

What are the Unmet Needs in the Management of IBD?

Shane Devlin, MD, FRCPC
Inflammatory Bowel Disease Group
The University of Calgary

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Some Real Cases: #1

- 32 yo male with pan UC.
- Grumbling phenotype with 8 BM per day with blood 75% of the time, modestly elevated CRP
- Poor quality of life
- No clinical or endoscopic response to dose escalated infliximab, weekly adalimumab and now failing golimumab

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Some Real Cases: #2

- 42 yo female with ileal and pan colonic CD
- Prior ileo-cecal resection in 2009
- Induction and maintenance infliximab in 2010
- Developed delayed type hypersensitivity reaction to infliximab in 2012
- Switched to adalimumab with incomplete response, but recently developed severe psoriaform lesions that are not responding to topical or UV therapy

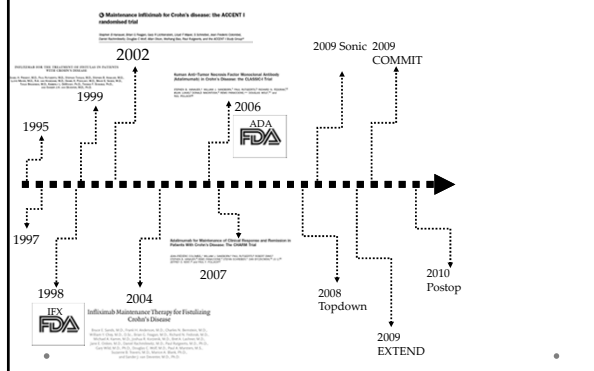
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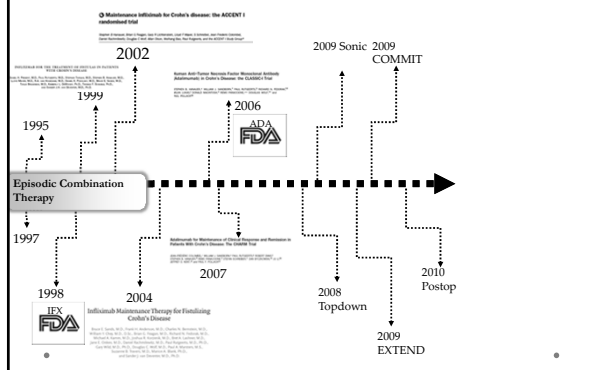
Some Real Cases: #3

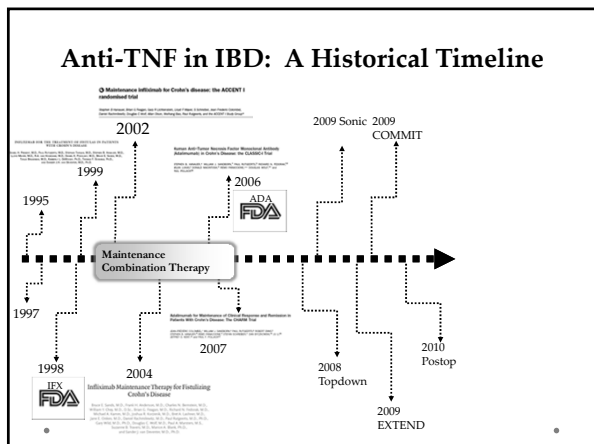
- 78 yo male patient
- Multiple comorbidities
- Newly diagnosed steroid dependent pan ulcerative colitis, non responsive to 5-ASA

