Positioning Biologics in Ulcerative Colitis

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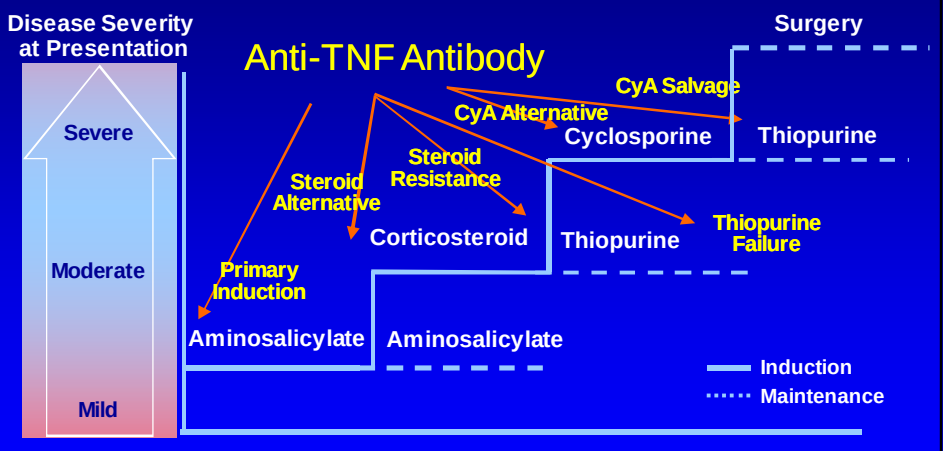
Sequential Therapies for UC



Step-Up according to severity at presentation or failure at prior step

Possible Positioning of Biologics in UC

- Thiopurine failure
- Steroid resistance
- Steroid alternative
- Cyclosporine alternative
- Cyclosporine salvage
- Primary induction

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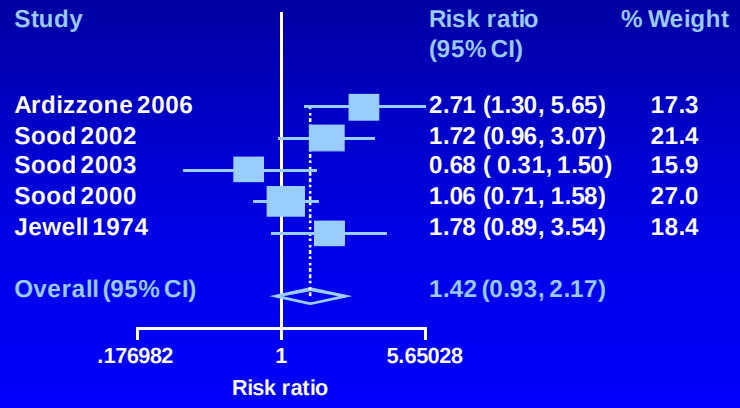
Estimate of Efficacy of AZA for Treatment Success in UC Patients: Meta-Analysis

Pooled RR Estimate Across 5 Trials



Leung Y et al. *Dig Dis Sci.* 2008;53:1455.

ACT 1 & 2 Baseline Characteristics

	ACT 1			ACT 2		
	Placebo	5 mg/kg	10 mg/kg	Placebo	5 mg/kg	10 mg/kg
	(N=121)	(N=121)	(N=122)	(N=123)	(N=121)	(N=120)
Duration of disease — yr	6.2±5.9	5.9±5.4	8.4±8.1	6.5±6.7	6.7±5.3	6.5±5.8
Mayo score‡	8.4±1.8	8.5±1.7	8.4±1.4	8.5±1.5	8.3±1.5	8.3±1.6
Concomitant medication — no. (%)						
Corticosteroids	79 (65.3)	70 (57.9)	73 (59.8)	60 (48.8)	60 (49.6)	66 (55.0)
≥20 mg/day	54 (44.6)	45 (37.2)	46 (37.7)	43 (35.0)	40 (33.1)	47 (39.2)
5-Aminosalicylates	85 (70.2)	82 (67.8)	86 (70.5)	89 (72.4)	92 (76.0)	91 (75.8)
Immunosuppressants	53 (43.8)	66 (54.5)	59 (48.4)	54 (43.9)	52 (43.0)	50 (41.7)
Corticosteroid-refractory disease	38 (31.4)	36 (29.8)	38 (31.1)	36 (29.3)	35 (28.9)	34 (28.3)

