Inflammatory Bowel Disease Challenging Cases

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No disclosures

Objectives

Through cases briefly discuss:

- New biologic therapies
- Drug monitoring
- Endoscopic therapy
- Very early onset- IBD

Case 1

Case 1

- 17-year old female with diarrhea 2-3 times/day and intermittent hematochezia
- No evidence of anemia
- Confluent colitis up to the splenic flexure on histology consistent with ulcerative colitis
- Symptoms not improved with oral and rectal 5-ASA
- Delayed release budesonide does not alleviate symptoms

Case 1

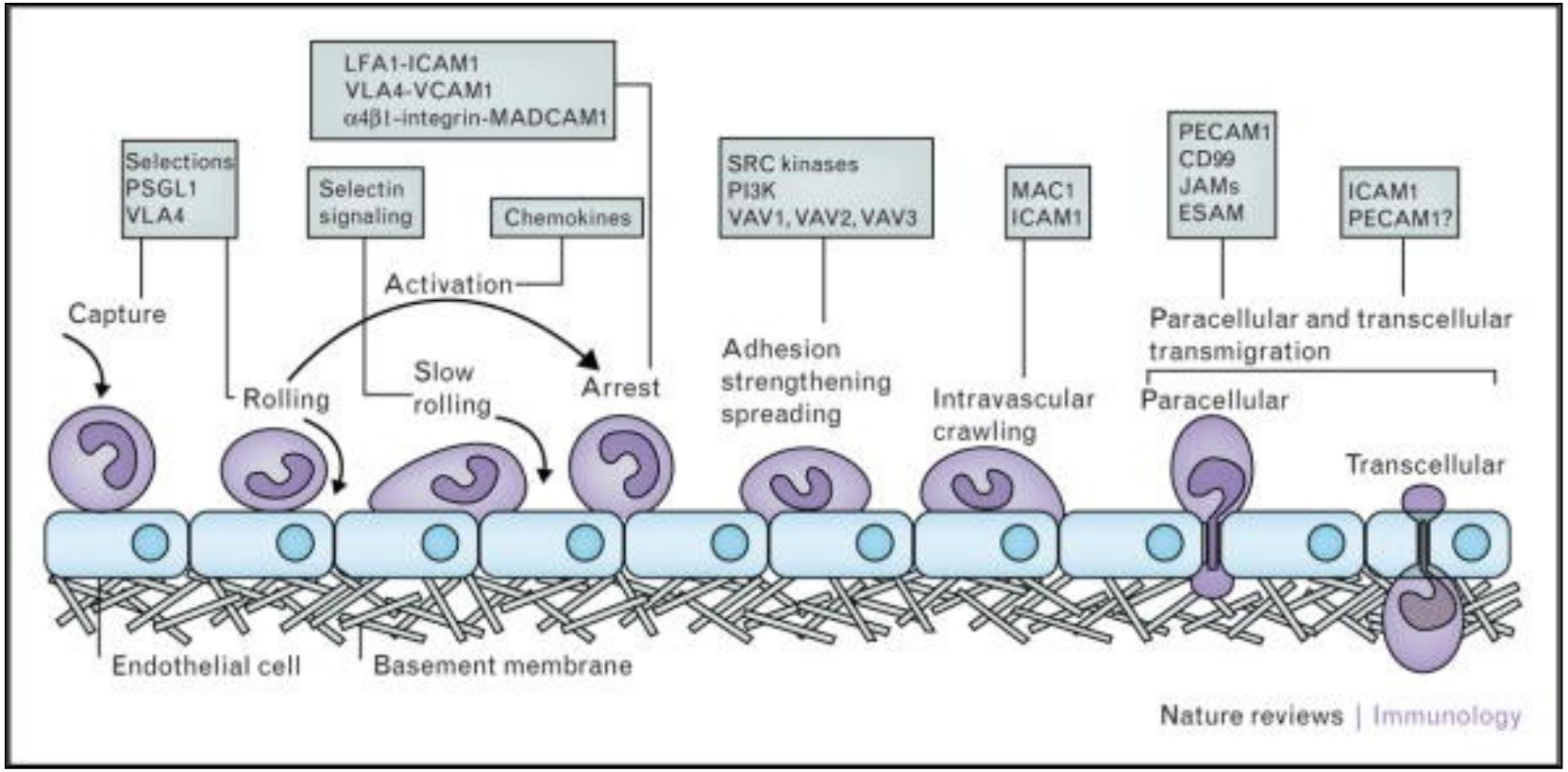
- Worsening symptoms and anemia
- Infliximab started
- After two years of sustained remission the patient has severe exacerbation not responding to increased dosing despite adequate drug level
- What would be your next step?

Biologic Therapy for Inflammatory Bowel Disease

- Anti-TNF-α therapies
  - Infliximab - FDA approval for Crohn disease and UC
  - Adalimumab - Crohn disease and adult UC
  - Certolizumab – Adult Crohn disease
  - Golimumab - Adult UC
  - Bio-similars

- Selective adhesion molecules
  - Natalizumab - FDA limited approval for Crohn disease as monotherapy
  - Ustekinumab – Adult Crohn disease
  - Vedolizumab – Adult Crohn disease and adult UC

Strategies that target leukocyte traffic in Inflammatory Bowel Diseases

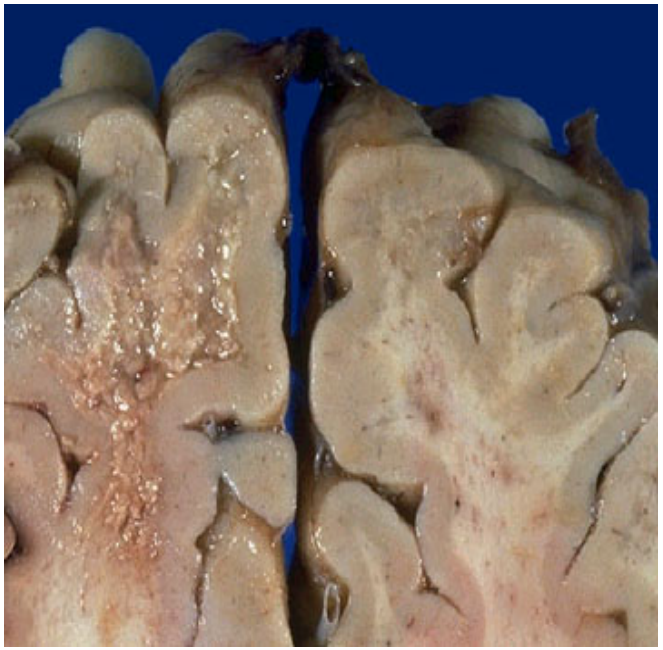


Progressive Multifocal Leukoencephalopathy

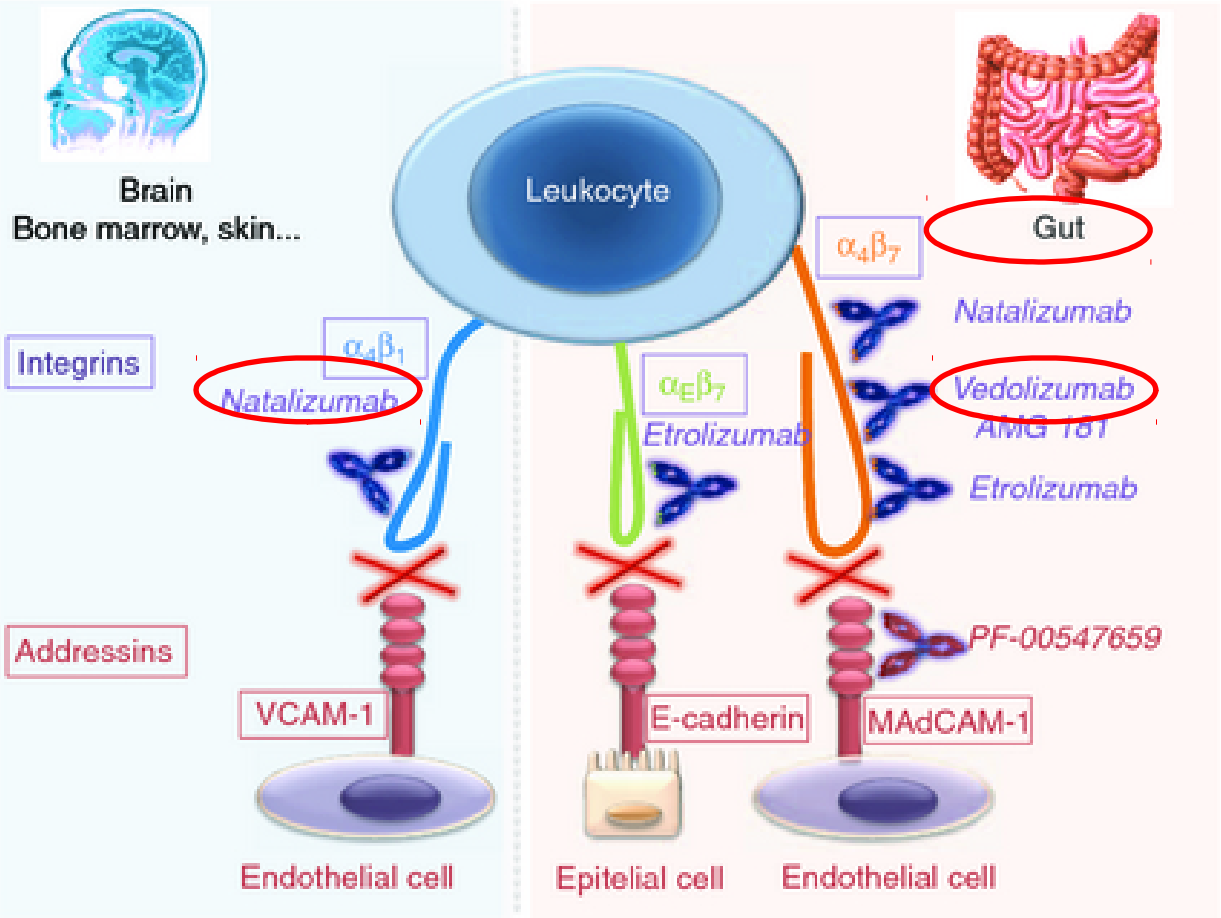
- Patients on natalizumab therapy (1:160 to 1:10,000 dependent on risk factors)

  –The risk factors are:

  1. The presence of anti-JCV antibodies
  2. Longer duration of natalizumab treatment, especially beyond 2 years.
  3. Prior treatment with an immunosuppressant medication (e.g., azathioprine, methotrexate, or mycophenolate mofetil).