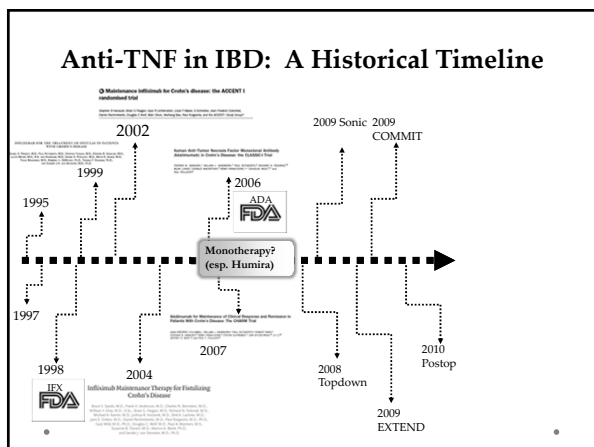
Anti-TNF in IBD: A Historical Timeline

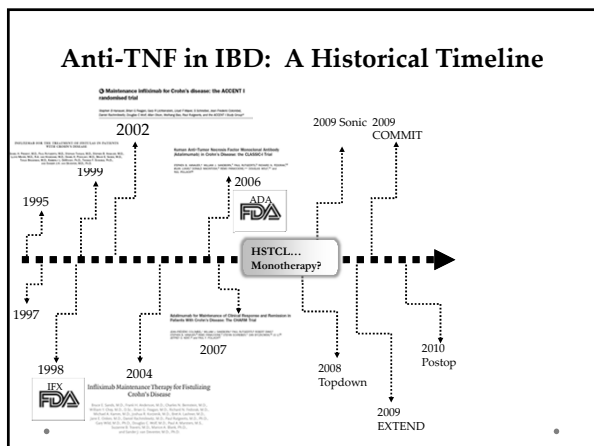


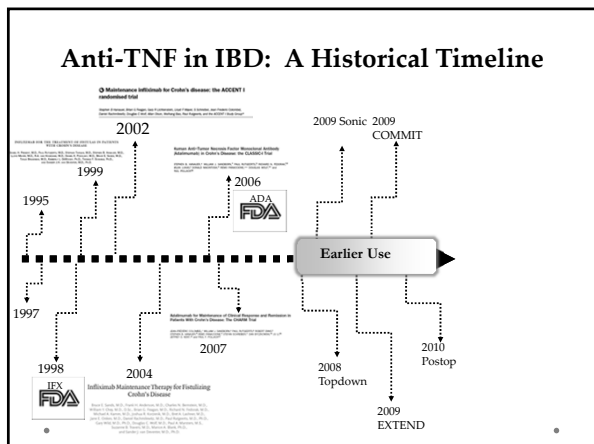
Anti-TNF in IBD: A Historical Timeline

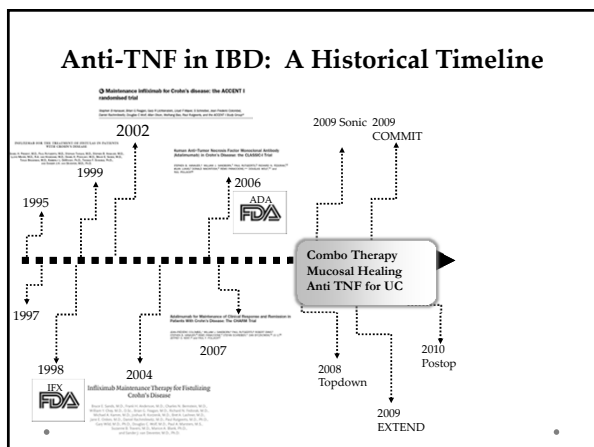


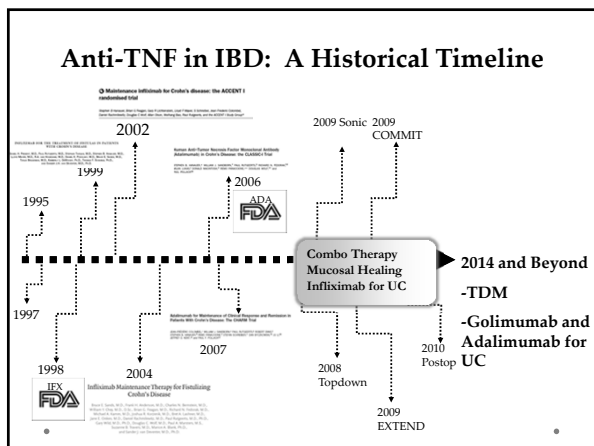












Maximize the Use of Anti-TNF Therapy

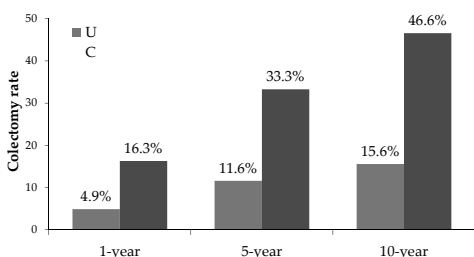


Yet...We have unmet needs

- IBD is a serious, systemic disease
- Primary non-response
- Inadequate response
- Secondary loss of response due to a variety of mechanisms
- Intolerance due to adverse events
- Ongoing steroid use

The Requirement for Colectomy in IBD remains Higher than we'd like

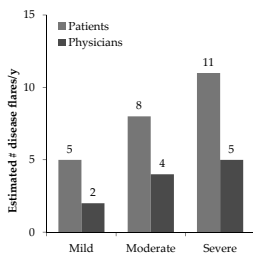
Colectomy rates in meta-analysis of 30 population-based studies



