

Debate:
Initiation of maintenance treatment in moderate to severe Crohn's disease:
Immunomodulators vs biologic agents

The case for immunomodulators

James Markowitz, MD
Cohen Children's Medical Center of NY
New Hyde Park, NY

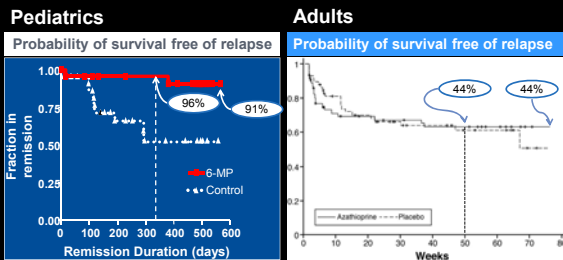
Disclosures

- In the past 12 months, I have served as a consultant with the following manufacturers of commercial product(s) discussed in this CME activity:
 - Janssen Pharmaceuticals (consulting fee)
 - UCB (consulting fee)
 - Abbvie (consulting fee)
- I will be discussing an unapproved use of a commercial product in my presentation.



DO THIOPURINES MAINTAIN REMISSION?

Do Thiopurines Maintain Remission?



Markowitz J et al. Gastro. 2000;119:895

Panes et al. Gastro 2013;145:766-774

Do Thiopurines Maintain Remission?

Pediatrics	6-MP	Control	Adult Study Population	
N	27	28	N	131
Age (yrs)	13.0 ± 2.3	13.4 ± 2.5	Mean age (yrs)	36
% male	55%	64%	% male	45%
% ileocolitis	70%	79%	% ileocolitis	35%
% current smokers	0%	0%	% current smokers	44%
Mean PCDAI	46.7±13.9	44.7±16.4	Mean CDAI at study onset	103
% PCDAI ≥30	100%	100%	% CDAI >150	27%
% on steroids	100%	100%	% on steroids	70%

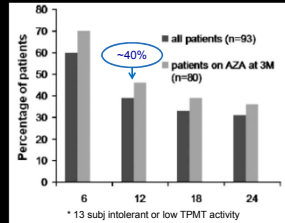
Markowitz J, et al. Gastro 2000;119:895

Panes J, et al. Gastro 2013;145:766-774

Azathioprine Efficacy in Peds CD: Paris

- Single pediatric IBD center
- AZA monotherapy ≥ 2 yrs f/u
- Indications for AZA
 - At Dx or 1st relapse
 - PCDAI >30
 - Severe/extensive mucosal lesions
 - Steroid or EN dependent
 - Post-resection (n=10)

Remission rates



- No risk factor predicted response except surgery as remission induction
- Few relapses after 12 months in those in remission at 1 yr

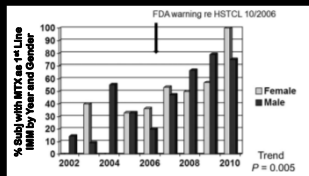
Riello R, et al. IBD 2011;17:2138-43

HOW ABOUT METHOTREXATE?

Methotrexate Use as First Line Immunomodulator is Increasing in CD

Data from the Pediatric IBD Collaborative Research Group Registry

22/81 (27%) receiving MTX as first IM experienced >1yr sustained steroid, thiopurine, surgery, and anti-TNF free clinical remission



Sunseri W. Inflamm Bowel Dis 2014;20:1341-1345

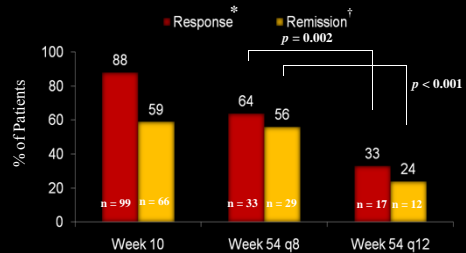
Methotrexate in Pediatric CD

Retrospective studies	Location	Steroid Free Remission	
		6 months	12 months
Turner D, et al. Am J Gastroenterol 2007;102:2804-2812	US and Canada	40-60%	42%
Uhlen S, et al. Inflamm Bowel Dis 2006;12:1053-1057	France	49%	45%
Willot S, et al. Inflamm Bowel Dis 2011;17:2521-6	Canada	37%	25%

