anti-TNF)
- Tofacitinib (Jak inhibitor)
- Vedolizumab (α4β7)

Budesonide MMX

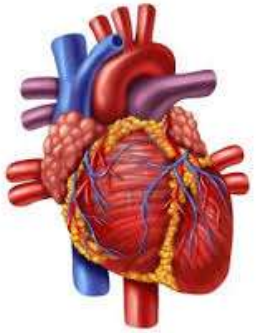
- Releases budesonide throughout colon
- Enteric coat dissolves at pH 7
- Proposed **indication**: induction of remission of active mild-to-moderate UC

Oral budesonide





90% metabolism in the liver

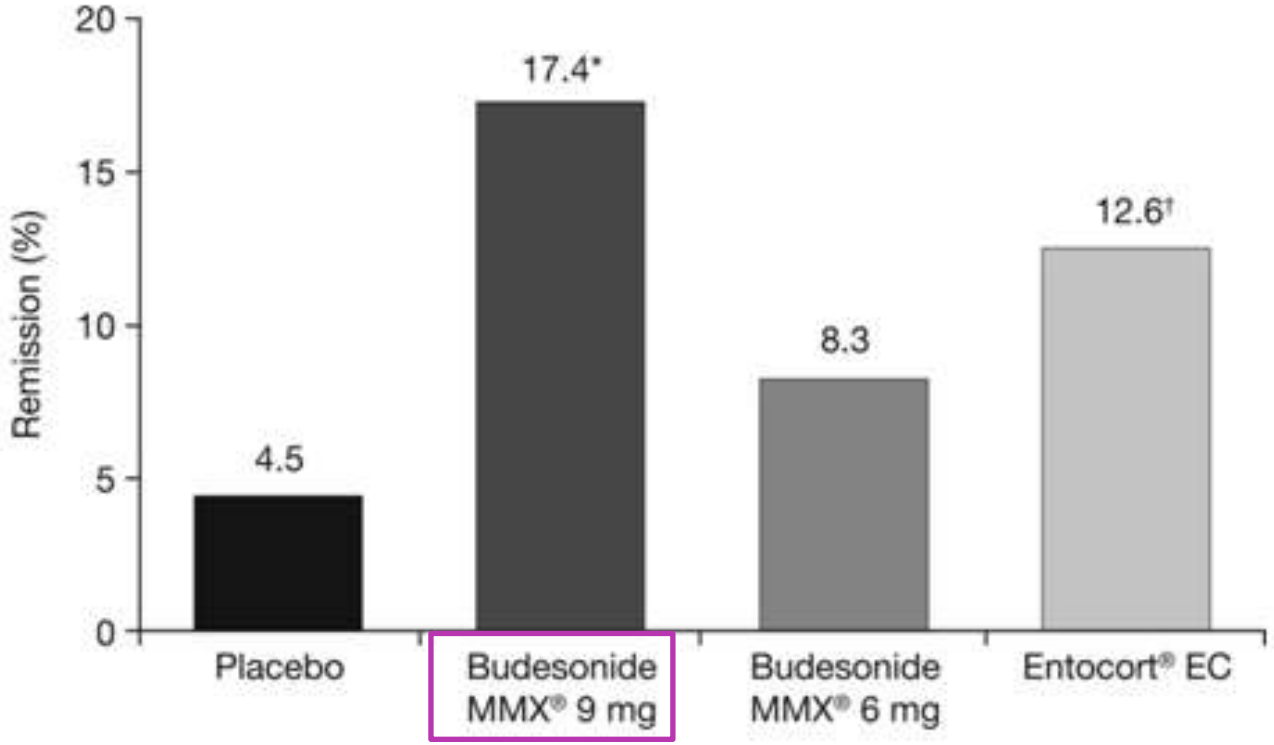


10 % systemic

Brunner M et al. Br J Clin Pharmacol 2006

Once-daily budesonide MMX in active, mild-to-moderate UC: results from the randomised CORE II trial

Primary endpoint: combined **clinical and endoscopic** remission at week 8 (n=410)