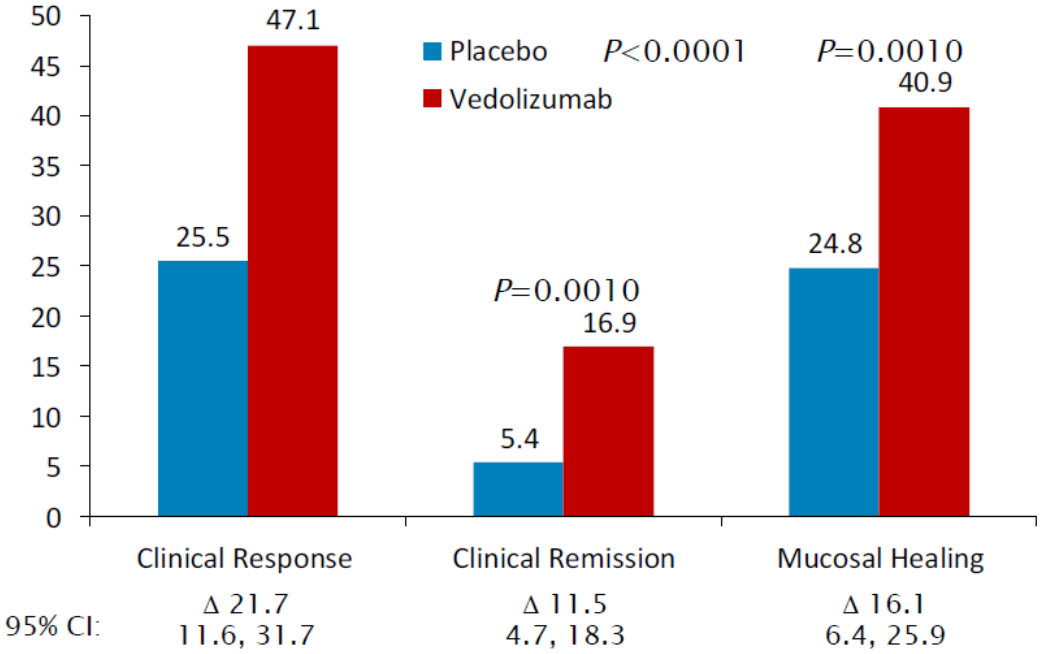


Anti-adhesion therapies for Inflammatory Bowel Disease



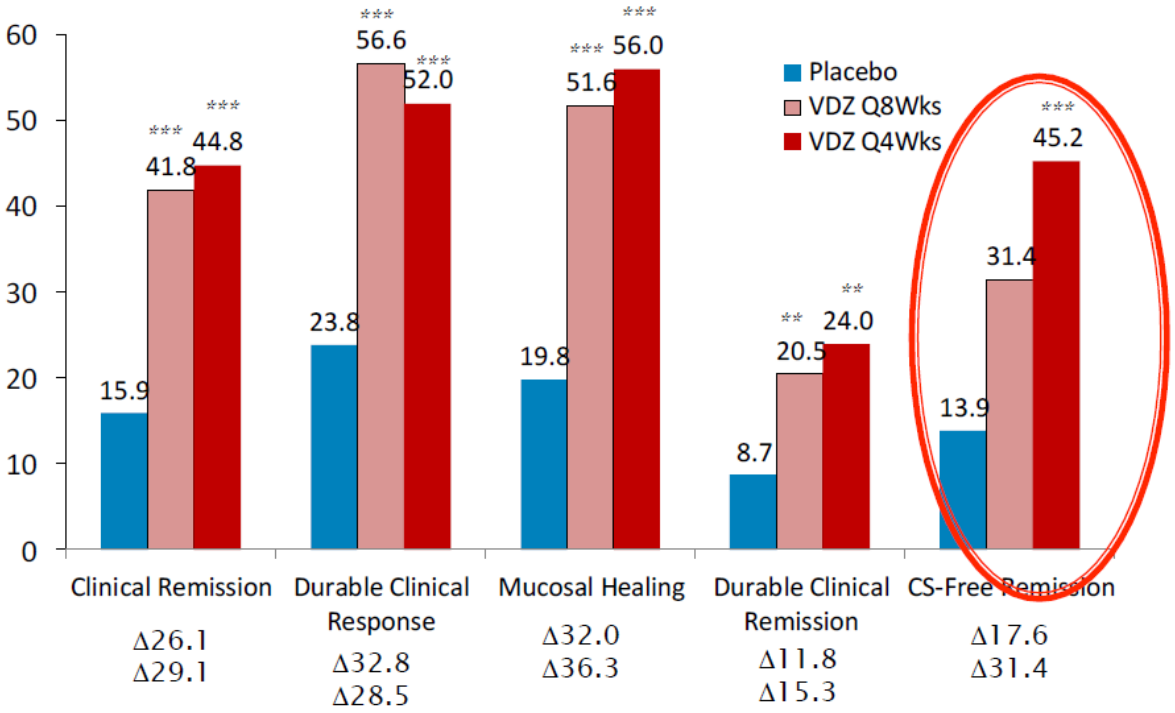
Alimentary Pharmacology & Therapeutics 39(6):579-594, 2014

Vedolizumab during Induction phase UC at 6 weeks (GEMINI 1)



Feagan BG et al. N Engl J Med. 2013; 22;369

GEMINI: UC Maintenance Therapy



Feagan BG et al. N Engl J Med. 2013; 22;369

Exposure-Adjusted Incidence Rates of Infections and Serious Infections in the Overall Safety Population

	Placebo		Vedolizumab	
	UC and CD (n = 504)[a]		UC and CD (n = 2830)[d]	
Adverse event: Infection	No. of patients with event	No. of patients with event/100 PY (95% CI)	No. of patients with event	No. of patients with event/100 PY (95% CI)
Any infection[e]	139	82.9 (68.3–97.5)	1606	63.5 (59.6–67.3)
Upper respiratory tract infections	67	34.7 (26.0–43.3)	967	28.6 (26.6–30.6)
Lower respiratory tract and lung infections	16	7.7 (3.9–11.5)	270	6.1 (5.3–6.8)

Colombel JF et al. Gut 2016 Feb 18

Vedolizumab in Paediatric Inflammatory Bowel Disease: A Retrospective Multi-Centre Experience From the Paediatric IBD Porto Group of ESPGHAN
Oren Ledder, Amit Assa, Arie Levine, Johanna C. Escher, Lissy de Ridder, Frank Ruemmele, Neil Shah, Ron Shaoul, Victorien M. Wolters, Astor Rodrigues, Holm H. Uhlig, Carsten Posovsky, Kaija-Leena Kolho, Christian Jakobsen, Shlomi Cohen, Dror S. Shouval, Tim de Meij, Javier Martin-de-Carpi, Lisa Richmond, Jiri Bronsky, Mira Friedman, Dan Turner
Journal of Crohn's and Colitis. 2017 June;
N=64

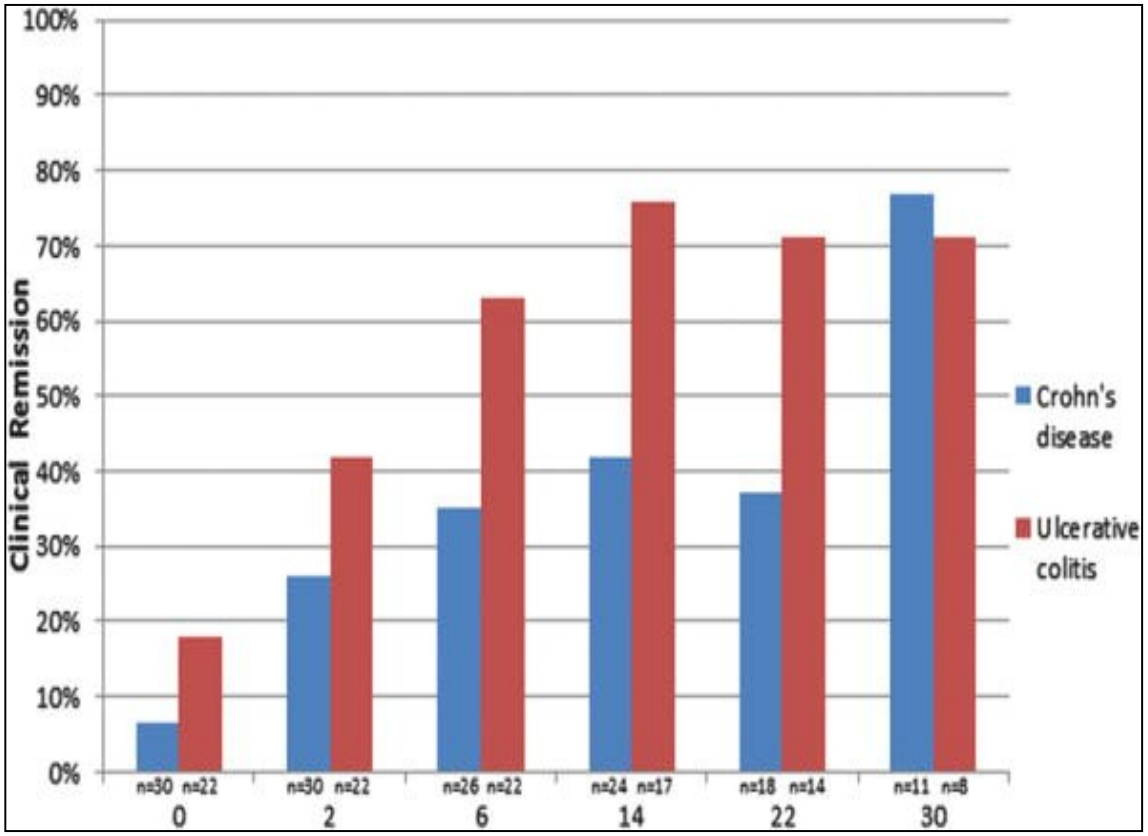
Multi-Center Experience of Vedolizumab Effectiveness in Pediatric Inflammatory Bowel Disease.
Namita Singh, Shervin Rabizadeh,Jacqueline Jossen, Nanci Pittman, Morgan Check, Ghonche Hashemi, becky L. Phan, Jeffrey Hyams, Marla Dubinsky.
Inflamm Bowel Dis. 2016 Sept;22 (9):2121
N=52