Frolkis et al. *Gastroenterology* 2013;Online doi:10.1053/j.gastro.2013.07.041

UC Negatively Impacts Patient Quality of Life

Patients & physicians differ in their perception of disease severity



- 62% say their disease made it difficult to lead a normal life
- Only 42% believed that remission means living without symptoms

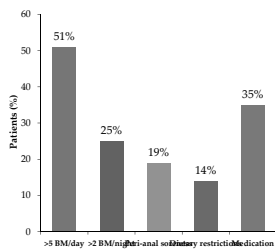
Rubin et al. *Inflamm Bowel Dis* 2009; 15:581-8

Colectomy and IPAA Is Not Optimal

Postoperative problems are frequent

- Pouchitis: 46%¹
- Female infertility: 48%²
 - (vs. 15% in medically-treated UC)
- Other complications¹
 - Sexual dysfunction, pouch leakage, abscess formation, fistula formation, small bowel ileus, anastomotic stenosis, and fecal incontinence

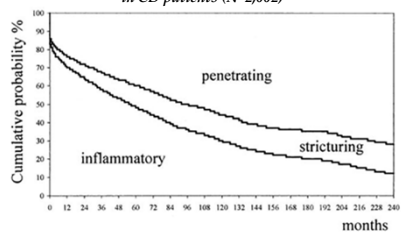
Functional outcomes after colectomy¹



1. Ferrante et al. *Inflamm Bowel Dis* 2008; 14:20-8; 2. Waljee et al. *Gut* 2006; 55:1575-8

Disease with Serious Complications

Probability of developing penetrating or stricturing complication in CD patients (N=2,002)

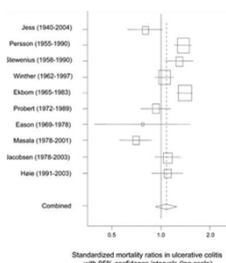


Patients at risk : 2002, 552, 229, 95, 37

Cosnes et al. *Inflamm Bowel Dis* 2002;8:244-50

Mortality in UC

Mortality rates in meta-analysis of 10 population-based studies

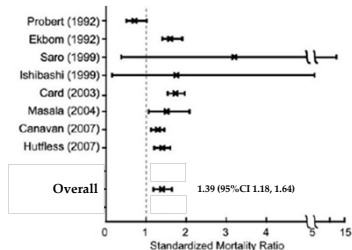


- Greater risk of dying during the first years of follow-up, and in patients with extensive colitis vs. general population
 - 17% of all deaths were UC-related mortality
 - Higher rates of mortality from GI diseases, nonalcoholic liver diseases, pulmonary embolisms, and respiratory diseases

Jess et al. *Am J Gastro* 2007;102:609-17

CD Associated with Increased Mortality Risk

Standardized mortality rates (SMR) in population-based cohort studies

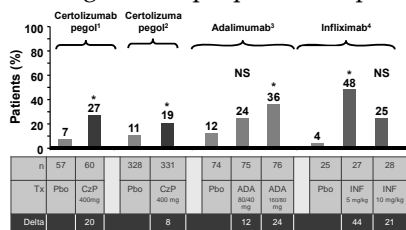


- Each year, 114 deaths in Canada are attributed to CD and UC

Bewtra et al. *Inflamm Bowel Dis* 2013; 19:599-613

Primary and Inadequate Response

We are not successful in inducing remission with a significant proportion of patients

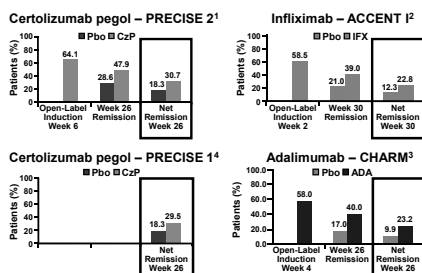


*P<.05
NS=not significant.

Overall induction of remission ~30-50%

- Schreiber S, et al. *Gastroenterology* 2006;126:907-18.
- Sandborn WJ, et al. *N Engl J Med* 2007;357:223-38.
- Hanauer SB, et al. *Gastroenterology* 2006;130:323-33.
- Targan SR, et al. *N Engl J Med* 1997;337:1029-38.

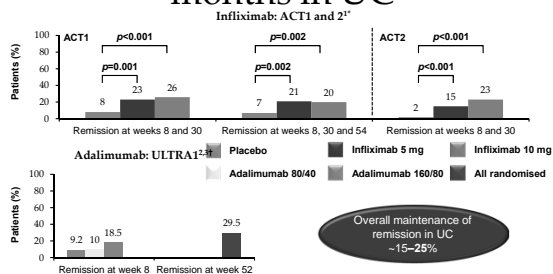
6 Month Data



- CD, Crohn's disease.
- Schreiber S, et al. *N Engl J Med* 2007;357:239-50.
 - Hanauer SB, et al. *Lancet* 2002;359:1541-9.
 - Colombel JF, et al. *Gastroenterology* 2007;132:82-93.
 - Sandborn WJ, et al. *N Engl J Med* 2007;357:228-38.