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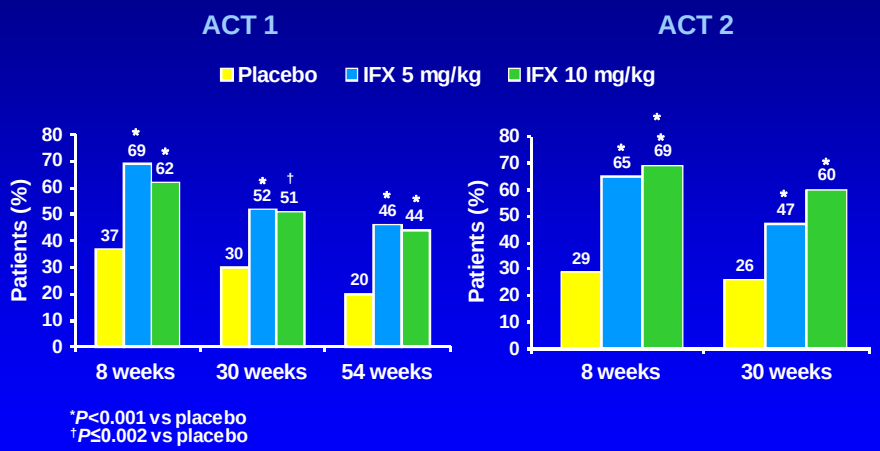
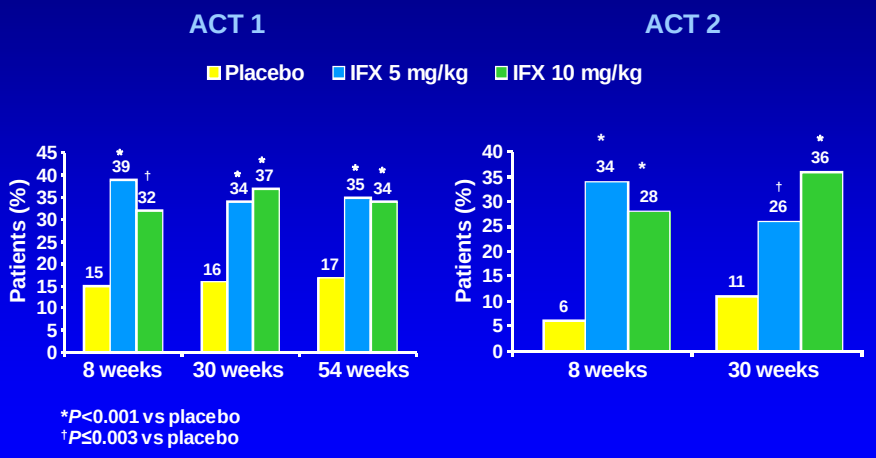
Infliximab in Patients With Ulcerative Colitis: Clinical Response



*P<0.001 vs placebo
†P≤0.002 vs placebo

Rutgeerts P et al. *N Engl J Med*. 2005;353:2462.

Infliximab in Patients with Ulcerative Colitis: Clinical Remission



*P<0.001 vs placebo
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Rutgeerts P et al. *N Engl J Med*. 2005;353:2462.

