Initiation of Maintenance Treatment in Moderate to Severe New Onset Crohn's Disease

The Case for Starting with Anti-TNFα Agents

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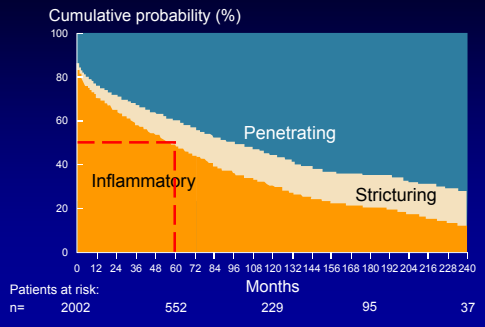
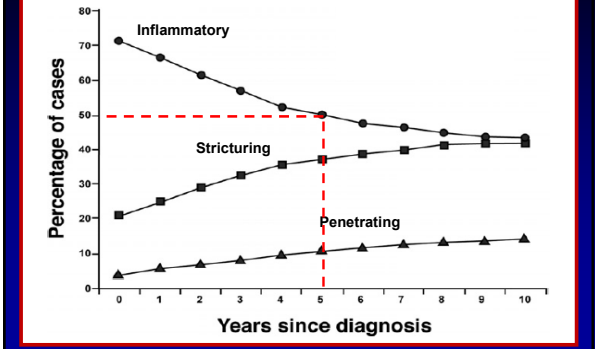
** Products or services produced by this company are relevant to my presentation.*

Long-Term Evolution of CD is Structural Damage



Cosnes J et al, *Inflamm Bowel Dis* 2002

CD Behavior in 404 Pediatric Patients

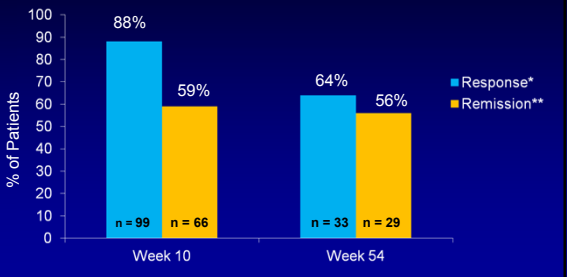


Vernier-Massouille G et al. *Gastroenterology* 2008

Shifting CD Therapeutic Goals

- **PREVIOUS GOALS**
  - relieve symptoms
  - optimize growth & development
  - improve quality of life
  - minimize steroid exposure
- **ADDED GOALS**
  - heal the mucosa
  - modify the natural course of disease to prevent complications

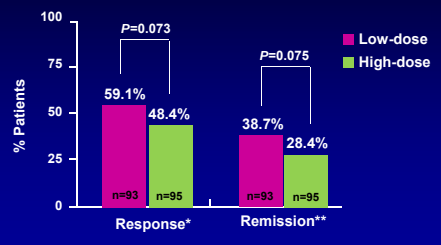
REACH Trial: Response & Remission Rates for Maintenance Infliximab Every 8 weeks



* ↓ from baseline of ≥ 15 points in PCDAI score & PCDAI score ≤ 30
** PCDAI score ≤ 10

Hyams J et al. *Gastroenterology* 2007

IMAgINE 1: Adalimumab Clinical Remission at Week 26 in Pediatric Crohn's disease



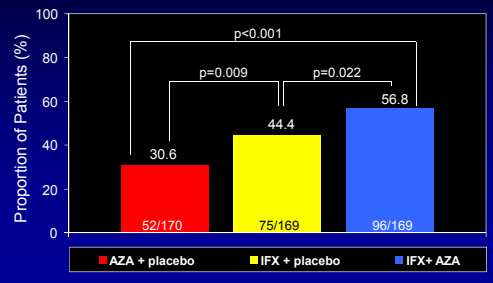
* ↓ from baseline of ≥ 15 points in PCDAI score
** PCDAI score ≤ 10

Hyams J et al, *Gastroenterology* 2012

Anti-TNFs are Effective in Induction and Remission of Luminal and Fistulizing CD

- Infliximab (FDA approval 1998 / Peds 2006)
  - ACCENT I — Hanauer SB et al. *Lancet* 2002
  - ACCENT II — Sands BE et al. *N Engl J Med* 2004
  - REACH — Hyams J et al. Gastroenterology 2007
- Adalimumab (FDA 2007/Peds 2014)
  - CLASSIC I — Hanauer SB et al. *Gastroenterology* 2006
  - CHARM — Colombel JF et al. *Gastroenterology* 2007
  - IMAgINE 1 — Hyams J et al. Gastroenterology 2012
- Certolizumab (FDA 2008)
  - PRECISE 1 — Sandborn WJ et al. *N Engl J Med* 2007
  - PRECISE 2 — Schrieber S et al. *N Engl J Med* 2007

SONIC Primary Endpoint: Corticosteroid-Free Clinical Remission at Week 26



N=509

Colombel JF et al. *N Engl J Med* 2010

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Effectiveness of Anti-TNFα for Crohn Disease: Research in a Pediatric Learning Health System