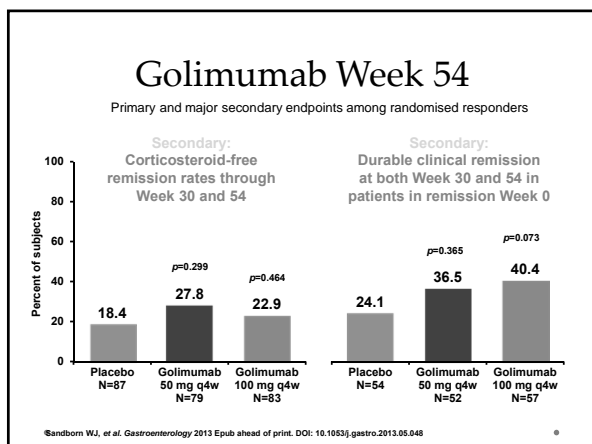
Overall maintenance of remission in CD ~25-30%

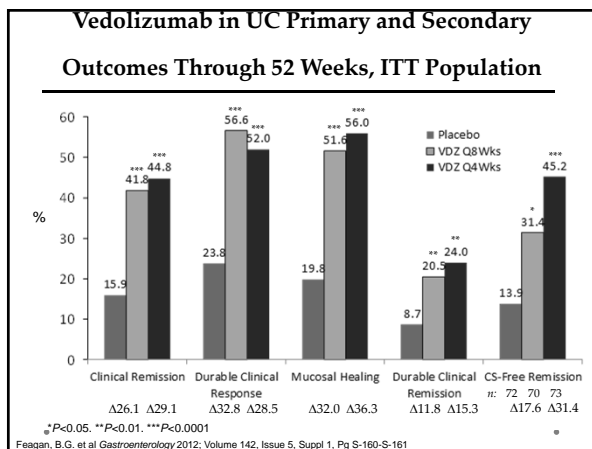
Sustained remission at 12 months in UC

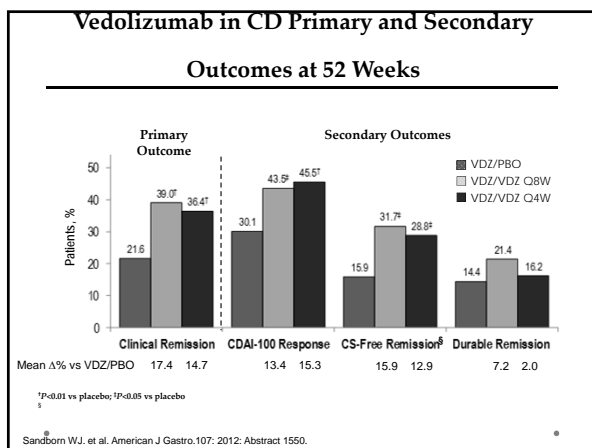


Overall maintenance of remission in UC ~15-25%

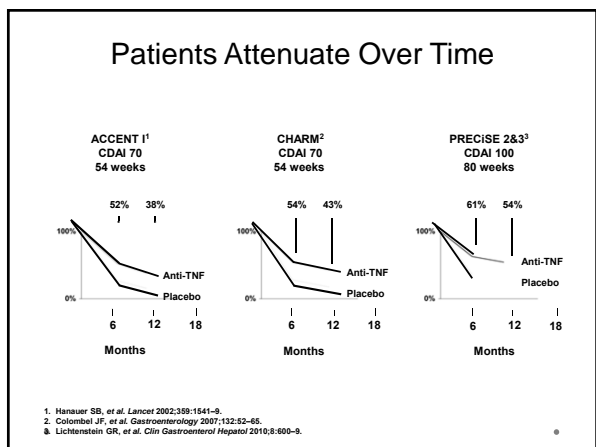
- *Clinical remission was defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point.
¹Non-responder imputation (NRI) analyses, Week 8; mNRI analyses, Week 52.
²mNRI (modified NRI): did not count patients who dose escalated (and were in remission) as failures (post-hoc analyses).
³Clinical remission: Mayo score <2 with no individual subscore >1.
⁴Rutgeerts P, et al. *N Engl J Med* 2005;353:2462-76. 2. Reinisch W, et al. *J Crohns Colitis* 2011;5:810. 3. Reinisch W, et al. *Gut* 2011;60:780-7.