Possible Positioning of Biologics in UC

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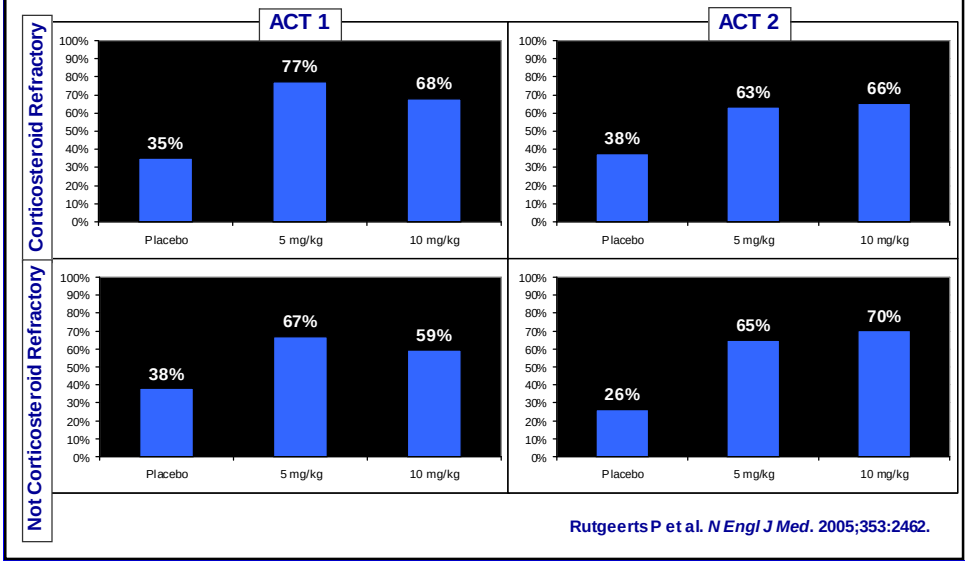
ACT 1 & 2

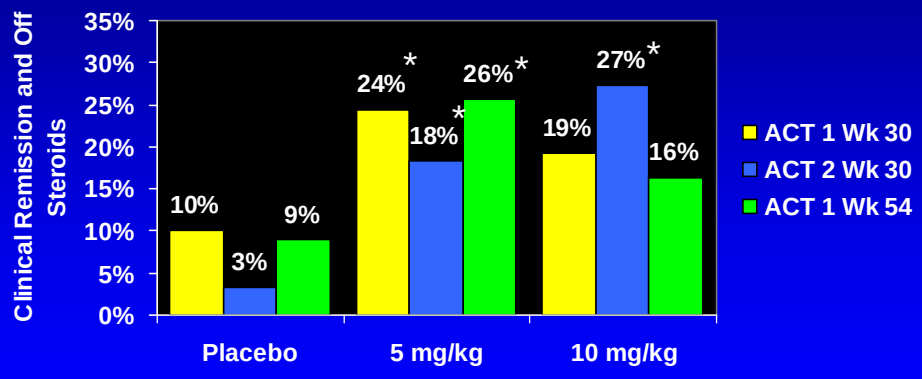
Response Rate, Corticosteroid Refractory vs. Not Corticosteroid Refractory



Rutgeerts P et al. *N Engl J Med*. 2005;353:2462.

ACT 1 & 2

Clinical Remission and Off Steroids



*P value <0.05

Rutgeerts P et al. *N Engl J Med*. 2005;353:2462.

Possible Positioning of Biologics in UC

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- Steroid resistance
- **Steroid alternative**
- Cyclosporine alternative
- Cyclosporine salvage
- Primary induction

Infliximab vs. Steroids for Severe Ulcerative Colitis in the Hospital Setting

				Response	
Study	N	Infliximab dose	Outcome measure	Infliximab	Steroid
Ochsenkuhn 2004	13	5 mg/kg × 3	↓Lichtiger score ≥5 to <10 at 3 and 13 weeks	83%	86%
Armuzzi 2004	20	5 mg/kg × 3	Sutherland score ≤2 at 2 weeks	100%	100%

Ochsenkuhn T et al. *Eur J Gastroenterol Hepatol*. 2004;16:1167.
Armuzzi A et al. *Eur Rev Med Pharmacol Sci*. 2004;8:231.