Travis S et al. Gut 2013

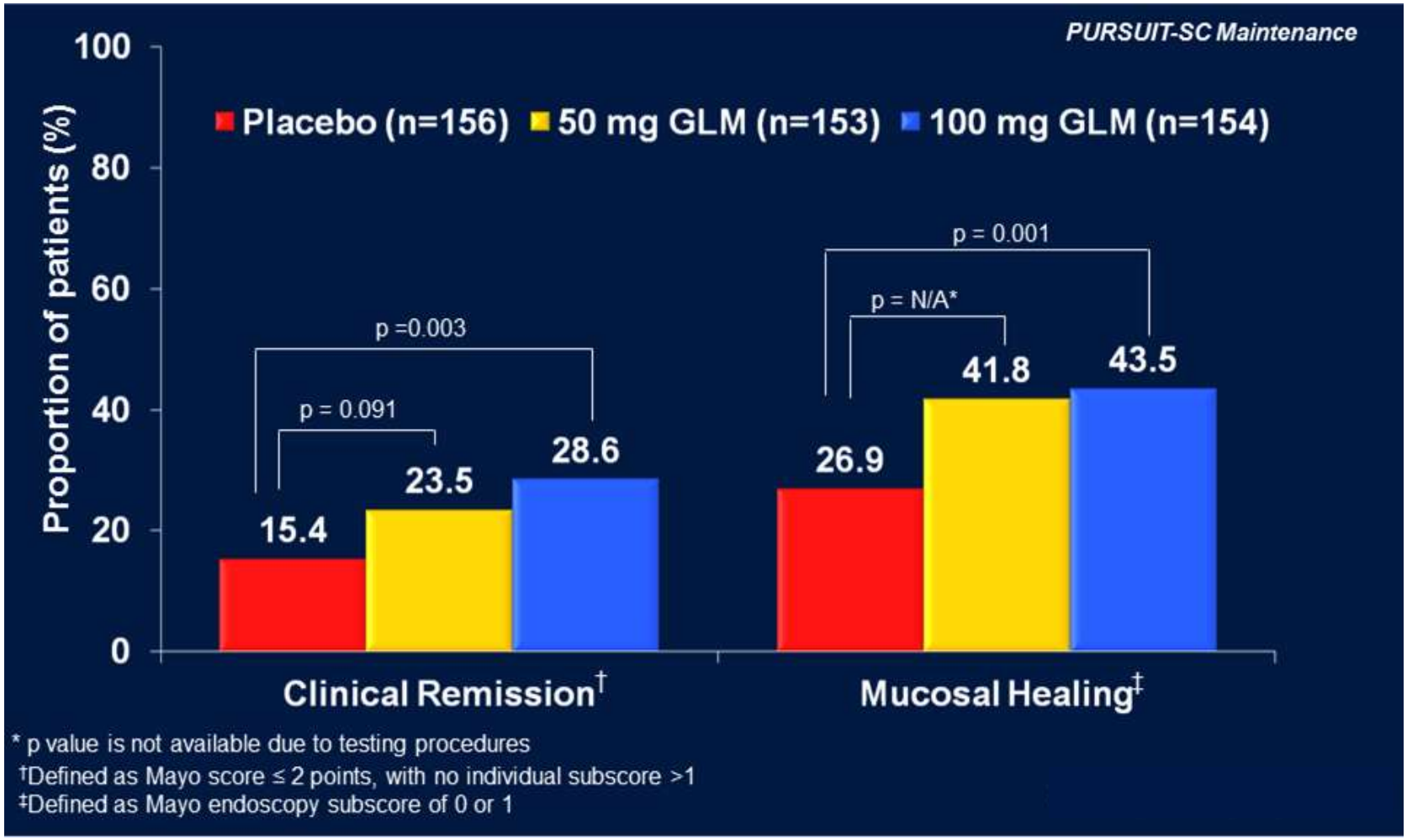
Subcutaneous Golimumab Induces Clinical Response and Remission in Moderate-to-Severe UC

- Phase III double-blind randomized

- Two phases
  - Induction (n=774; efficacy & safety week 6)
    - PBO
    - Golimumab 400, 200 mg/eow
    - Golimumab 200, 100 mg/eow
  - Maintenance (n=464; wk 52)
    - PBO
    - Golimumab (50 mg or 100 mg)/4 weeks