ANTI-TNF EFFICACY

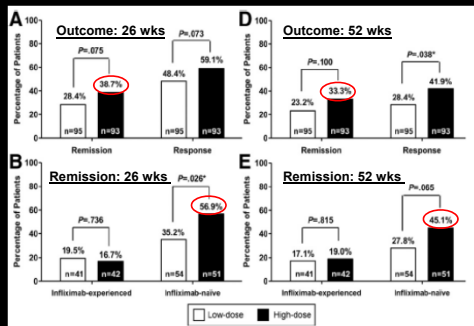
REACH

Pediatric Infliximab Trial



Hyams et al. Gastroenterology 2007;132:863-873

IMagINE 1: Adalimumab in Peds CD



Hyams J, et al Gastro 2012;143:365-74

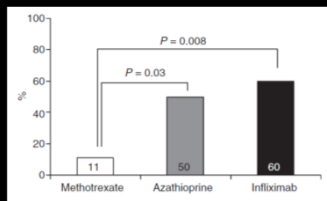
DO IMMUNOMODULATORS RESULT IN MUCOSAL HEALING?

Mucosal Healing with CD Monotherapy

Single center adult CD trial
2007-2009
N=51

Inclusions:

- Previously identifiable ulcerations on ileocolonoscopy
- Clinical remission for at least 3 months on monotherapy

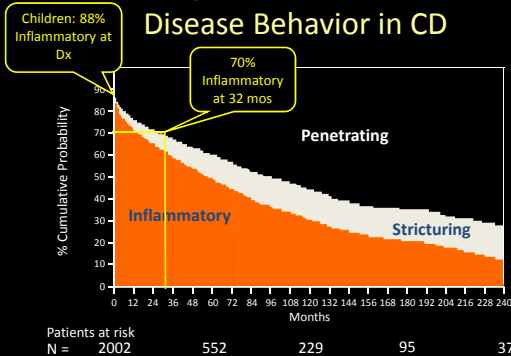


No difference in histologic inflammation score among the three different therapies

Laharie D, et al. Aliment Pharmacol Ther 2011; 33: 714-721

DO IMMUNOMODULATORS AFFECT THE PROGRESSIVE CHANGE IN CD BEHAVIOR?

Long-Term Evolution of Disease Behavior in CD



Dubinsky et al. Clin Gastro Hepatol 2008;6(10):1105-1111

Cosnes J et al. Inflamm Bowel Dis. 2002;8:244.

Effect of Thiopurine Rx on Change in CD Behavior

Paris, France

- 230 adults
 - 42 on 6MP/AZA
- All B1 at inclusion
- At 5 yrs
 - All subj: B1 → B2 = 10%
 - 6MP/AZA: B1 → B2 = 10%
 - All subj: B1 → B3 = 26%
 - 6MP/AZA: B1 → B3 = 17%

Cosnes J, et al. IBD 2002;8:244-50

Olmsted County, MN, USA

- 248 adults
 - 22 on 6MP/AZA
- All B1 at study inception
- 6MP/AZA associated with nonsignificant decrease in risk for B2 or B3
 - OR 0.87 (0.31-2.40), p=0.78

Thia KT, et al. Gastroenterol; 2010;139:1147-55

Evolution of Pediatric CD Behavior: PIBDCRG

- Data extracted from a larger study evaluating serologic and genetic predictors of complicated pediatric CD
- All subjects with uncomplicated inflammatory (B1) CD behavior at diagnosis

