


**Biologics in IBD: When to Consider, What to Choose?**

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**Relevant Disclosures**

- Abbott: consultant, grant support
- Centocor: consultant
- Elan: consultant
- Prometheus: consultant, grant support
- Takeda: consultant
- UCB: consultant

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**Therapeutic Goals in IBD c. 2009**

- Normal bowel function and improved quality of life (QOL)
- Induce remission rapidly
- Maintain steroid-free remission over time (deep remission)
- Modify long-term outcomes of the disease
  - Avoid hospitalization and surgery
  - Eliminate disability
  - Minimize exposure to steroids

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**Overview:  
Biologic Therapy in IBD c 2009-2010**

- **Why:** to achieve steroid-free remission and change outcomes
- **What:** currently includes 3 anti-TNF therapies and one anti-integrin therapy
- **Who:** positioning has been for patients with moderately to severely active IBD who have "failed conventional therapies"; we are moving to a model of prognosis to choose therapy
- **When:** we have learned that treating earlier increases benefit and decreases risks; waiting for failure of all other therapies is often too late to use these
- **How:** minimize risk, maximize responsiveness, maintain remission
- **Where:** infusion suites, your office, at home

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**Biological Therapies in IBD**

- Treatment to stimulate or restore the ability of the immune system to fight infection and disease.
- Approved anti-TNF $\alpha$  therapies
  - infliximab
  - adalimumab
  - certolizumab pegol
- Approved anti-integrin therapy
  - natalizumab
- Challenges of biologic therapy in IBD
  - Safety
  - Loss of response
  - Immunogenicity
  - Cost
  - Tolerability

Investigational agents:  
Anti-IL-12  
Vedolizumab (anti-integrin)  
Abatacept  
Others

Safety:  
Infections  
Reactivation of latent TB  
Screening for Hepatitis B  
Fungal  
Concerns about lymphoma  
Others

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**Anti-TNF $\alpha$  Agents in IBD**

**Infliximab**

**Adalimumab**

**Certolizumab pegol**

■ = murine     ■ = human

— Monoclonal antibody     PEGylated humanized Fab' fragment containing 2x20 kDa PEG molecules

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**Comparison of Maintenance Trials of Anti-TNF $\alpha$  Therapies in Crohn's Disease**

Key Factor	ACCENT 1 infliximab (IFX)	CHARM adalimumab (ADA)	PRECISE II certolizumab pegol (CZP)
Patient population	Moderate to severe CD patients responding to 5 mg/kg at week 2	Moderate to severe CD patients responding to initial 2 dose induction at week 4	Moderate to severe CD patients responding to initial 3 doses at week 6

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Inclusion criteria	Stable doses of prednisone, and 6MP/AZA allowed; only anti-TNF naive patients	Stable doses of steroids and 6MP/AZA allowed; 50% of patients treated with prior IFX	Stable doses of steroids and 6MP/AZA allowed; 30% of patients treated with prior anti-TNF

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Primary outcome	Clinical Remission at week 30 and time to loss of response at week 54	Co primary endpoints: Clinical Remission at week 26 and week 56	Clinical response (Decrease in CDAI $\geq$ 100 points) at week 26

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### Hepatosplenic T-cell lymphoma

- Hepato/splenomegaly; B symptoms
- 9 cases in IBD with 6MP/AZA alone
- 15 cases in IBD patients taking infliximab (n=13) or adalimumab (n=2) with 6MP/AZA
  - Age range 12-40 years old
  - Most are male (14/15)
  - Infusions ranged from 1-24
  - Appears to be universally fatal
- Has NOT been reported with monotherapy of anti-TNF
- Has NOT been reported with methotrexate combo

Mackey et al. J Pediatr Gastroenterol Nutr 2007; 44: 265.  
 Data on file, Centocor (letter to physicians May 2008).  
 Data on file, Abbott (letter to physicians August 2008).