Sandborn W, Gastroenterology 2014

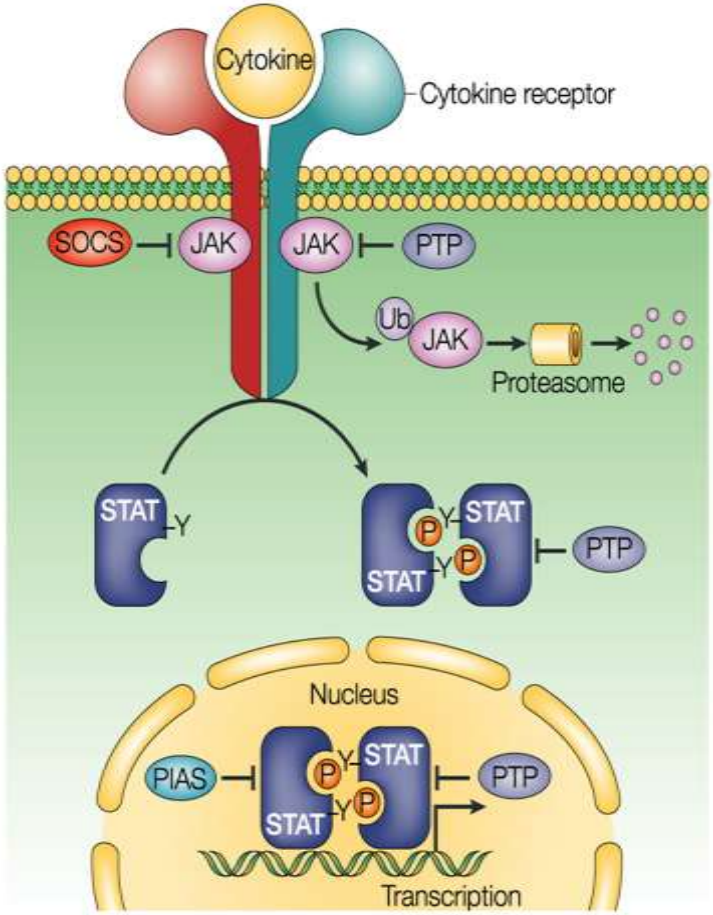
Clinical Remission and Mucosal Healing at both Week 30 and 54: Randomized Patients in Clinical Response to Golimumab Induction



Sandborn W, Gastroenterology 2014

Tofacitinib

- Small molecule (oral)
- JAK kinase inhibitor
  - Affinity for JAK 1 and 3
  - Inhibits cytokine signaling
- Metabolized by liver (CYP3A4)
- Phase 2 clinical trial suggests efficacy in UC



Nature Reviews | Immunology

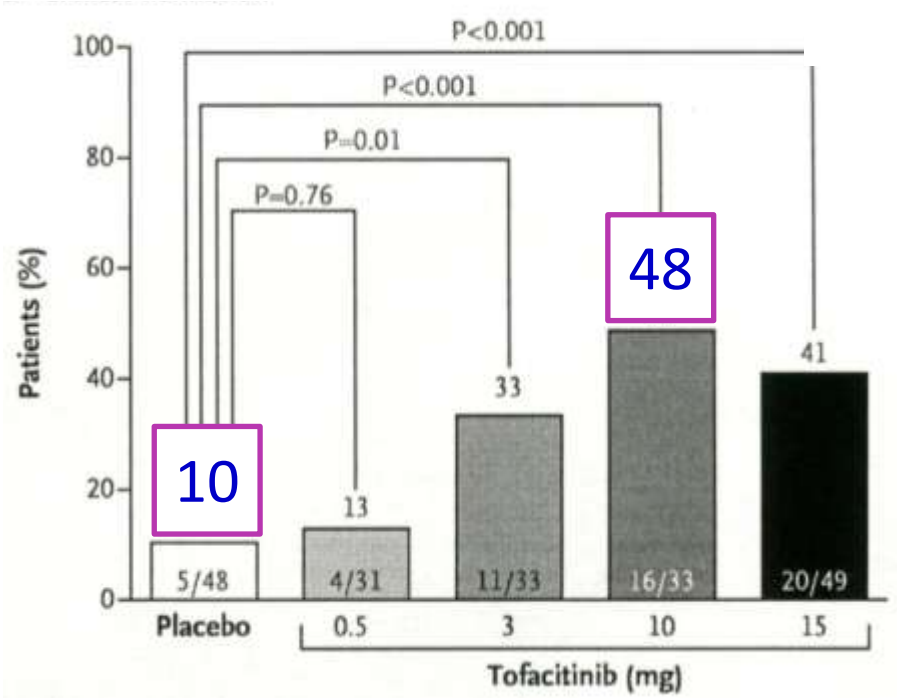
Tofacitinib, an Oral Janus Kinase Inhibitor, in Active Ulcerative Colitis

- Phase 2 placebo RCT (n=194)
- Mayo 6-12 (endoscopy ≥ 2) | 40% IMM failure | 30% prior anti-TNF
- Treatment arms:
    - PBO (n=48)
    - Tofacitinib 0,5 mg (n=31)
    - Tofacitinib 3 mg (n=33)
    - Tofacitinib 10 mg (n=33)
    - Tofacitinib 15 mg (n=33)
- Short term trial – 2 months