Possible Positioning of Biologics in UC

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Meta-analysis of intravenous corticosteroids in severe ulcerative colitis

- Cohort studies and controlled trials published between 1974–2006 that reported the short-term colectomy rate in severe UC or reported variables that could predict treatment failure
- 581 of 1991 patients required **colectomy (weighted mean 27%** [95% CI, 26%–28%])
- 22 died (**1% mortality rate**; 95% CI, 0.7%–1.5%)
- **No dose-colectomy response of methylprednisolone therapy beyond 60 mg daily** (*R*2 <0.01, *P* =*0*.98)
- Predictors of medical failure: **disease extent, stool frequency, temperature, heart rate, C-reactive protein, albumin, and radiologic assessment.**

Turner D, et al. *Clin Gastroenterol Hepatol*. 2007;5:103–110

Cyclosporine for Severe Ulcerative Colitis in the Hospital Setting

				Response			
Study	N	CyA dose	Outcome measure	CyA 4 mg/kg	Placebo	Steroids	CyA 2 mg/kg
Lichtiger 1994	20	4 mg/kg IV	↓ Lichtiger score to <10 for 2 days	82%	0%	—	—
D'Haens 2001	30	4 mg/kg IV	↓ Lichtiger score ≥3 to <10 on days 7 and 8	64%	—	53%	—
Van Assche 2003	73	4 or 2 mg/kg IV	↓ Lichtiger score ≥3 to <10 on day 8	84%	—	—	86%

Lichtiger S et al. *N Engl J Med.* 1994;330:1841.
D'Haens G et al. *Gastroenterology.* 2001;120:1323.
Van Assche G et al. *Gastroenterology.* 2004;125:1025.

Meta-analysis of intravenous corticosteroids in severe ulcerative colitis

- **Cyclosporine** was used in only 100 patients, with a **51% (95% CI, 41%–60%) short-term success rate**

Turner D, et al. *Clin Gastroenterol Hepatol.* 2007;5:103–110

Serious Infections and Death From High-Dose IV Cyclosporine for IBD

- Mt. Sinai
  - 111 patients (2 deaths, 1.8%)
  - *Pneumocystsis carinii,* 1 patient
  - Septic shock, 1 patient
- University of Chicago
  - 74 patients (1 death, 1.4%)
  - *Pneumocystis carinii,* 1 patient
- University of Leuven
  - 142 patients (4 deaths, 2.8%)
  - *Pneumocystsis carinii,* 1 patient
  - Systemic aspergillosis, 2 patients
  - CML, 1 patient

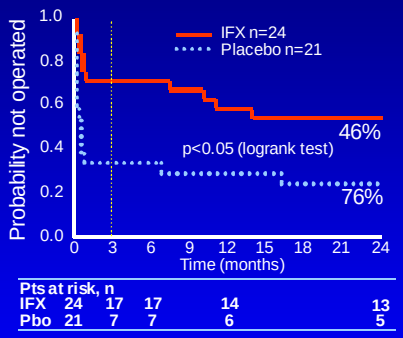
Sternthal MB et al. *Am J Gastroenterol.* 2008;103:937.
Stein R et al. *Gastroenterology.* 1997;112:A1096.
Moskovitz DN et al. *Clin Gastroenterol* Hepatol;4:760.

Infliximab for Severe Ulcerative Colitis in the Hospital Setting

				Response	
Study	N	Infliximab dose	Outcome measure	Infliximab	Placebo
Sands 2001	11	5, 10, 20 mg/kg × 1	↓Lichtiger score ≥5 to <10 at 2 weeks	50%	0%
Jarnerot 2005	45	5 mg/kg × 1	No colectomy at 90 days	71%	33%

Sands BE et al. *Inflamm Bowel Dis.* 2001;7:83.
Jarnerot G et al. *Gastroenterology.* 2005;128:1805.

Infliximab for severe, steroid refractory UC: Two year follow-up of colectomy rate



Cyclosporine: 30–43%
Cohen 1999
Moskovitz 2006
Campbell 2005

- IFX group 13/15 initial responders started on AZA vs 3/7 in placebo group
- Only 4/24 received more than one IFX infusion

Gustavsson A, et al. *Gastroenterology* 2007;132(4 Suppl 2):A146-7

Infliximab for ulcerative colitis: Long-term outcomes

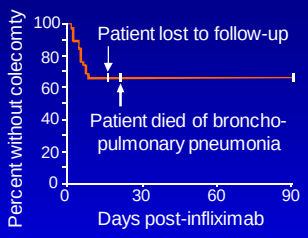
- Retrospective cohort of **30 pts** treated at Oxford from 2000-06
- Sixteen **(53%) came to colectomy** a median of 140 days after their first infusion (range 4-607)
- No difference in colectomy between those receiving infliximab for acute severe ulcerative colitis failing intravenous steroids (8/14) and out-patients with steroid-refractory ulcerative colitis (8/16)
- Only **17% (5/30) achieved a steroid-free remission after a median follow-up of 13 months** (range 2-72).