Vedolizumab Therapy in Severe Pediatric Inflammatory Bowel Disease.
Maire Conrad, Ronen E. Stein, Elizabeth C. Maxwell, Lindsey Albenberg, Robert N. Baldassano, Noor Dawany, Andrew B. Grossman, Petar Mamula, David Piccoli, Judith Kelsen.
Inflamm Bowel Dis. 2016 Oct;22(10):2425
N=21

Pediatric Vedolizumab Studies

- All retrospective
- Majority of patients were previously treated with anti-TNF medications
- Dosing- 0, 2, 6, and then q8 weeks
  - Adult dosing of 300 mg IV for >40 kg
  - Children <40 kg
    - Porto Group – median 7.3 mg/kg (3.6-10.3 mg/kg)
    - Multi-Center USA – 6 mg/kg (2 patients received 5 mg/kg)
    - CHOP – no patients under 40 kg (5 mg/kg)

Remission rates in Pediatric CD and UC on Vedolizumab



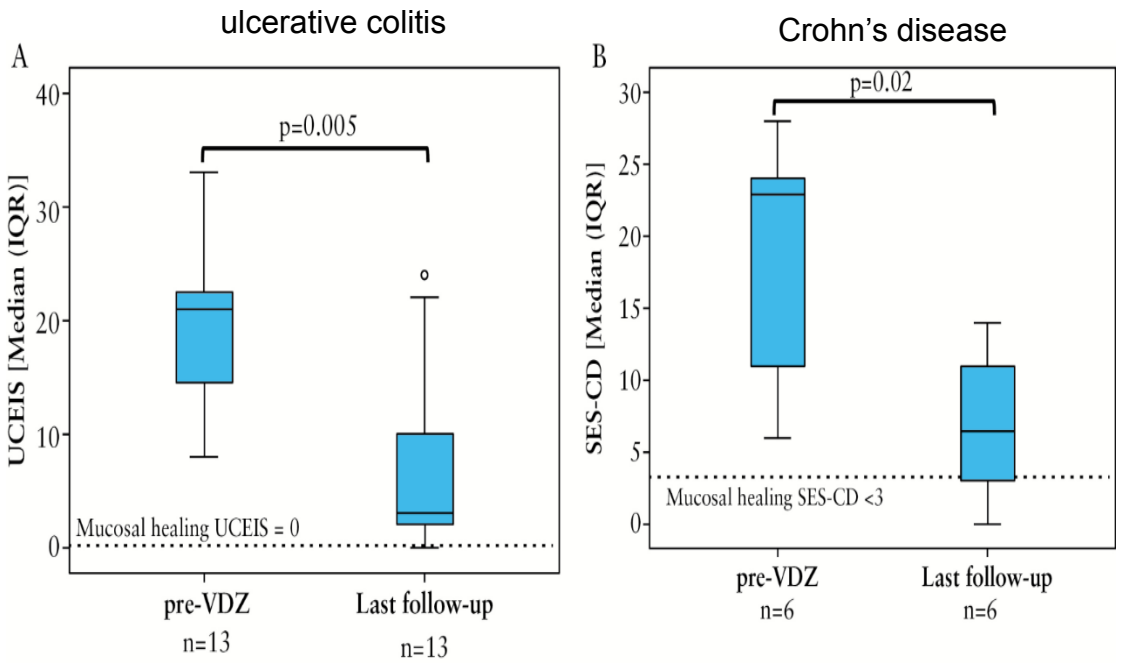
Singh N, et al. Inflamm Bowel Diseases. 22(9):2121-2126, September 2016.

Response rate in Pediatric CD and UC on Vedolizumab

- Clinical Response
  - PCDAI<12.5 for CD
  - PUCAI<20 for UC and IBD-U
- Clinical Response
  - 31.6% by week 6
  - 52.6% by week 14
  - 57.9% by week 22

Conrad M, et al. Inflamm Bowel Dis. 22(10): 2425-2431, Oct 2016

Change in Endoscopic Scores with Vedolizumab in Pediatric IBD



Repeat colonoscopy at median 14 weeks (interquartile range [IQR] 14–22)

Ledder O, et al. J Crohn's & Colitis 2017. doi:10.1093/ecco-jcc/jjx082

Predicting Response to Vedolizumab in Pediatric Inflammatory Bowel Diseases (IBD) Including Drug Levels: a Multi-center Prospective Cohort Study, From the Pediatric IBD Porto Group of European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)

Sponsor: Shaare Zedek Medical Center

Ages = up to 18 years

Estimated Enrollment:	120
Actual Study Start Date:	January 2017
Estimated Study Completion Date:	July 2021
Estimated Primary Completion Date:	July 2019 (Final data collection date for primary outcome measure)

A Phase 2, Randomized, Double-Blind, Dose-Ranging Study to Determine the Pharmacokinetics, Safety and Tolerability of Vedolizumab IV in Pediatric Subjects With Ulcerative Colitis or Crohn's Disease

Sponsor: Takeda
Estimated Enrollment=80
Ages = 2 years to 17 years

- Primary Outcome
  - Measures: Serum Vedolizumab Concentrations Over Time (Week 14)

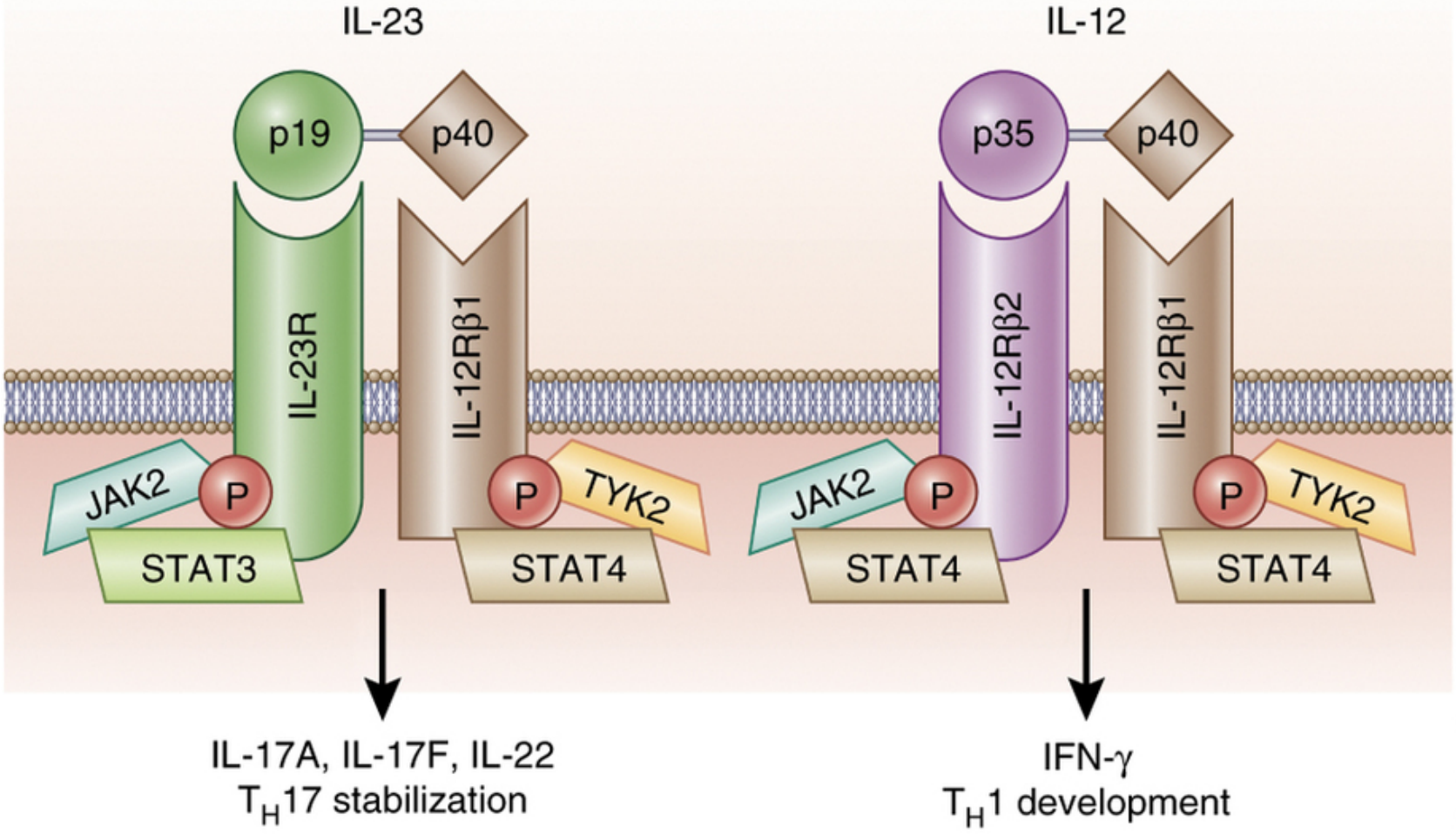
- Secondary Outcome Measures
  - % of Ulcerative Colitis Participants who Achieve Clinical Response (Week 14)
  - % of Crohn’s disease Participants who Achieve Clinical Response (Week 14)