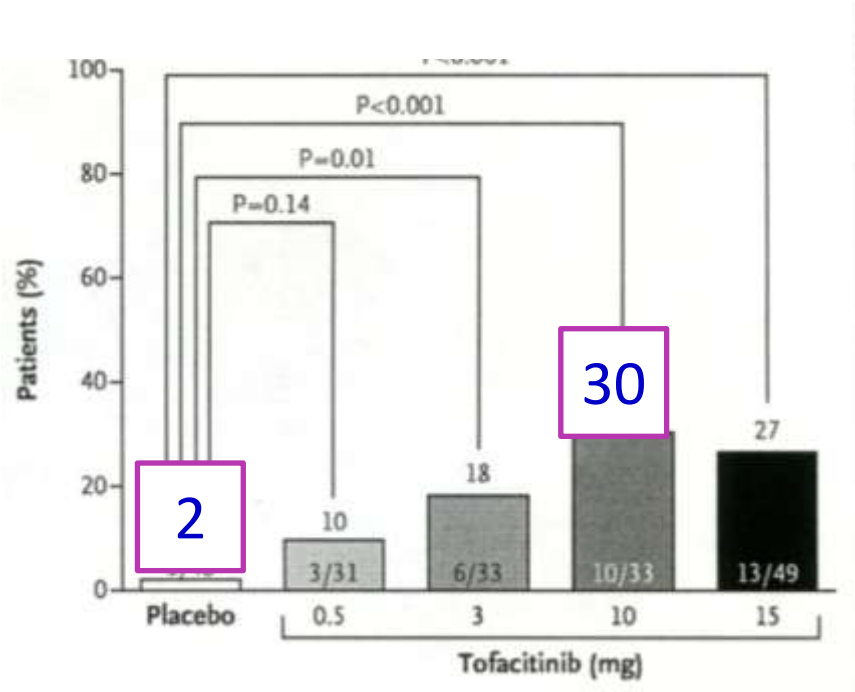
Sandborn et al NEJM 2012

Tofacitinib

Clinical Remission



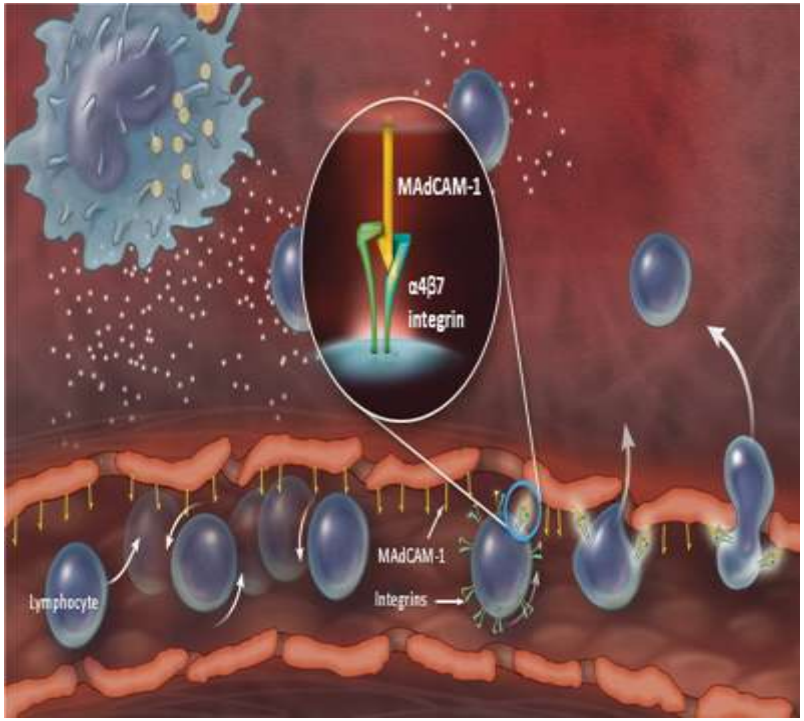
Endoscopic Remission



Sandborn et al NEJM 2012; 367:616.

Vedolizumab

- Humanized IgG 1 monoclonal antibody to α4β7 integrin
- Modulates gut, but **NOT brain** lymphocyte trafficking
- Less risk of PML compared to natalizumab