Jakobovits SL, et al. *Aliment Pharmacol Ther*. 2007;25:1055-60.

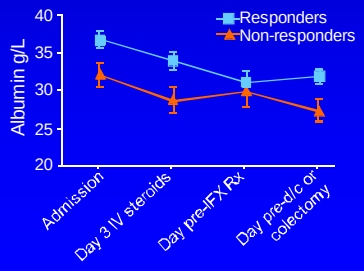
Infliximab as rescue therapy in acute severe UC

- Inclusion criteria: **Hospitalization for acute UC, failure to respond to IV steroids, IFX therapy during acute admission**
- Results **(N=39 patients):**
  - **26/39 (66.6%) patients avoided urgent colectomy at hospital discharge**
  - **17/24 initial responders off steroids at 90d**
  - **1 death (Pseudomonas aeruginosa)**
  - **Serum albumin but not CRP or stool frequency predicted response to IFX**
    (Pts with albumin <34g/L on d3 more likely to undergo colectomy)

Influence of IFX on colectomy



Albumin levels and response to IFX



Lees CW, et al. DDW 2007: S1136

Colectomy rates after infliximab for refractory UC (Leuven)

- **N=130 from January 2000 – October 2006**
  - **62% extensive – 47% Mayo score ≥3**
  - **31% received induction**
- **43% complete short term response**
- **20% partial short term response**
- **37% did not respond**
- **18% required colectomy in 2.5 years of follow up**

Ferrante M et al. DDW 2007. #960

Impact of Infliximab on Post-Surgical Complications in UC

Author (year)	Diagnosis	N (IFX)	N (non-IFX)	Increase in complications (yes/no)
Schluender 2007	UC	17	134	no
Selvasekar 2007	UC	47	254	yes
Mor 2008	UC	46	46	yes

Mor et al, Dis Colon Rectum 2008
Selvasekar et al, J Am Coll Surg 2007

Anastomotic Leak Rates: UC

Center	Infliximab	Non-infliximab
Cleveland Clinic	17.4%	2%
Mayo Clinic	9%	2%
MGH	3%	2.9%

Risk Factors for Mortality With Colectomy for UC

- Nationwide Inpatient Sample (1995-2004)
  - 6502 discharges for UC patients who underwent a total abdominal colectomy
- Postoperative mortality: 2.3%
- Emergently admitted patients whose surgery was performed after 11 days in hospital were at higher risk of
  - Death: aOR 3.18 (1.59-6.34)
  - Complications: aOR 1.42 (1.05-1.93)

Kaplan GG et al. *Gastroenterology.* 2008;134:680.

Possible Positioning of Biologics in UC

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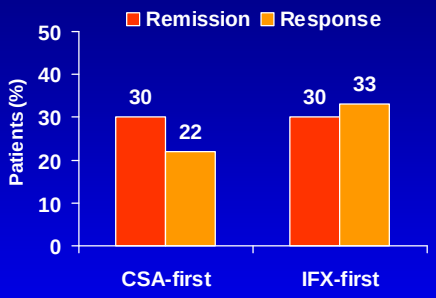
Cyclosporine (CSA) and IFX as acute salvage therapies for each other in severe steroid refractory UC

Salvage information	CSA–first (n=10)	IFX–first (n-9)
Avg IFX infusions	**3**	**1.9**
Avg CSA duration	**3 months**	**6.2 months**
Avg interval between drugs	**17 days (range 1–30)**	**21 days (range 3–31)**
Concomitant use of IMM	**77% (7/9)**	**66% (6/9)**
Colectomy within 1 y	**33.3% (3/10)**	**44.4% (4/9)**