Case 2

Case 2

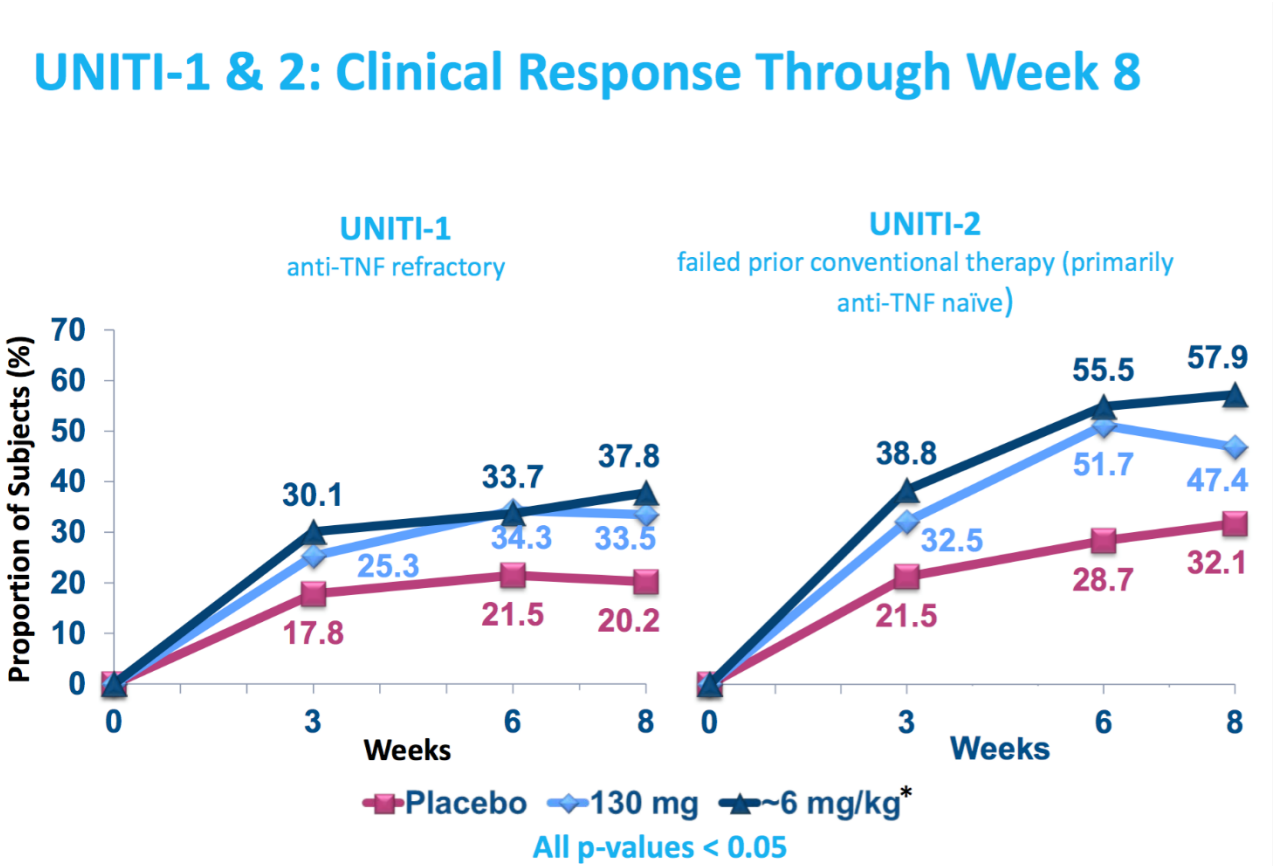
- 14-year old male with Crohn disease, persistent growth failure, and symptoms suggestive of active disease
- Evaluation (MRE, video capsule endoscopy, endoscopy and colonoscopy)- extensive small and large bowel disease
- Failed 5-ASA, antibiotics, nutritional and anti-TNF therapy, and immunomodulators
- Not a surgical candidate

IL-12 and IL-23, and their receptors and downstream signaling pathways



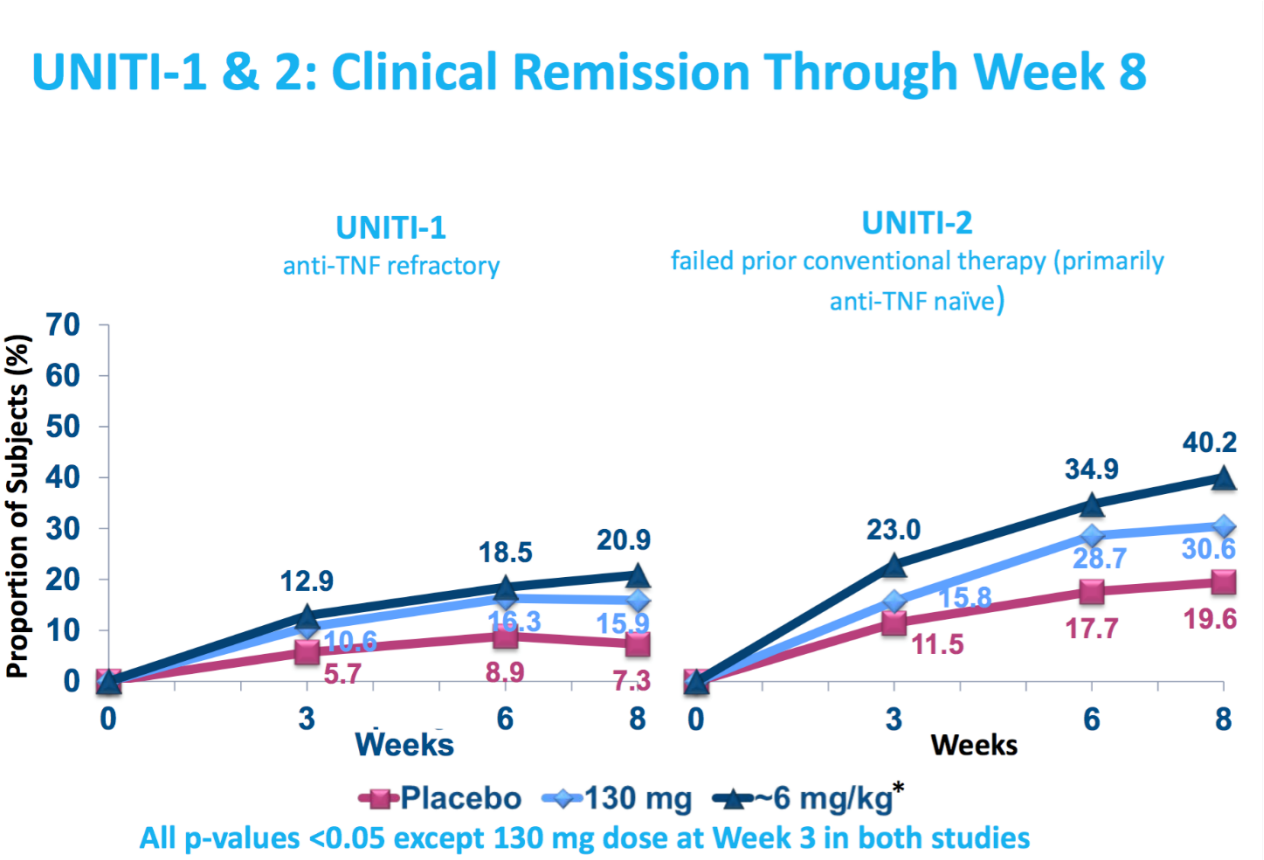
Teng MW, et al. Nature Med 2015; 21(7): 719

Ustekinumab for Crohn disease UNITI-1 and UNITI-2



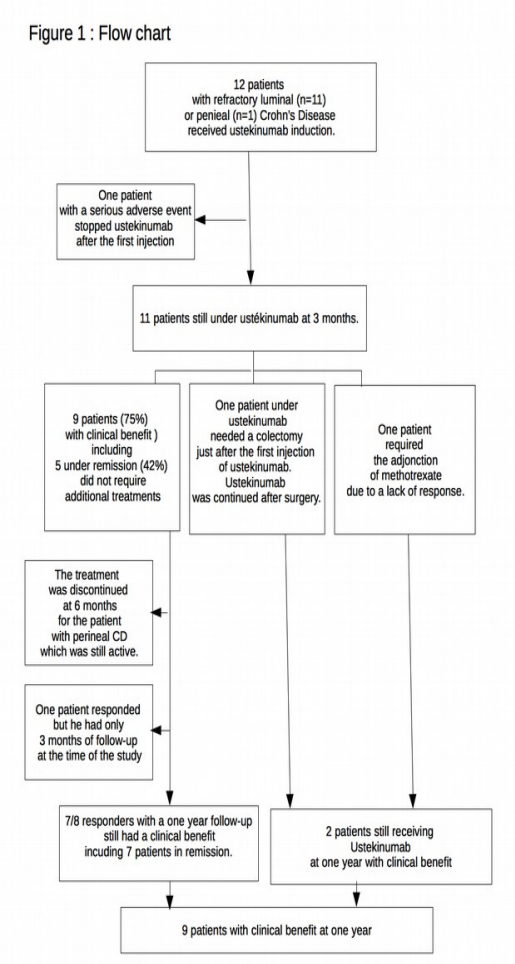
Feagan BG, et al; New Engl J Med 2016;375:1946

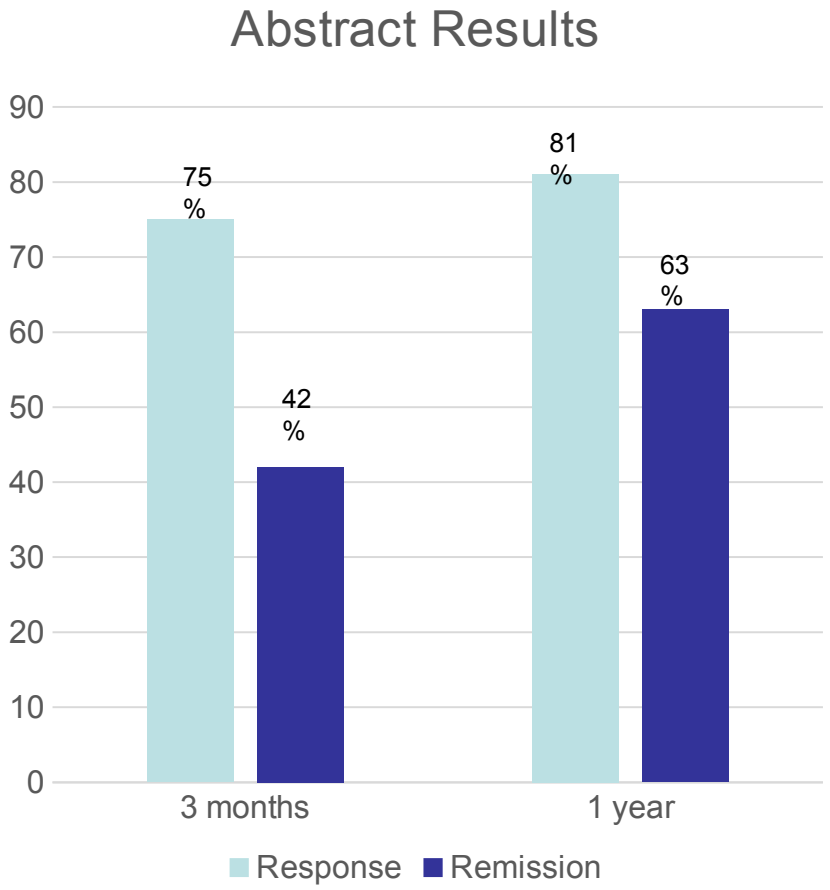
Ustekinumab for Crohn disease UNITI-1 and UNITI-2