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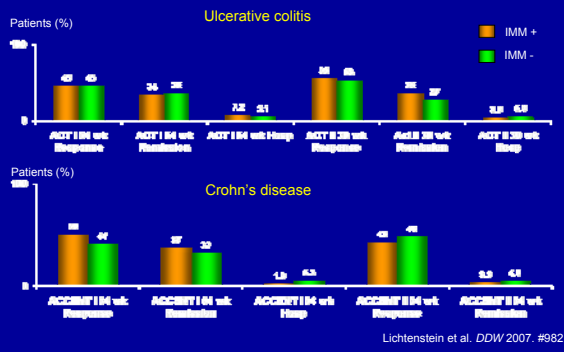
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### Continuation of IMM does not improve efficacy of IFX in CD and UC: post-hoc analysis




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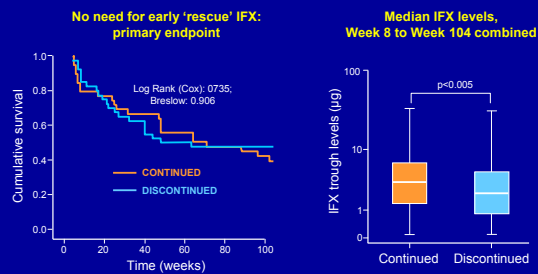
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### Withdrawal of Concomitant IMM in Crohn's disease while on Infliximab ≥6 months of remission



Van Asche G, et al. Gastroenterol 2008.

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## Evidence for Earlier Treatment of CD with Biologic Therapy

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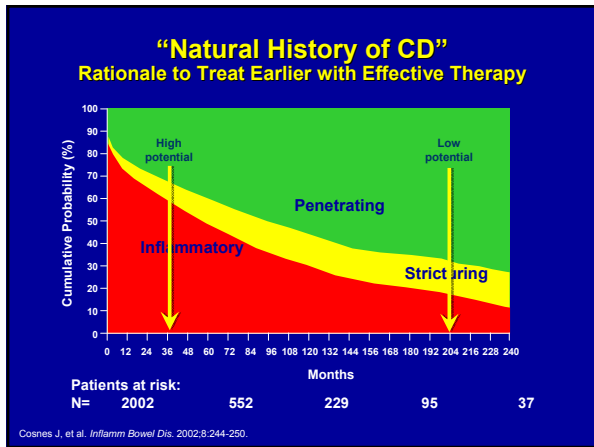
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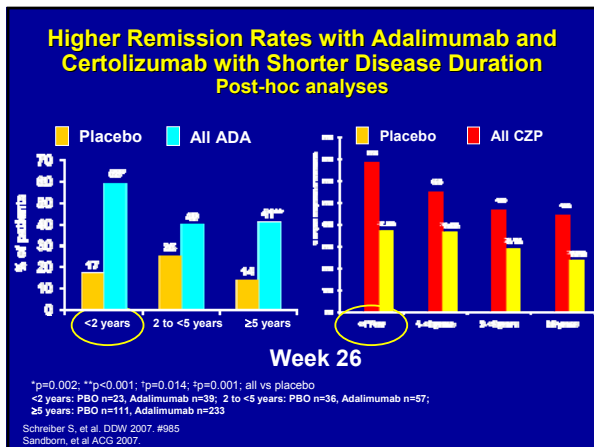
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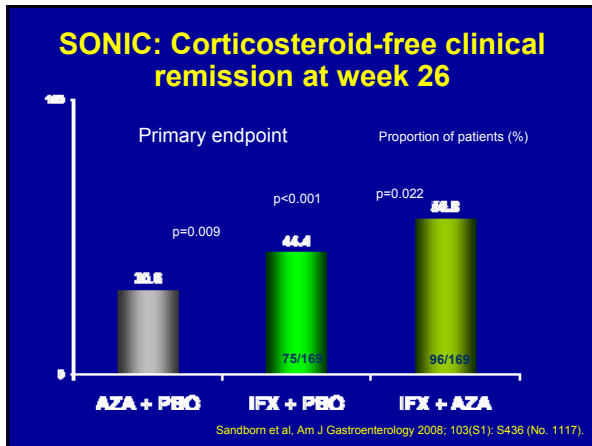
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### Switching to Another Biologic Therapy

#### What to choose and when to choose it?

- Evidence only exists in one direction (infliximab first), assumption is the opposite is true
- Primary non-responder:** anti-TNF $\alpha$  loading dose with no response: try a different mechanism (not a different anti-TNF $\alpha$  therapy!)
- Primary responder now relapsing**
  - Assess for inflammation
  - If suspect immunogenicity, switching to second anti-TNF is reasonable<sup>1-3</sup>
  - If not immunogenicity, consider a different mechanism of treatment
    - Methotrexate?
    - Natalizumab?
    - Surgery?