N	116
Mean Age @ Dx (yrs)	11.5 ± 2.6
Gender (% male)	65%
Duration of F/U (yrs)	5.2 ± 1.7
CD Phenotype at last f/u	
B1	91
B2	6
B3	8
Perianal penetrating	11

13/14
within 5 yrs
of Dx

Markowitz J et al, DDW 2011

Treatments: Complicated vs Inflammatory CD

	Treatments (n=68)		
	Corticosteroids	Immunomodulators	Anti-TNF
B1^	46/55 (84%)	45/55 (89%)	24/55 (44%)
B2+B3*	12/13 (93%)	7/13 (54%)	2/13 (15%)
P Value	0.6734	0.0077	0.1100

^ Treatments prescribed at any time during the first 5 years of f/u

* Treatments prescribed prior to the development of B2 or B3

Markowitz et al, DDW 2011

DO THIOPURINES AFFECT THE RATE OF SURGERY?

Immunosuppressive Rx Does Not Decrease the Rate of Intestinal Resection

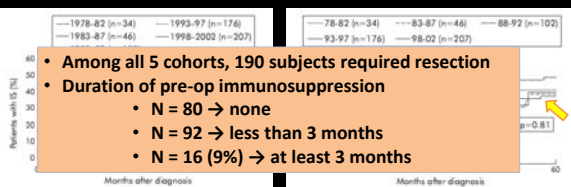


Figure 1. Kaplan-Meier estimates of the cumulative risk of receiving immunosuppressants in five chronologic cohorts of patients with Crohn's disease.

Figure 2. Kaplan-Meier estimates of the cumulative risk of intestinal resection in five chronologic cohorts of patients with Crohn's disease.

Cumulative 5 yr risk of receiving IS ranged from 0.13 – 0.56 (p<0.001)

Cumulative risk of intestinal resection at 5 yrs unchanged (0.34-0.36 in each cohort)

Cosne J et al. Gut 2005;54:237-41

Thiopurines Decrease Risk of Surgery in Crohn's Disease

Study	Location	Years of study	Hazard or Odds Ratio
Ramadas AV, et al. Gut 2010;59:1200-6	Cardiff, Wales, UK	1986-2003	Thiopurine use in the 1st year of dx: OR 0.47 (0.27-0.79; p=0.005)
Picco MF, et al. Am J Gastro 2009;104:2754-9	Jacksonville, FL, USA	1994-2005	Immunomodulator use (> 6 mos): HR 0.41 (0.21-0.81; p=0.011)
Lakatos L et al. Am J Gastro 2012; 107:579-88	Hungary	1997-2009	AZA started within 1.5 yrs of Dx: HR 0.40 (0.18-0.83; p<0.023)
Vernier-Massouille et al. Gastro 2008;135:1106	France	1988-2002	Azathioprine use: HR 0.51 (0.33-0.78; p<0.001)

Surgery in Pediatric CD: Effect of Thiopurines

	Vernier-Massouille 2008	Gupta 2006	Schaeffer 2010
Number of subjects	404	989	854
Years assessed	1988-2002	Before 2003	2002-2008
Surgery rate: 1 yr	7%	5.7%	3.4%
Surgery rate: 5 yrs	34%	17%	13.8%
% on 6MP/AZA	61% at some time during course	60% at some time during course	44% by 3 months 88% by 1 year
Immunomodulator effect			
Hazards ratio (95% CI)	0.51 (0.33-0.78)	"Not significant"	0.8 (0.4-1.4)
p value	p<0.001		p=NS

Vernier-Massouille, et al. Gastroenterol 2008;135:1106-1113
Schaeffer M, et al. Clin Gastroenterol Hepatol 2010;8:789-794
Gupta N, et al. Gastroenterol 2006;130:1069-1077

THIOPURINES AND GROWTH

Growth is Not Improved after Thiopurine Therapy

North American Registry (PIBDCRG) 2009

- N = 176
- Started 6MP/AZA by:
 - 3 months = 49%
 - 1 year = 60%
 - 2 years = 86%
- Compared to baseline, growth velocity not improved at 1 or 2 years after Dx