Feagan BG, et al; New Engl J Med 2016;375:1946

Subcutaneous ustekinumab provided clinical and biological benefit for 9/12 refractory pediatric Crohn disease





C. Martinez-Vinson, et al. ESPGHAN 2017

A Pharmacokinetic Study of Ustekinumab in Pediatric Subjects With Moderately to Severely Active Crohn's Disease

Sponsor: Janssen Research & Development, LLC
Estimated Enrollment=40
Ages = 2 years to 17 years

- Primary Outcome
  - Measures: Serum Ustekinumab Concentrations Over Time (Time Frame: Up to Week 16)

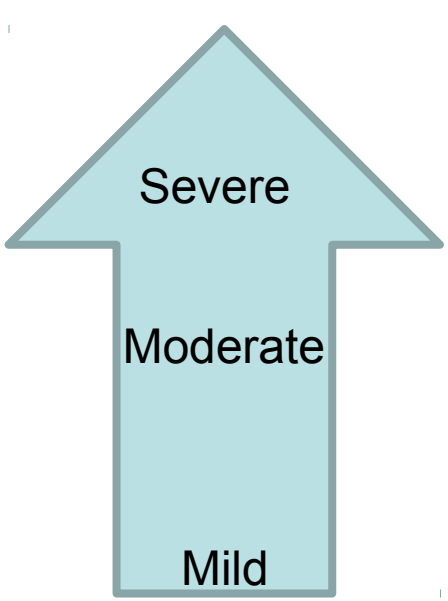
- Secondary Outcome Measures
  - Clinical Response as Measured by the Pediatric Crohn's Disease Activity Index (PCDAI) Score (Time Frame: Week 6)
  - Clinical Remission as Measured by the Pediatric Crohn's Disease Activity Index (PCDAI) Score (Time Frame: Week 8)

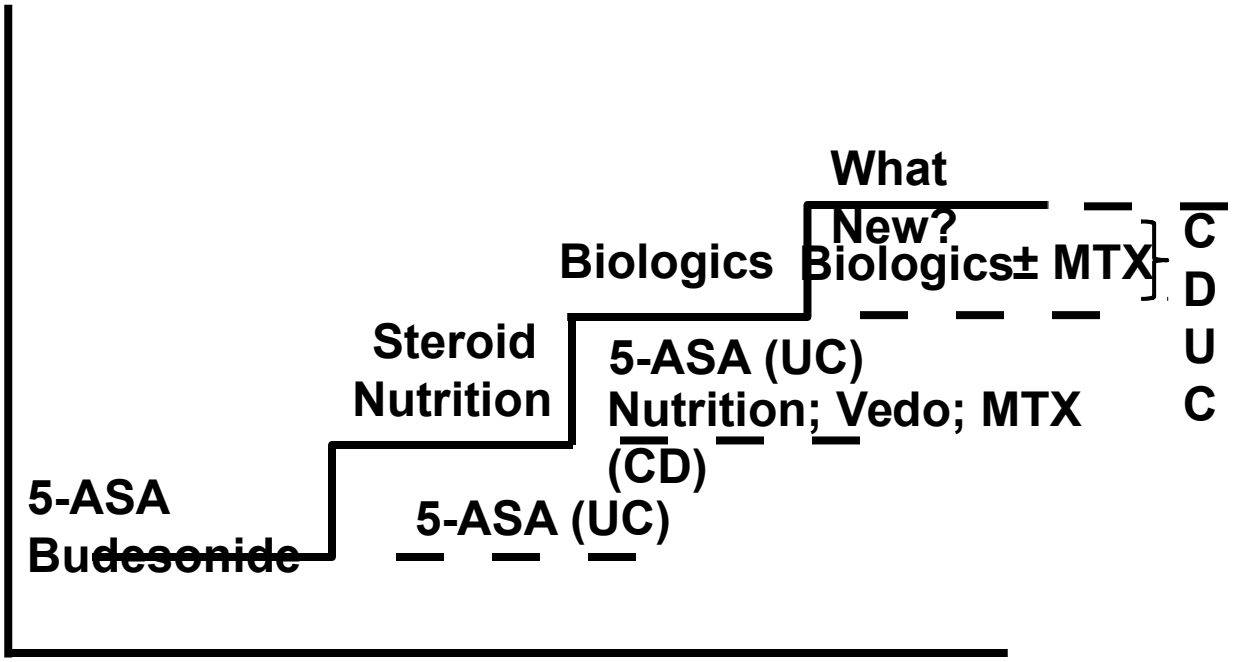
A Pharmacokinetic Study of Ustekinumab in Pediatric Subjects With Moderately to Severely Active Crohn's Disease

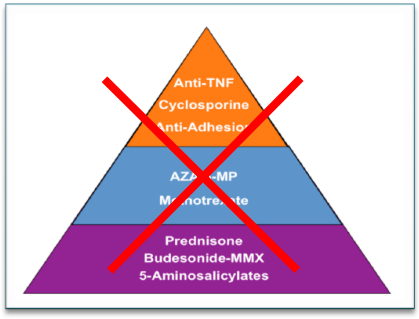
- Group 1: Single IV induction dose at week 0
  - 3 mg/kg for < 40 kg
  - 130 mg >= 40 kg
- Group 2: Single IV induction dose at week 0
  - 9 mg/kg <40 kg
  - 390 mg >= 40 kg

- Group 1 and 2: IV infusion followed by SC maintenance dose at week 8
  - 2 mg/kg for subjects <40 kg
  - 90 mg for subjects >= 40 kg at week 8.

The Concept of Step-Therapy in IBD for Everyone is Flawed







Case 3

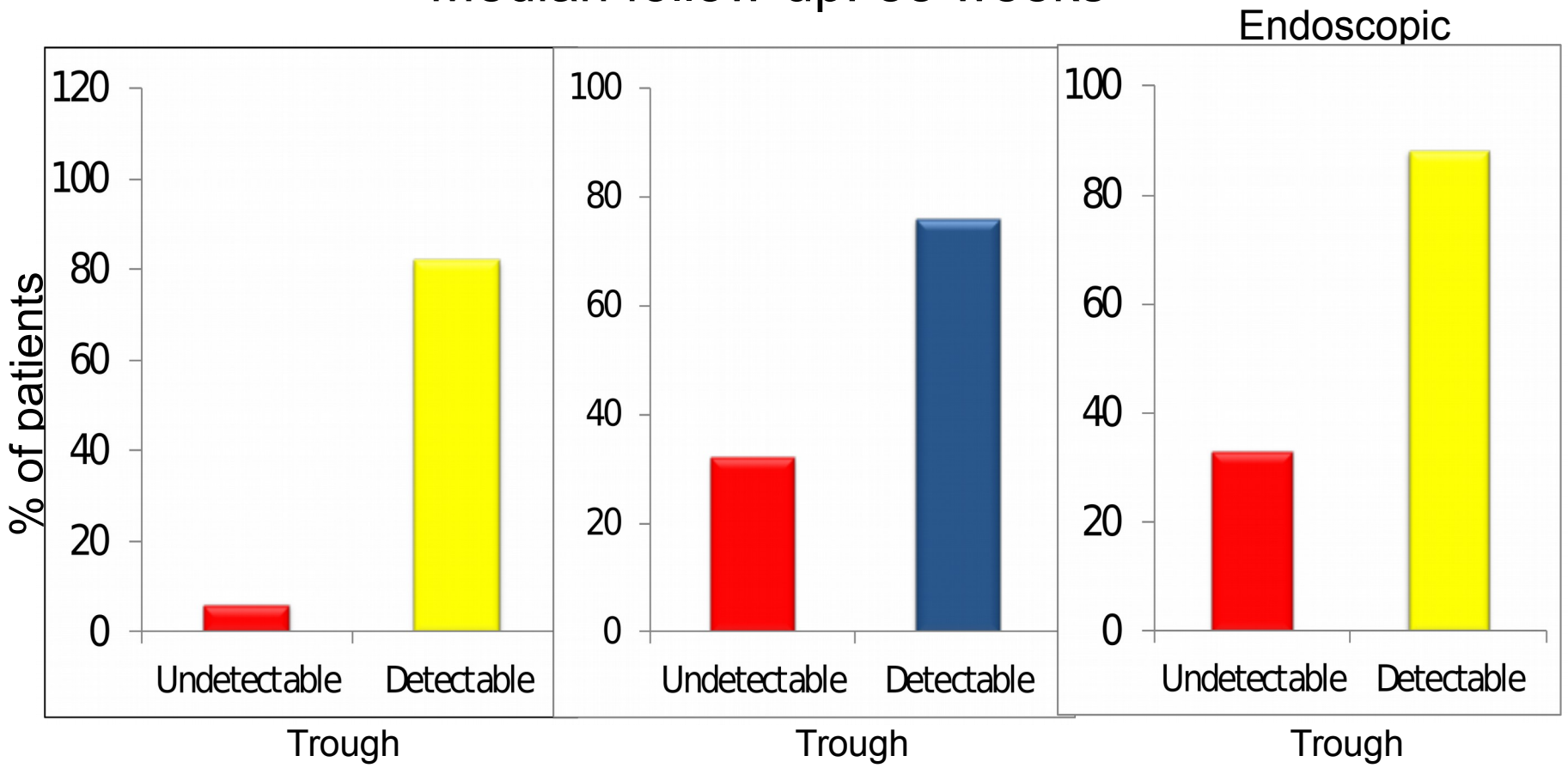
Case 3

- 9-year old male with newly diagnosed small and large bowel, and severe perianal Crohn disease
- Imaging- no evidence of abscess
- Started on antibiotic therapy while awaiting work-up and approval for infliximab therapy
- How would you monitor anti-TNF therapy?

Value of Trough Level/Anti-Drug Antibody (ADA)

Higher Infliximab (IFX) Levels Associated with Better Outcomes

Prospective cohort (n=105)
Median follow-up: 88 weeks



Maser EA, *et al. Clin Gastroenterol Hepatol* 2006;4:1248–54.