Christopher B. Forrest, Wallace V. Crandall, L. Charles Bailey, Peixin Zhang, Marshall M. Joffe, Richard B. Colletti, Jeremy Adler, Howard I. Baron, James Berman, Fernando del Rosario, Andrew B. Grossman, Edward J. Hoffenberg, Esther J. Israel, Sandra C. Kim, Jenifer R. Lightdale, Peter A. Margolis, Keith Marsolo, Devendra I. Mehta, David E. Milov, Ashish S. Patel, Jeanne Tung and Michael D. Kappelman

Pediatrics 2014;134;37; originally published online June 16, 2014;
DOI: 10.1542/peds.2013-4103

Rate Ratios in For Initiator Trials vs. Non-Initiator Trials at 26 and 52 weeks of Follow-Up

Outcome	Duration of Follow-up	Unadjusted Rate Ratios (95% CI)	Adjusted Rate Ratios[a] (95% CI)
		Initiator versus Non-Initiator Trials	
Clinical remission	26 wk	1.44 (1.17–1.77)	1.53 (1.20–1.96)
	52 wk	1.46 (1.22–1.74)	1.52 (1.23–1.89)
Corticosteroid-free remission	26 wk	1.73 (1.38–2.16)	1.74 (1.33–2.29)
	52 wk	1.63 (1.35–1.97)	1.62 (1.28–2.04)

[a] Rate ratios were adjusted for patient age, gender, and race, disease location, duration, and phenotype, and concurrent medications, all measured at baseline of the trial.

Forest CB et al. *Pediatrics* 2014

Gastroenterology 2014;146:383-391

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

Thomas D. Walters,[1,*] Mi–Ok Kim,[2,*] Lee A. Denson,[3] Anne M. Griffiths,[1] Marla Dubinsky,[3] James Markowitz,[4] Robert Baldassano,[5] Wallace Crandall,[6] Joel Rosh,[7] Marian Pfefferkorn,[8] Anthony Otley,[9] Melvin B. Heyman,[10] Neal LeLeiko,[11] Susan Baker,[12] Stephen L. Guthery,[13] Jonathan Evans,[14] David Ziring,[15] Richard Kellermayer,[16] Michael Stephens,[17] David Mack,[18] Maria Oliva–Hemker,[19] Ashish S. Patel,[20] Barbara Kirschner,[21] Dedrick Moulton,[22] Stanley Cohen,[23] Sandra Kim,[24] Chunyan Liu,[2] Jonah Essers,[25] Subra Kugathasan,[26] and Jeffrey S. Hyams,[27] for the PRO-KIIDS Research Group

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1-Year Steroid-Free Remission: Effect of Early Therapy on Propensity Score-Matched Cohorts

Early therapy	N	%	P value
Anti-TNFα only	58	85.3	0.0003 vs IM & no early immunRx
IM only	41	60.3	0.49 vs no early immunoRx
No early immunoRx	37	54.4	

n= 68 for each group

Walters TD et al, *Gastroenterology 2014*

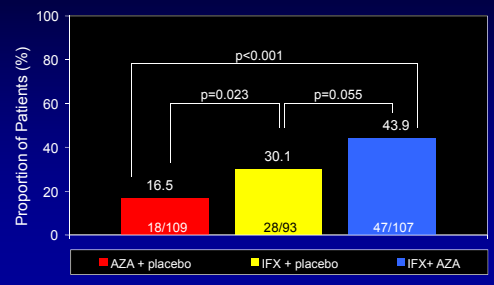
Effect of Early Therapy on Height Z-Score in Study Cohort

	Mean Δ-Height z-score (standard deviation)	P Value*
Anti-TNFα only	+0.14 (0.4)	0.002
IM only	-0.02 (0.4)	0.6
No early immunoRx	-0.06 (1.1)	0.2
All patients	-0.02 (0.71)	0.7

n= 68 for each group
*paired sample *t* test, baseline vs 1 yr

Walters TD et al, *Gastroenterology 2014*

SONIC Secondary Endpoint: Mucosal Healing at Week 26



Colombel JF et al. *N Engl J Med* 2010

Mucosal Healing ~1 year Following Infliximab and Adalimumab Treatment in Children

	Mucosal Healing	Response	No Response
Infliximab	22.2%	44.4%	33.4%
Adalimumab	25%	50%	25%

Nobile S et al, *Eur J Gastroenterol Hepatol 2014*

Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease

F.M. Ruemmele[a,b,c,*,1], G. Veres[d,1], K.L. Kolho[e,1], A. Griffiths[f,1], A. Levine[g,1], J.C. Escher[h,1], J. Amil Dias[i,1], A. Barabino[j,1], C.P. Braegger[k,1], J. Bronsky[l,1], S. Buderus[m,1], J. Martin-de-Carpi[n,1], L. De Ridder[o,1], U.L. Fagerberg[p,1], J.P. Hugot[q,r,1], J. Kierkus[s,1], S. Kolacek[t,1], S. Koletzko[u,1], P. Lionetti[v,1], E. Miele[w,1], V.M. Navas López[x,1], A. Paerregaard[y,1], R.K. Russell[z,1], D.E. Serban[aa,1], R. Shaoul[ab,1], P. Van Rheenen[ac,1], G. Veereman[ad,1], B. Weiss[ae,1], D. Wilson[af,1], A. Dignass[ai,1], A. Eliakim[aj,1], H. Winter[ag,1], D. Turner[ah,1]