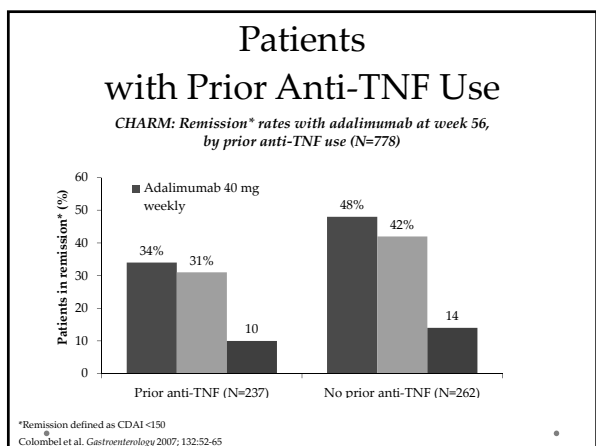






Secondary Loss of Response





Outcomes of maintenance therapy with 3rd anti-TNF

Retrospective, single-center cohort study (N=664) of CD patients on maintenance anti-TNF therapy examining long-term outcomes by number of prior anti-TNFs (1, n=444; 2, n=176; 3, n=42)

SIBDQ

Number of anti-TNFs received	Average score
1	50.9
2	47.9
3	40.3

HBI

Number of anti-TNFs received	Average score
1	2.9
2	3.9
3	5.2

- Two thirds of patients on long-term anti-TNF maintenance therapy remained on 1st agent
- Patients on their 1st or 2nd anti-TNF had similar long-term outcomes. Those on their third anti-TNF agent had significantly worse disease control and higher healthcare utilisation

HBI, Harvey-Bradshaw Index; SIBDQ, Short Inflammatory Bowel Disease Questionnaire.
Bertora et al. Gastroenterology 2012; 142(Suppl):S-357. DDW 2012, Abstract Sa1916.

Sometimes we need to stop therapy

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Uncommon but Remains a Relevant Concern

Adverse events of interest in patients treated with adalimumab in 6 global clinical trials (N=3160)

Adverse Event	Events/100 pt-y (N=3401.9 p-y)
Any SAE	34.4
Serious infection	6.6
Malignant neoplasms	1.3
Opportunistic infections	2.0
Congestive heart failure	<0.1
Demyelinating disorder	0.2
Lupus-like syndrome	0.2
Any fatal adverse event	0.1 (4 patients)

- Most common infectious SAEs were: abscess 2.5%, GI infection (excluding abscess) 1.0%, and pulmonary infection 0.9%

Colombel et al. Inflamm Bowel Dis 2009;15:1308-19.

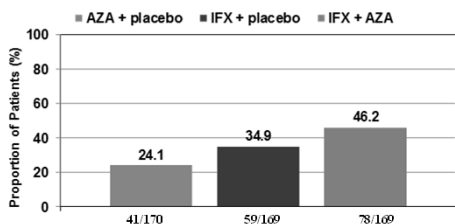
Infection and TNF Antagonists

- TREAT registry n > 6,000, f/u > 5yrs
- Factors independently associated with serious infections (Descending order of risk) :
 - Disease activity mod-severe (HR = 2.24, 95% CI = 1.57, 3.19; P < 0.001),
 - Narcotic analgesic treatment (HR = 1.98, 95% CI = 1.44, 2.73; P < 0.001)
 - Prednisone therapy (HR = 1.57, 95% CI = 1.17, 2.10; P = 0.002)
 - Infliximab treatment (HR = 1.43, 95% CI = 1.11, 1.84; P = 0.006).

Lichtenstein GR. Am J Gastroenterol. 2012 Sep;107(9):1409-22.

Our Best Treatment With Earlier Use and Combination Therapy

All randomised patients (N=508)*



Fewer than half are in remission and off of steroids
In most anti TNF trials, the rate of SFR at one year is around 25-30%

*Patients who did not enter the Study Extension were treated as non-responders
Columbel JF, et al. N Eng J Med 2010; 362:1383-95.

In Summary...

- IBD is a serious systemic condition with significant potential complications
- Anti TNF therapy has, and will continue to markedly enhance our ability to treat patients with a view to affecting a longer term change in disease course
- However, more than 10 years of wide-spread use has taught us the limitations and heightened our awareness of a need for alternative therapies
- Loss of response, continued steroid use, systemic effects remain relevant concerns
- There is considerable room to improve upon as we continue to strive for the safest and most efficacious treatments for our patients with IBD.