IFX Trough Levels Predict Future Loss of Response (LOR)

- 90 adult IBD patients (59% with known ATI)
  - Retrospectively measured 1,232 serum IFX levels via mobility shift-assay (HMSA)
- Greatest predictor of IFX failure
  - Any IFX trough < 0.91 µg/ml
- IFX trough <2.2 µg/ml at week 14 predicts
  - Develop antibodies to infliximab (ATI) ($p<0.0001$)
  - Discontinue IFX for LOR/hypersensitivity ($p=0.003$)

Vande Casteele N et al. *Am J Gastroenterol* 2013; 108(6):962-71

Early Infliximab Trough Associated with Persistent Remission in Pediatric IBD

- Prospective observational cohort (n=58) of pediatric patients (<21 y/o) starting IFX
  - 50/58: Primary responders; entered maintenance phase
- 60% (30/50) achieved persistent remission (PR)
- Median infliximab trough at week 14
  - Persistent remission: **4.7 µg/ml**
  - Not persistent remission: **2.6 µg/ml**

p<0.03

PR: Week 54 remission (PCDAI, CDAI, or partial Mayo); no IFX dose escalation

Singh N, et al. *Inflamm Bowel Dis* 2014; 20: 1708-1713

Variables Affecting Clearance of Biological Therapies

Factors Affecting Pharmacokinetics of Monoclonal Antibodies

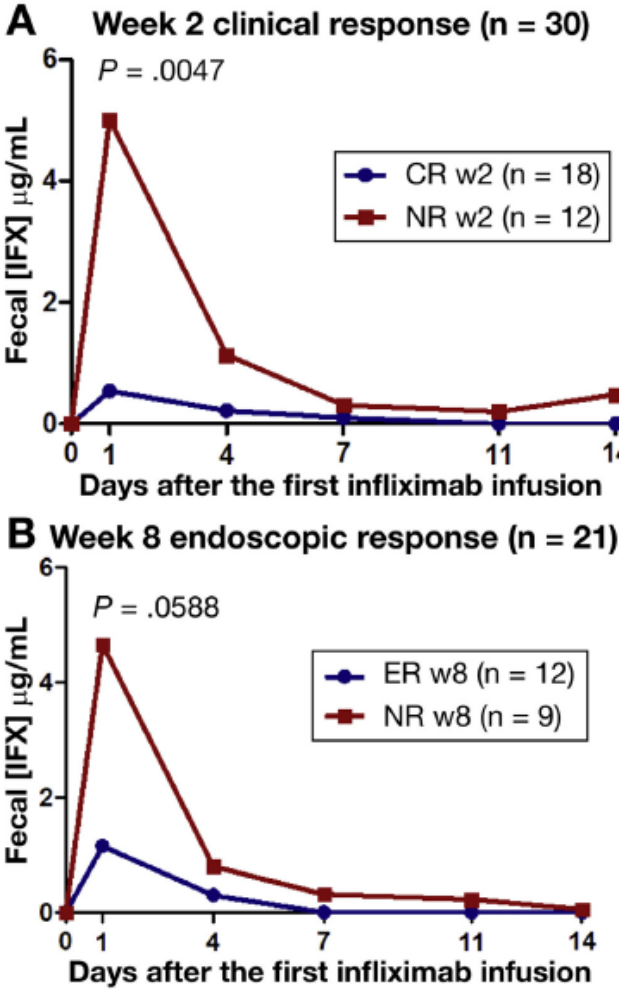
	Impact on pharmacokinetics
Presence of ADAs	Decreases serum (mAbs) Threefold-increased clearance Worse clinical outcomes
Concomitant use of IS	Reduces ADA formation Increases serum (mAbs) Decreases mAbs clearance Better clinical outcomes
High baseline (TNF-α)	May decrease (mAbs) by increasing clearance
Low albumin	Increases clearance Worse clinical outcomes
High baseline CRP	Increases clearance
Body size	High body mass index may increase clearance
Gender	Males have higher clearance

ADA, antidrug antibody; CRP, C-reactive protein; IS, immunosuppressive agent; mAb, monoclonal antibody; TNF-α, tumor necrosis factor-α. Terms in parentheses refer to serum concentration.

Ordas I et al. *Clin Pharmacol Ther.* 2012;91:635

Fecal Loss of IFX Contributes to Lack of Response in Acute Severe Colitis

- Moderate to severe UC, anti-TNF naïve (n=30)
  - Fecal samples collected within first 14 days following 1st IFX (5 mg/kg)
- During 1st 2 weeks of treatment
  - 83% had detectable IFX in feces
  - Peak concentrations: Day 2
- Non-responders:
  - Higher fecal IFX at Day 1 (p=0.02)
  - Lower serum IFX at Day 14 (p=0.03)



Clinical response: Simple Clinical Colitis Activity Index 4 points, or drop of 50% from the baseline value
Endoscopic response: Mayo score improvement of at least 1 point

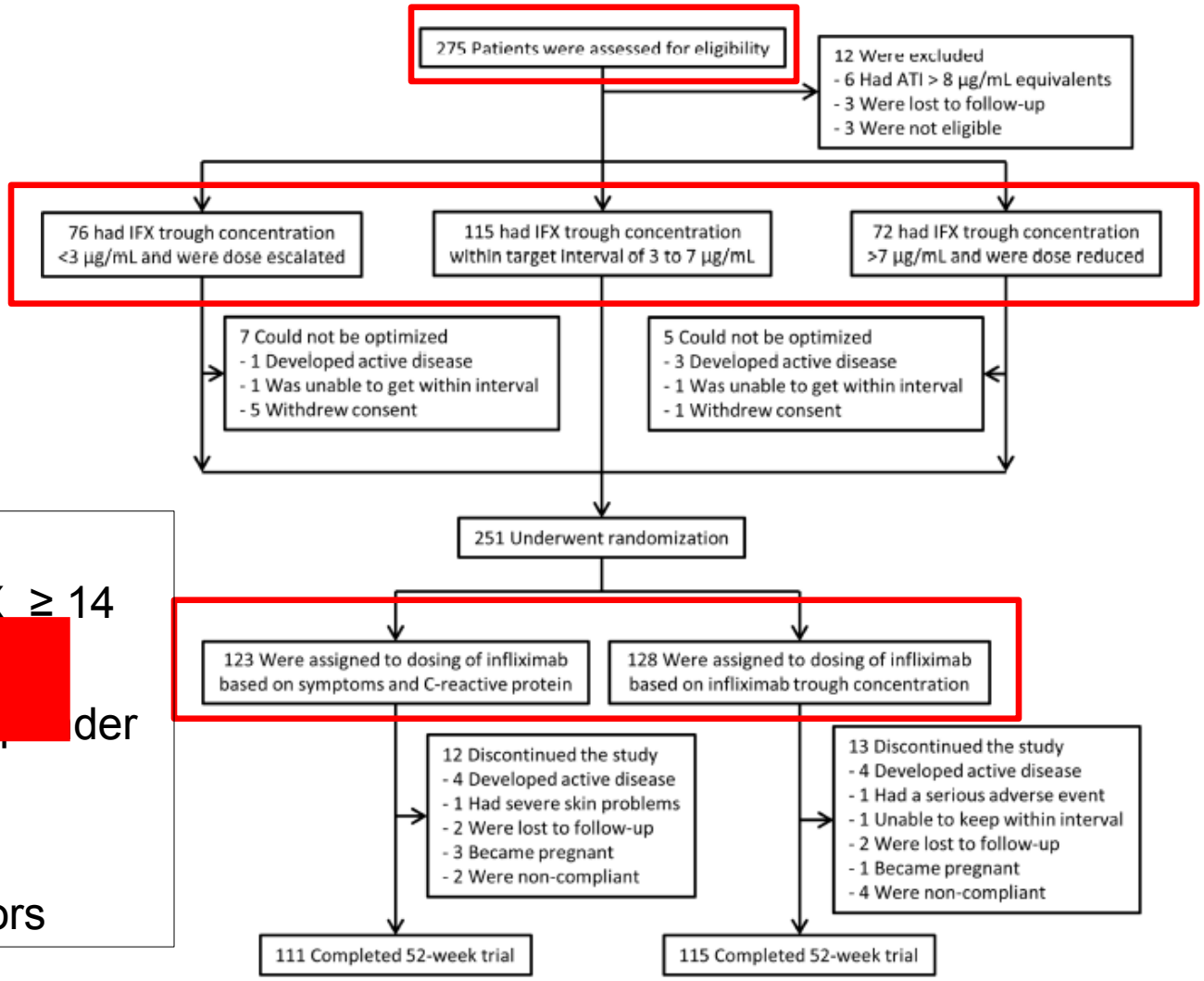
Brandse JF et al *Gastroenterology* 2015; 149:350-355

Proactive and Reactive TDM

TAXIT

Trough Concentration Adapted InfliXImab Treatment

Dose optimization phase



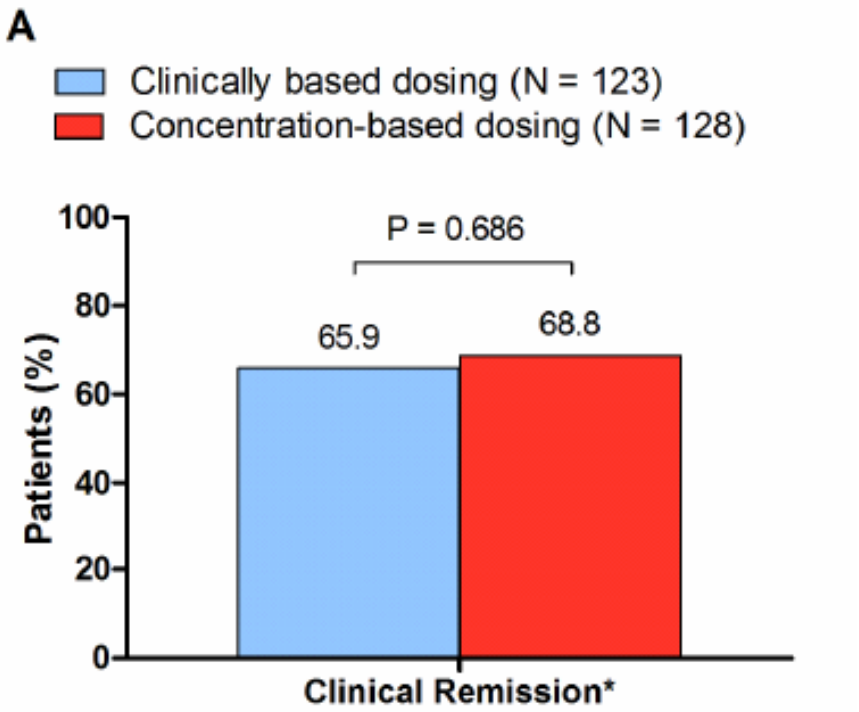
Maintenance phase

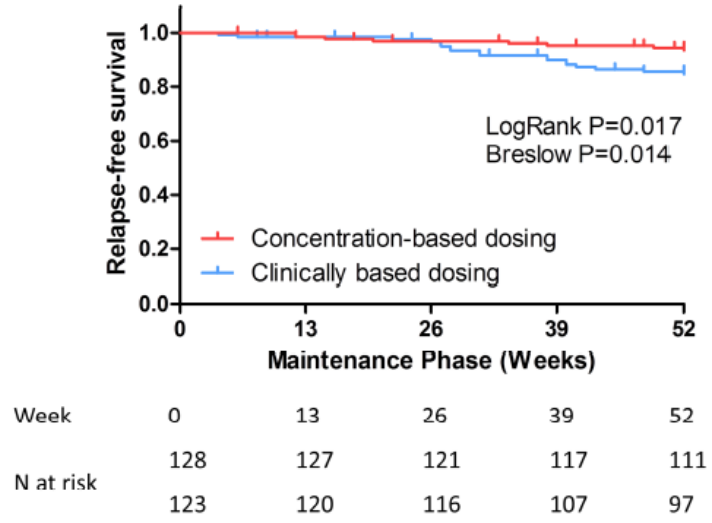
Eligibility

- Maintenance IFX ≥ 14
- [illegible] der
- No ATI > 8 µg/ml
- Stable dose immunomodulators