Maser EA et al. DDW 2007. S1132

Cyclosporine (CSA) and IFX as acute salvage therapies for each other in severe steroid refractory UC

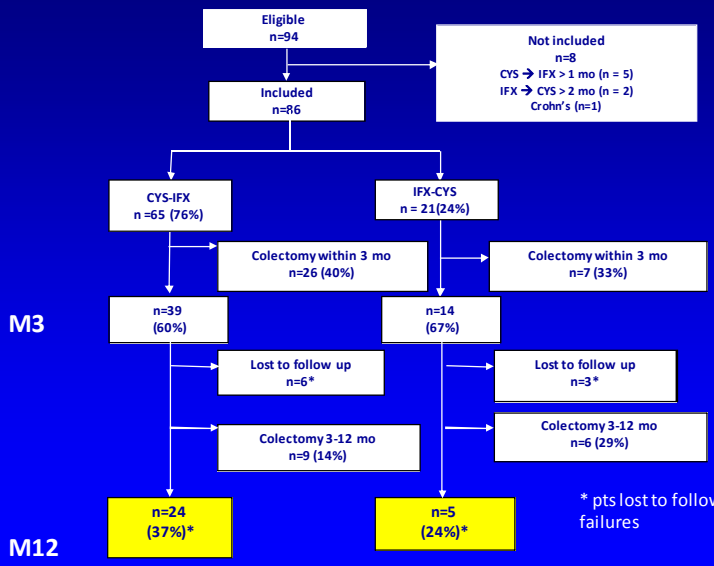


SAEs total = 16% (3/19)	Other immune suppression	Drug sequence	Medical interval
Death gram –ve sepsis	**AZA**	**CSA-first**	**1 day**
Pancreatitis Enterococcus, and Klebsiella bacteremia	**AZA**	**IFX-first**	**4 weeks**
Herpes esophagitis	**Prednisone taper**	**IFX-first**	**5 days**

- **The likelihood of achieving steroid-free remission, in severe steroid-refractory UC patients who fail CSA or IFX, is low and similar despite which drug is used first**
- **Incidence of a SAE of 13%, including 1 fatality, suggest the risks outweigh the benefit of acute salvage therapy**

Maser EA et al. DDW 2007. S1132

Successive treatment with cyclosporine and infliximab in severe ulcerative colitis



* pts lost to follow up were counted as failures

Leblanc S, et al. DDW 2009. #561.

Successive treatment with cyclosporine and infliximab in severe ulcerative colitis

Adverse Events	N	CIS-IFX (n=65)	IFX-CIS (n=21)	Steroids (n=74)	AZA/MP (n=63)	Non op. (n=37)	Before surgery (n=49)	After surgery (n=49)
Death[1]	1	1	-	1	1	-	-	1
Infection	17	14	3	11	13	6	6	5
Renal	6[2]	4	2	6	4	1	4	1
Hepatic	3[2]	2	1	3	3	2	1	-
SB obstruction	2	2	-	2	2	-	-	2
Cardiac	1	1	-	1	1	1	-	-
Pulmonary	1	1	-	1	1	-	-	1
Rash	1[2]	1	-	1	1	1	-	-
Total events	32	26	6	26	26	11	11	10
Pts	23	18	5	20	18	7	10	9
% Pts	27%	28%	24%	27%	29%	19%	20%	18%

[1] postoperative death due to thromboembolism in a 40 year-old man
[2] n=4, n=3 and n=1 were related to cyclosporine, respectively

Leblanc S, et al. DDW 2009. #561.