Glasgow, Scotland 2012

- N = 116
- Started 6MP/AZA by:
 - “early” = 12%
 - 1 year = 43%
- Slight improvement in height velocity at 2 and 3 years
- Multivariate regression analysis: negative association between height Z-score and azathioprine use

Pfefferkorn M, et al. JPGN 2009;48:168–174

Malik S, et al. Arch Dis Child 2012;97:698–703

Effect of Immunomodulators on Natural History of CD

Corticosteroid free maintenance	+++
Change from B1 → B2 or B3	+
Decrease risk of 1 st surgery	++
Improve growth	0

WHAT ABOUT TOXICITY?

Immunomodulator Toxicity

Thiopurines

- Leukopenia (3.8%), severe (1.2%)
- Severe infection (<1%) - sepsis, varicella
- Pancreatitis (<5%)
- Abnormal LFT (?10-15%)
- Intolerance (nausea, vomiting, diarrhea)
- Malignancy

Methotrexate

- TERATOGENICITY: Pregnancy Class X
- Pneumonitis/pulmonary fibrosis
- Severe hepatotoxicity
- Intolerance (nausea, vomiting, diarrhea)
- Photosensitivity

Potential Adverse Effects of Infliximab

- Hypersensitivity reactions
 - Acute
 - Delayed/Serum sickness
- Immunogenicity
- Headache
- Rash
- Infections
- Demyelinating disorders
- Autoantibodies
 - SLE-like
- Pancytopenia
- Hepatotoxicity
- Heart Failure
- Malignancy

Systematic Review: Infection and Lymphoma in Pediatric IBD

Infection Risk	Pediatric anti-TNF/ 10,000 PYF	Thiopurine/ 10,000 PYF	Corticosteroids/ 10,000PYF
Serious infection	352	333	730

Lymphoma Risk	Pediatric anti-TNF/ 10,000 PYF	SEER/ 10,000 PYF	Thiopurine/ 10,000 PYF	Adult anti-TNF/ 10,000 PYF
Lymphoid neoplasias	2.1	0.58	4.5	6.1
Hodgkin lymphoma	1.05	0.12	2.25	-
NHL	1.05	0.46	2.25	6.1

All comparisons not significant

Dulai PS, et al. Clin Gastro Hepatol 2014 (online ahead of press)

Thiopurines and Hepatosplenic T-Cell Lymphoma in IBD: No Anti-TNF Therapy

N	16 (9 CD, 7 UC/IC)
Age, yr: Median (Range)	22.5 (15-35)
% male	62.5% (31.5% ??)
Duration TP Rx, yr: Median (Range)	6 (3-17)

Risk Estimates for HSTCL with Thiopurine But No Anti-TNF

All patients on thiopurine Rx	1:45,000
All males <35 yrs on thiopurine	1.4/10,000 pt-yrs
	1:7404

Kotlyar D et al. Clin Gastroenterol Hepatol 2011;9:36-41

Skin Cancer and IBD Therapy

Table 2 Impact of medications on skin cancer risk among inflammatory bowel disease patients.

	NMSC	Melanoma
Thiopurines	+	-
Methotrexate	-	-
Calcineurin inhibitor ^a	-	-
Biologic ^b	+(CD)	+
Combination therapy	+(CD)	?

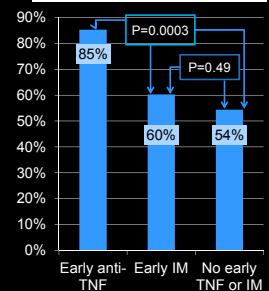
NMSC, non-melanoma skin cancers; CD, Crohn's disease.
^a Tacrolimus or cyclosporine.
^b Infliximab or adalimumab.