1. Sandborn, et al. Ann Int Med. 2007  
 2. Panaccione R, et al. DDW 2008: #920  
 3. Rutgeerts PJ, et al. DDW 2008: #434

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### SAFETY Overview

(no head-to-head studies performed)

% of patients	IFX – ACCENT I <sup>1</sup> (54 weeks)		ADA – CHARM <sup>2</sup> (56 weeks)		CZP – PRECISE 2 <sup>3</sup> (26 weeks)	
	PLB n = 188	IXF 5 mg/kg n = 193	PLB n = 261	ADA 40 mg E2W n = 260	PLB n = 212	CZP 400 mg n = 216
AEs	NR	NR	85	89	68	65
SAEs	29	28	15	9	6.6	5.6
AEs leading to study discontinuation	3	15	13	7	13.2	8.3
Serious infections	4	4	3	3	1	3
Malignancies	2 cases	3 cases	1 case	-	-	-
Cases of TB	-	1 case	-	2 cases	-	1 case
Deaths	-	3 cases	-	1 case (during open label phase)	-	1 case* (fentanyl overdose - open-label)

NR: Not reported

1. Hanauer et al. Lancet 2002;359:1541-49  
 2. Colombel et al. Gastroenterology 2007;132:52-65  
 3. Schreiber et al. Gastroenterology 2006;130(Suppl)  
 4. A-479 (Poster T1126)

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### Safety Of Infliximab And Other Crohn's Disease Therapies TREAT Registry Data

Current Medication	Adjusted Odds Ratio (95% CI)		Odds Ratio (95% CI)	
	Serious Infections*	Mortality*	All Cancer	Lymphoma
Infliximab	1.28 (0.87-1.90)	0.93 (0.59-1.45)	0.74 (0.49-1.12)	0.8 (0.22-2.99)
6-MP/AZA/MTX	0.91 (0.63-1.31)	0.75 (0.49-1.14)	NR	NR
Corticosteroids	2.04 (1.42-2.93**)	1.96 (1.28-3.00*)	NR	NR
Narcotic analgesics	2.17 (1.51-3.14**)	2.06 (1.33-3.21**)	NR	NR

NR = not reported.  
\*Multivariate; \*\*P<0.001; \*P=0.002.  
Lichtenstein et al. *Gastroenterology*. 2007;132(4 Suppl 2):A-178.

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### ENCORE registry: Serious infections

- ENCORE: Prospective post-marketing safety surveillance registry
  - 5-year safety data in CD patients treated with IFX or non-biologic therapy

	IFX (n=1166) (1506 pt-yrs)	Non-biologic group (n=842) (1016 pt-yrs)
Median follow-up (months)	13.2	12.7
Mean disease duration (years)	9.1	8
Initial disease severity (HBI score)	8.4	6.3
Overall AEs (%)	53.7	41.2
CD-related AEs (%)	12.9	8.05
Serious infections (%)	2.8	1.7
Severe infections (1,000 pt-yrs)	21.9	13.8

- 122 patients switched from non-biologic to IFX group
- Hospitalization, need for narcotics, treatment with MTX and AZA greater at baseline for IFX group

Colombel et al. *Gastroenterology*. 2008; 134(4, Suppl 1):A472 (T1048)

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### Safety of anti-TNF antagonists in Crohn's disease: Meta-analysis of placebo-controlled trials

- MEDLINE, Cochrane Library, EMBASE: 21 studies; n=5356
- Overall and individual efficacy and safety of infliximab, adalimumab, certolizumab pegol, etanercept, onercept and CDP571

Overall analysis	Anti-TNF group (n=3341) (%)	Control group (n=2015) (%)	95% CI
Serious infections	2.09	2.13	-0.45 - 0.65
Malignancies	0.24	0.39	-0.45 - 0.18
Deaths	0.21	0.05	-0.21 - 0.29

- Anti-TNF therapy is safe and effective in patients with CD refractory to standard medical therapy

Peyrin-Biroulet et al. *Clin Gastroenterol Hepatol*. 2008; 6:644-53

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### Histoplasmosis

- FDA warning 9/4/08 for invasive fungal infections associated with anti-TNF treatment
- Histoplasmosis
  - 241 cases (infliximab 207; etanercept 17; adalimumab 16; certolizumab 1)
  - 21 unrecognized early, 12 of these died
- Also cases of coccidiomycosis and blastomycosis