Vande Casteele N et al. *Gastroenterology* 2015;148:1320-1329

Maintenance Phase



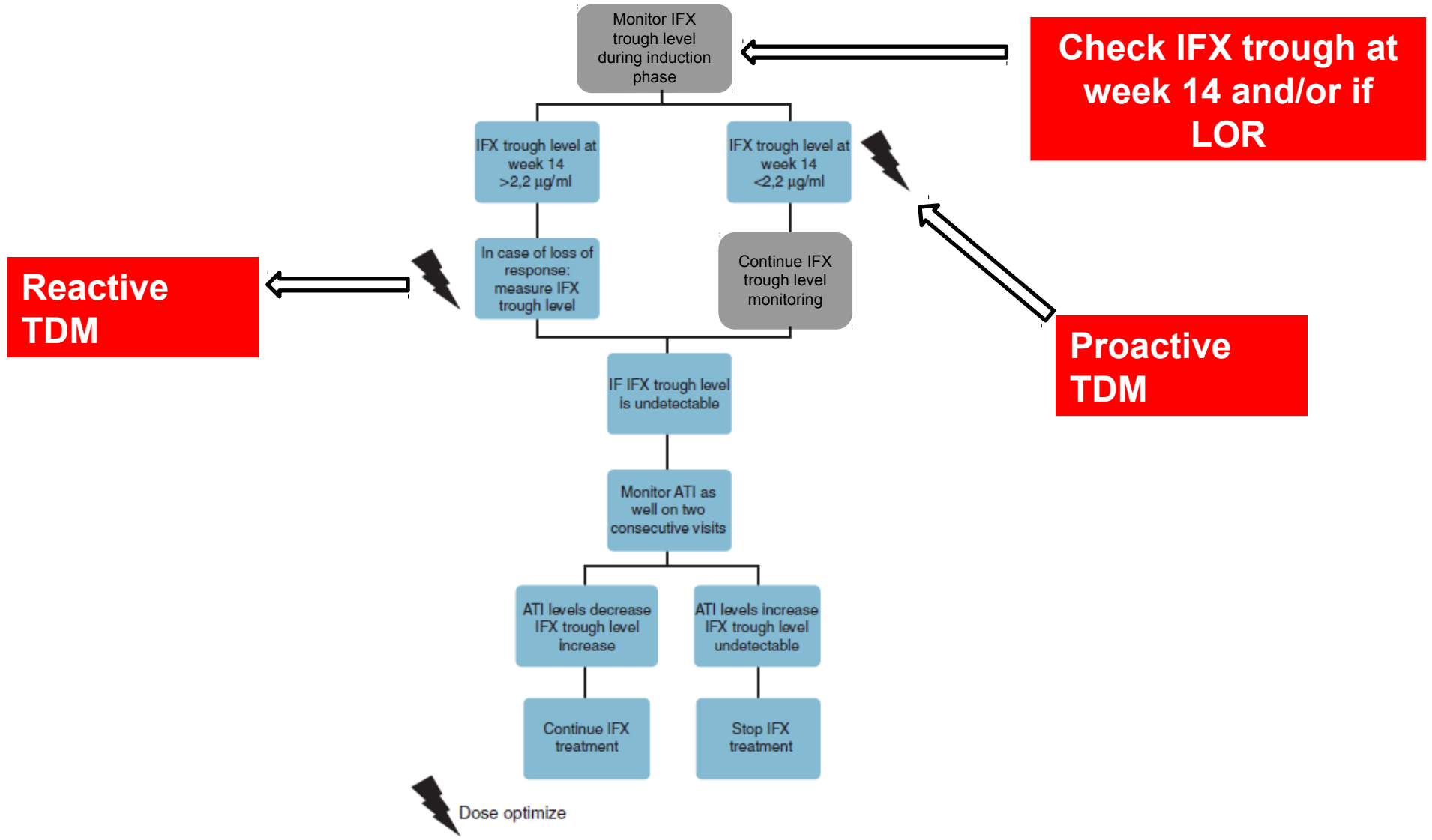


Week	0	13	26	39	52
N at risk	128	127	121	117	111
	123	120	116	107	97

- Clinically based vs. concentration-based:
  - More relapses
  - Required more rescue therapy
  - Had lower IFX troughs/more ADA

Vande Casteele N et al. *Gastroenterology* 2015;148:1320-1329

Suggested Algorithm: Proactive and Reactive

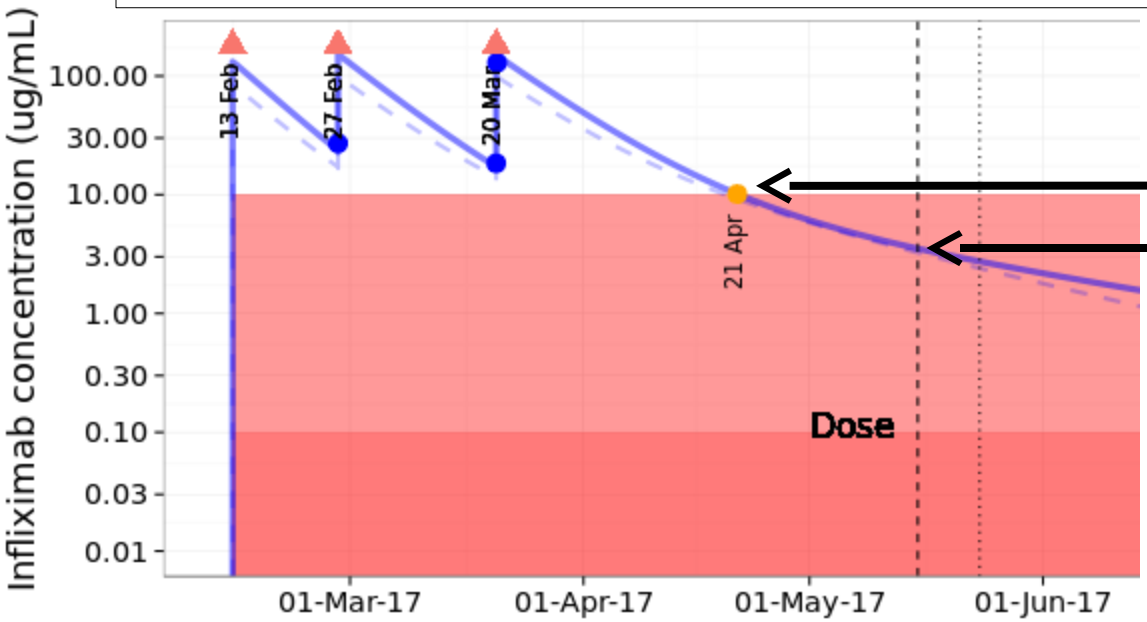


Vande Casteele N et al. *Am J Gastroenterol* 2013; 108(6):962-71

Future – Individualized Dashboards

PK Dashboard Optimizing IFX

Input: Age, gender, weight, albumin, disease activity, previous dose, levels, etc.



Expected target IFX=10
0n **4/21** (4 wk, 4 d)

First maintenance if 8 weeks from Inf#3: **5/15**
Predicted IFX level ~ 3.48

Inf#	Date	Dose	ALB	CRP	Pre-IFX	Post-IFX	ATI
1	2/13	5 mg/kg	3.6	4.7	-	-	-
2	2/27	5 mg/kg	4.0	0.2	27.1	-	<3.1
3	**3/20**	**5 mg/kg**	**4.4**	**4.0**	**18.1**	**129.2**	**<3.1**

Units: Albumin levels in g/dL, C-reactive protein levels in mg/dL, IFX levels in ug/mL

Take Home Points

- Measureable drug levels ☾ Better outcomes
  - Less risk of ADA
- Standard dosing regimen often inadequate
- **Reactive TDM** should be utilized
- **Proactive TDM** makes sense, but need more data
  - Optimization vs. maintenance phase
- Target trough may vary
- Personalized dosing may be the future

Case 4

Case 4

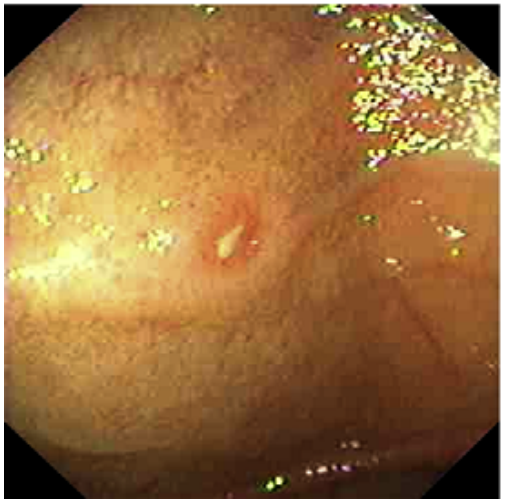
- 19-year old male with Crohn disease who underwent resection of two strictures (distal ileum with primary anastomosis, as well as terminal ileal stricture with ileo-cecectomy)
- Intermittent obstructive symptoms
- Endoscopic evidence of disease recurrence, but the family not interested in repeat surgery or biologic therapy