***J Crohn's Colitis* 2014:8, 1179**

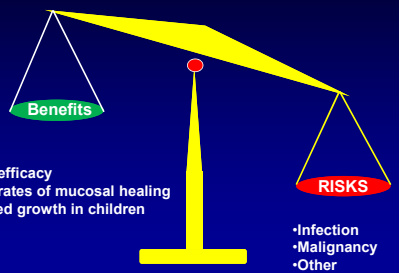
- Anti-TNF therapy as primary induction therapy may be considered for selected children with high risk for poor outcome

Patients at Risk for Poor Outcomes

- Extensive small bowel disease
- Significant growth retardation
- Significant perianal disease
- Stricturing and fistulizing disease
- Severe extraintestinal manifestations
- Significant osteoporosis
- Severe upper GI tract disease
- Increased immune responses (e.g. ASCA, anti-CBir1

Beaugerie L et al. *Gastroenterology* 2006
Loly C et al. *Scand J Gastroenterol* 2008
Dubinsky M et al. *Clin Gastroneterol Hepatol* 2008
Ruemmele FM et al. J Crohn's Colitis 2014

Balancing the Benefits/Risks of Anti-TNFα Therapy



- Higher efficacy
- Higher rates of mucosal healing
- Improved growth in children

- Infection
- Malignancy
- Other

Risk of Non-Hodgkin Lymphoma with Anti-TNFs & Immunomodulators (IM)

	NHL rate per 10,000 pt-yrs	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

*Surveillance Epidemiology & End Results cancer registry
* *Rate from Kandiel A et al, *Gut* 2005

Siegel CA et al, *Clin Gastroenterol Hepatol* 2009

Rate of Pediatric Lymphoma with Anti-TNF Therapy and Comparison with Expected Rates

	Anti-TNF/ 10,000 PYF	SEER/ 100,000 PYF*	SIR (95%CI)	Thiopurine/ 10,000 PYF**	SIR (95%CI)	Adult anti-TNF/ 10,000 PYF ***	SIR (95%CI)
Lymphoid Neoplasias	2.1	5.8	3.5 (0.35-19.6)	4.5	0.47 (0.03-6.44)	6.1	0.34 (0.04-1.51)

* Surveillance Epidemiology & End Results cancer registry
** Rate from Ashworth LA et al, *Inflamm Bowel Dis* 2012
*** Rate from Siegel CA et al, *Clin Gastroenterol Hepatol* 2009

Dulai PS et al, *Clin Gastroenterol Hepatol* 2014

39 Hepatosplenic T-Cell Lymphoma Cases in IBD

Product	# of Cases	Concommitant Agent
Infliximab	20	18 Aza/6MP
IFX/adalimumab	5	4 Aza/6MP
Azathioprine	11	Steroids / 5ASA / none (7)
6-Mercaptopurine	3	None reported

FDA Drug Safety Communication, April 2011

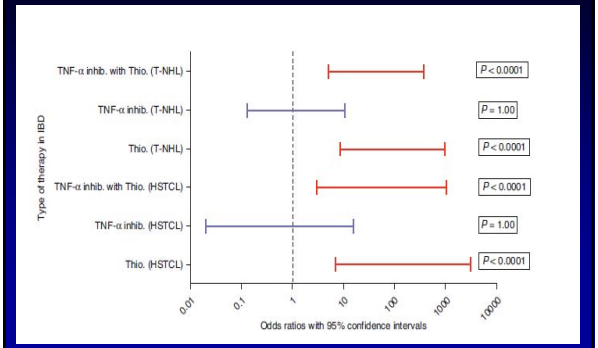
Risk Estimates for Hepatosplenic T-Cell Lymphoma in IBD

All patients on thiopurine only Rx	1:45,000
All patients on infliximab/thiopurine	1:21,947
All males <35 yrs on thiopurine only Rx	1:7404
All males <35 yrs on thiopurine + anti-TNF	1:3534

The risk appears to be particularly increased in patients receiving thiopurines, either as monotherapy or in combination with anti-TNF agents. IBD patients receiving longterm thiopurine therapy are possibly at even greater risk.

Kotlyar D et al. Clin Gastroenterol Hepatol 2011

NHL Reported to FDA Adverse Event Reporting System with Anti-TNFα



Deepak P et al, Am J Gastroenterol 2013

Key Points

	Anti-TNFα	6MP/AZA
Induction of remission	+++	-
Maintenance of remission for luminal CD	+++	++
Maintenance of remission for fistulizing CD	+++	++
Steroid sparing	+++	+++
Mucosal healing	+++	+
Improved height velocity	+++	-
NHL Risk	Yes for combo; ? for anti-TNF alone;	Yes
HTSCL	Yes for combo ? for anti-TNF alone	Yes