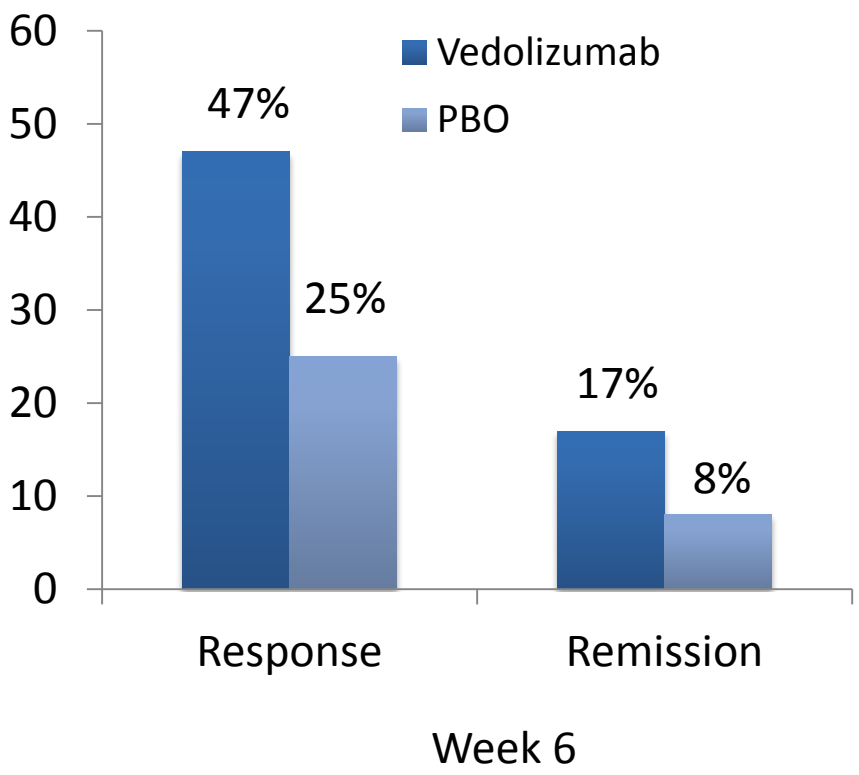


Vedolizumab as Induction and Maintenance Therapy for UC

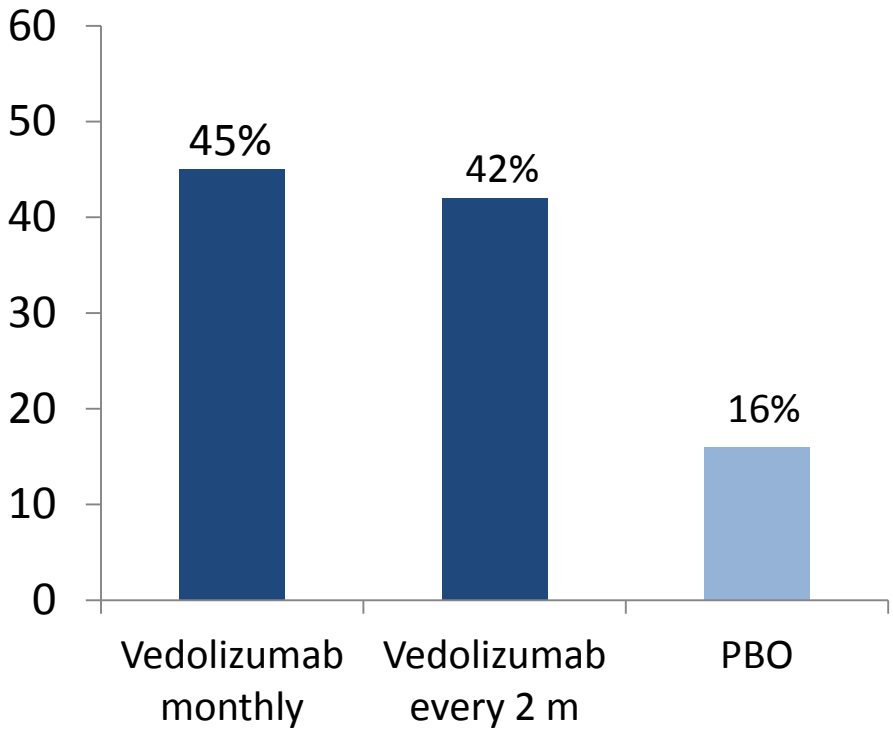
- Combination PBO controlled and open-label trial
  - 374 patients – vedolizumab or placebo
  - 521 patients – open label vedolizumab
- Active UC (Mayo 6-12, endoscopy subscore 2)
- Induction – two doses – week 0 and 2
- Maintenance: responders continued on active drug, or randomized to PBO

Feagan et. al. NEJM 2013

Vedolizumab - Results



Week 6



Week 52
(remission in the responders)

Feagan et. al. NEJM 2013

Final Remarks

- Chronic unremitting UC is relatively frequent
- Optimization of available therapies is crucial to achieve better outcomes
- With regard to anti-TNF therapies, a better knowledge of their PK profile is needed
- In the forthcoming years new therapies will be available