Possible Positioning of Biologics in UC

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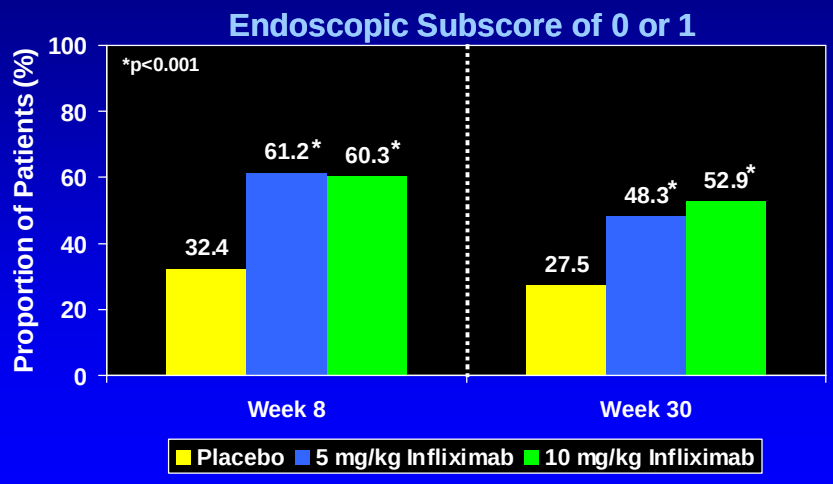
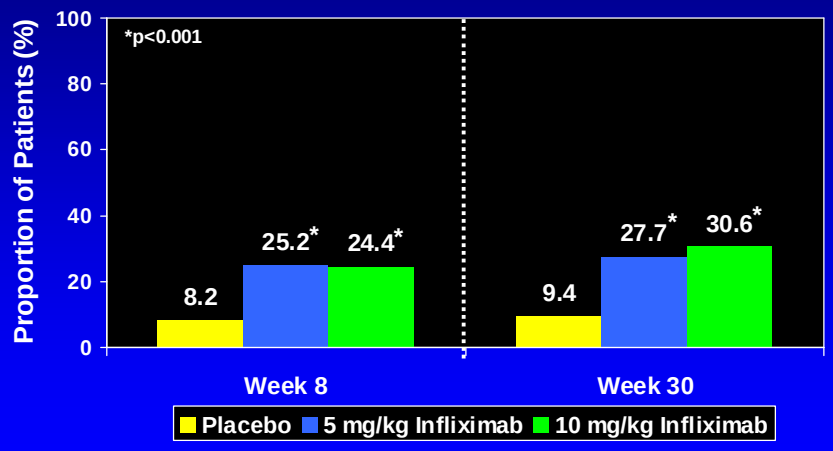
ACT 1 & 2: Mucosal Healing



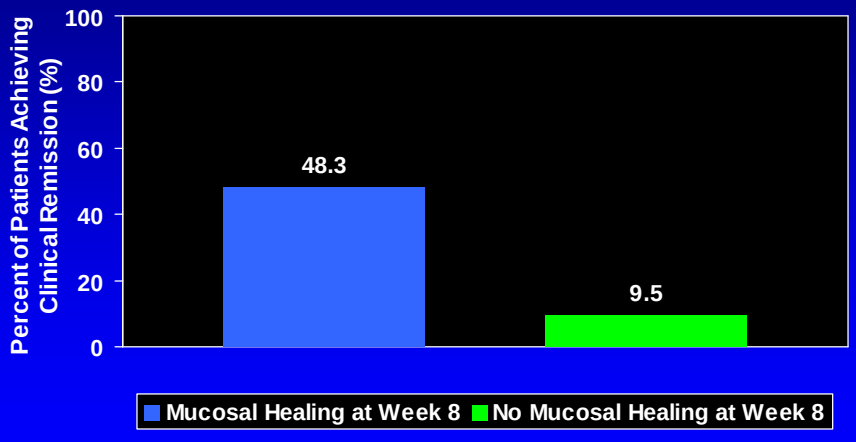
Rutgeerts P et al. *N Engl J Med*. 2005;353:2462.

ACT 1 & 2: Endoscopy Subscore of 0



Rutgeerts P et al. *N Engl J Med*. 2005;353:2462.

ACT 1& 2
Clinical Remission at Week 30 by Mucosal Healing Status at Week 8



Rutgeerts P et al. *N Engl J Med*. 2005;353:2462.

Possible Positioning of Biologics in UC

- **Thiopurine failure:** Yes
- **Steroid resistance:** Yes
- **Steroid alternative:** Insufficient evidence
- **Cyclosporine alternative:** Yes; ?increased risk for surgical complications
- **Cyclosporine salvage:** Probably not
- **Primary induction:** No evidence