Magro F, et al. Journal of Crohn's and Colitis (2014) 8, 31-44

Increased Effectiveness of Early Therapy With Anti-Tumor Necrosis Factor-α vs an Immunomodulator in Children With Crohn's Disease

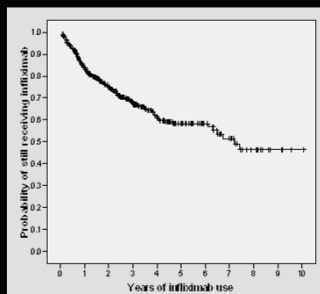
- RISK observational cohort
- Triads matched to clinical characteristics of the children treated with infliximab monotherapy in first 3 months after dx
 - Disease activity by PCDAI
 - Age at dx
 - Linear growth
 - Perianal disease
 - Deep ulceration on initial colonoscopy
 - CD location
 - Laboratory studies
- Propensity score analysis

Steroid-free Remission at 1 Yr



Walters T et al. Gastro 2014;146:383-391

Overall Durability of IFX

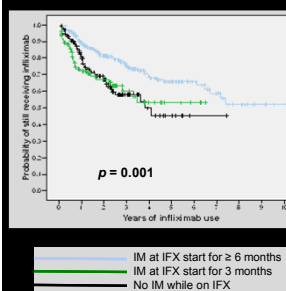


Time	Probability ± standard error
1 year (n=346)	0.84 ± 0.02
2 years (n=248)	0.75 ± 0.02
3 years (n=155)	0.67 ± 0.03
4 years (n=102)	0.61 ± 0.03
5 years (n=69)	0.58 ± 0.03
7 years (n=25)	0.52 ± 0.04

Data from the Pediatric IBD Collaborative Research Group Registry

Grossi V, et al. DDW 2014

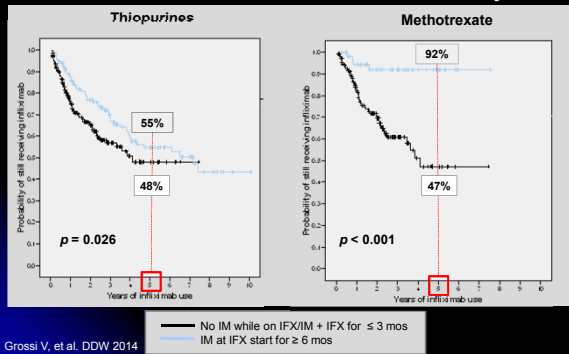
Effect of Concomitant IM Use on IFX Durability



Time	Probability ± standard error		
	No IM while on IFX	IM at IFX start	
1Y	0.81 ± 0.04	≤ 3 months	0.72 ± 0.05
		≥ 6 months	0.89 ± 0.02
2Y	0.67 ± 0.05	≤ 3 months	0.67 ± 0.05
		≥ 6 months	0.81 ± 0.03
3Y	0.58 ± 0.05	≤ 3 months	0.60 ± 0.06
		≥ 6 months	0.75 ± 0.03
4Y	0.50 ± 0.07	≤ 3 months	0.53 ± 0.07
		≥ 6 months	0.69 ± 0.04
5Y	0.45 ± 0.08	≤ 3 months	0.53 ± 0.07
		≥ 6 months	0.66 ± 0.04

Grossi V, et al. DDW 2014

Effect of Thiopurines versus Methotrexate on IFX Durability



We need to risk stratify our CD patients

- Children with characteristics of severe disease do best with early infliximab therapy (but not all children have severe CD)
- Immunomodulator efficacy ~40-60% over 18 months with relatively stable long term maintenance benefit after 2 years
- Anti-TNF efficacy 50-85% over 12 months, but with progressive loss of durability over time for monotherapy
- Benefit of combination therapy (IM + biologic) greatest if IM therapy >3-6 months at initiation of anti-TNF
- **Start maintenance with an immunomodulator!!**
 – ?Gender specific? → MTX: ♂, 6-MP/AZA: ♀