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### Meta-analysis of lymphoma rate associated with anti-TNF agents

- 8905 patients representing 20,602 pt-years
- 13 Non-Hodgkin lymphomas (mean age 52, 62% male)
- 10/13 exposed to IM (not reported in 2)
- 1/2 died as a result of NHL

	NHL rate per 10,000	SIR	95% CI
SEER all ages	1.9	-	-
IM alone	3.6	-	-
Anti-TNF vs SEER	6.1	3.23	1.5-6.9
Anti-TNF vs IM alone	6.1	1.7	0.5-7.1

Siegel et al. Clin Gastroenterol Hepatol. 2009.

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### Key points: Combination therapy

- Understanding study design and patient type is necessary for predicting the benefit of combination therapy:
  - Patients failing IMMs before biologic therapy may not benefit from combination approach
  - Patients who failed IMMs before biologic therapy and are stable on combination therapy may be withdrawn from the IMMs, without loss of response to the biologic for at least two years
  - Patients who are IMMs-naïve have efficacy benefit of combination therapy, particularly with endoscopic evidence of disease and elevated CRP

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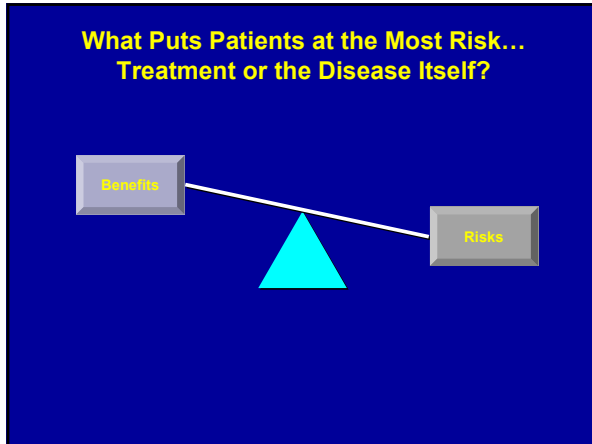
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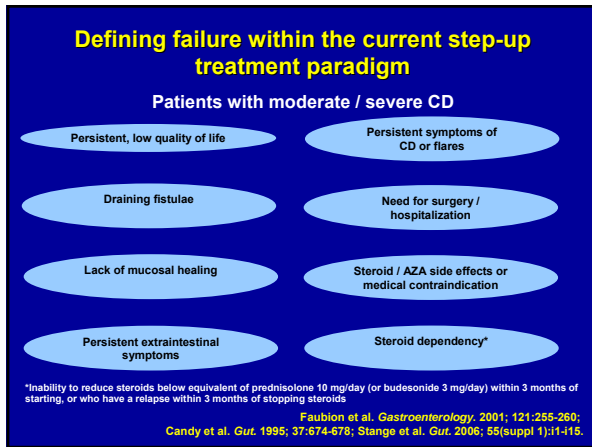
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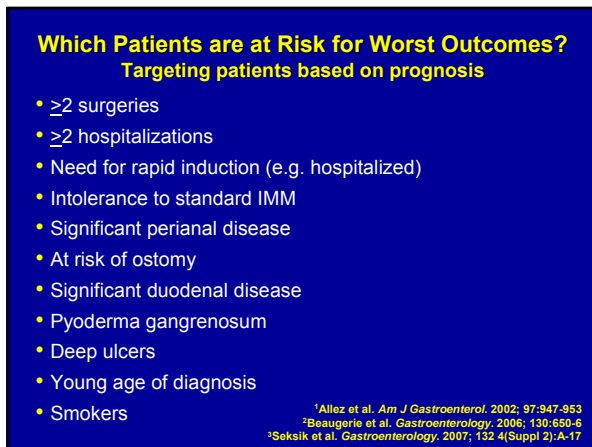
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**Summary: Biologics in IBD 2009-2010**

- Available biologic therapy is effective in IBD.
- Evolving evidence supports the role of biologic therapy earlier in the treatment algorithm to improve efficacy and affect outcomes.
- Maximize response and maintenance of response!
  - Loss of response to therapy is common. Distinction between primary non-response and secondary loss of response is important.
  - The long-term need for concomitant immune-modulator therapy remains uncertain, but recent evidence supports its use in most patients.
- We are moving from a failure model of therapy to a prognostication model of therapy selection.

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