Post-operative recurrence

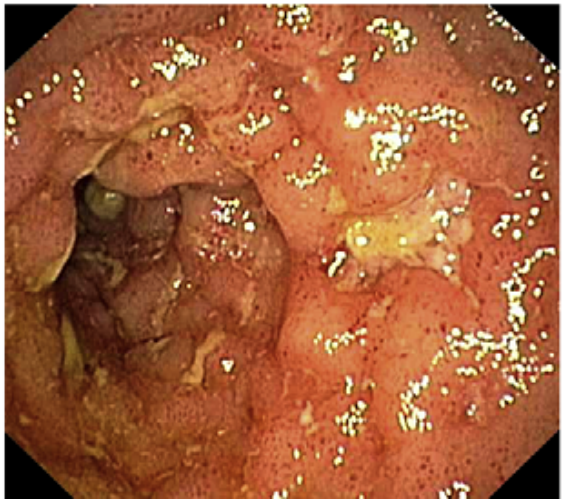
Table 1
Endoscopic recurrence score[6]

Endoscopic Score	Definition
i0	No lesions
i1	≤5 aphthous lesions
i2	>5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions, or lesions confined to the ileocolic anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with already larger ulcers, nodules, and/or narrowing

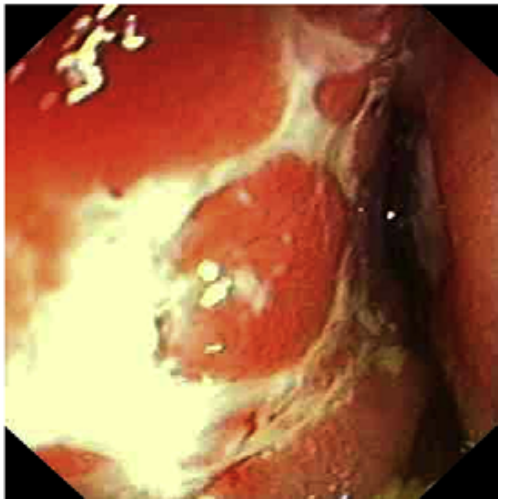
I1



I3

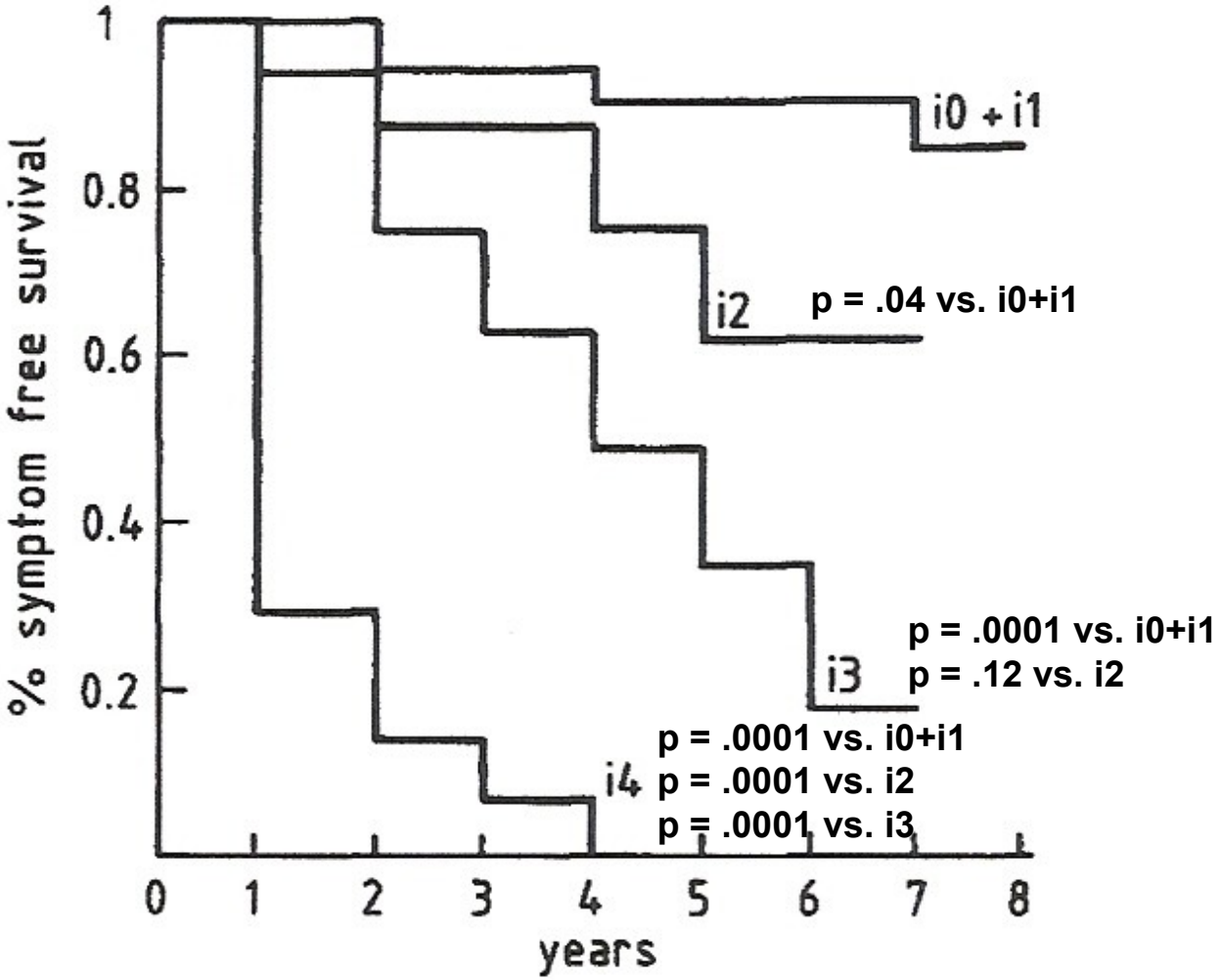


I4



Rutgeerts et al. Gastroenterology 1990.

Post-operative recurrence



Rutgeerts et al. Gastroenterology 1990.

Stricture therapy

1. Crohn disease – inflammatory stricture (not longer than 4-5 cm and not associated with fistula or abscess)

2. Post-operative

– Anastomosis (18-20 mm)
– Pouch (18-20 mm)

Location- colon

- Systematic review of 347 patients with Crohn disease in 13 studies who underwent balloon dilation

- Dilation sizes varied from 18-25 mm
- Successful instrument passage 45-100%
- Short-term improvement 71-100%
- Long-term improvement 50-100%

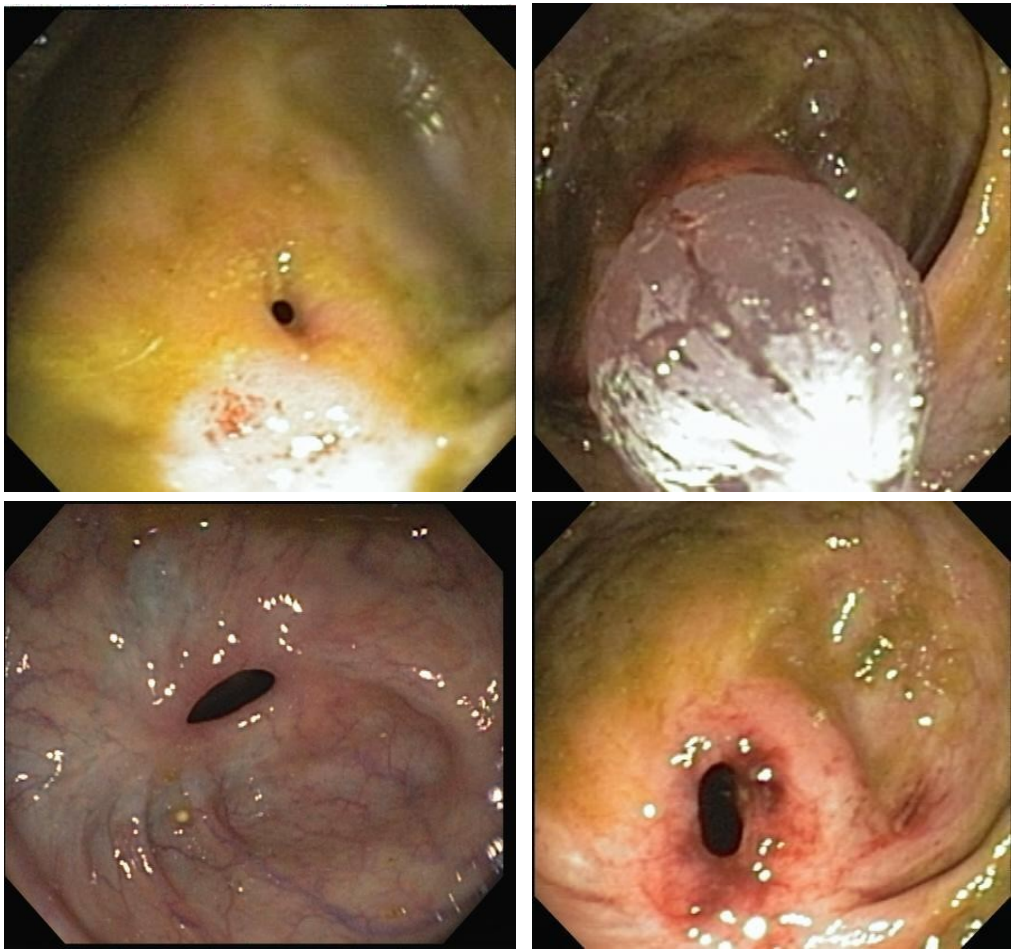
Hassan et al. Aliment Pharm Ther, 2007.

Pre-operative dilation

- 29 pediatric patients randomized to receive intra-stricture corticosteroid (CS) injection or placebo after endoscopic balloon dilation
- Followed clinically with SB contrast, US and MR imaging at 1, 3, 6, and 12 months; and colonoscopy at 12 months
- 1/15 patients receiving CS required re-dilation vs. 5/14 placebo patients ($p<.04$)
- Surgery needed in 4 of the placebo patients, and none of those receiving CS ($p<.02$)

Di Nardo et al. Gastrointest Endosc. 2010.

Post-operative dilation



Complications

- Perforation
- Bleeding

Complications- perforation

- A meta-analysis showed rate of 1.9% with therapeutic procedures
- The perforation rate with pouch stricture dilation reported at 0.46%
- Conservative treatment
- Endoscopic therapy with clip and over-the-scope clip placement, and stent placement
- Surgical repair

Paine et al. GIE, 2013.

Complications- bleeding

- Frequency reported up to 1.4% of dilations
- Most can be successfully managed with cautery or hemoclip placement

Case 5

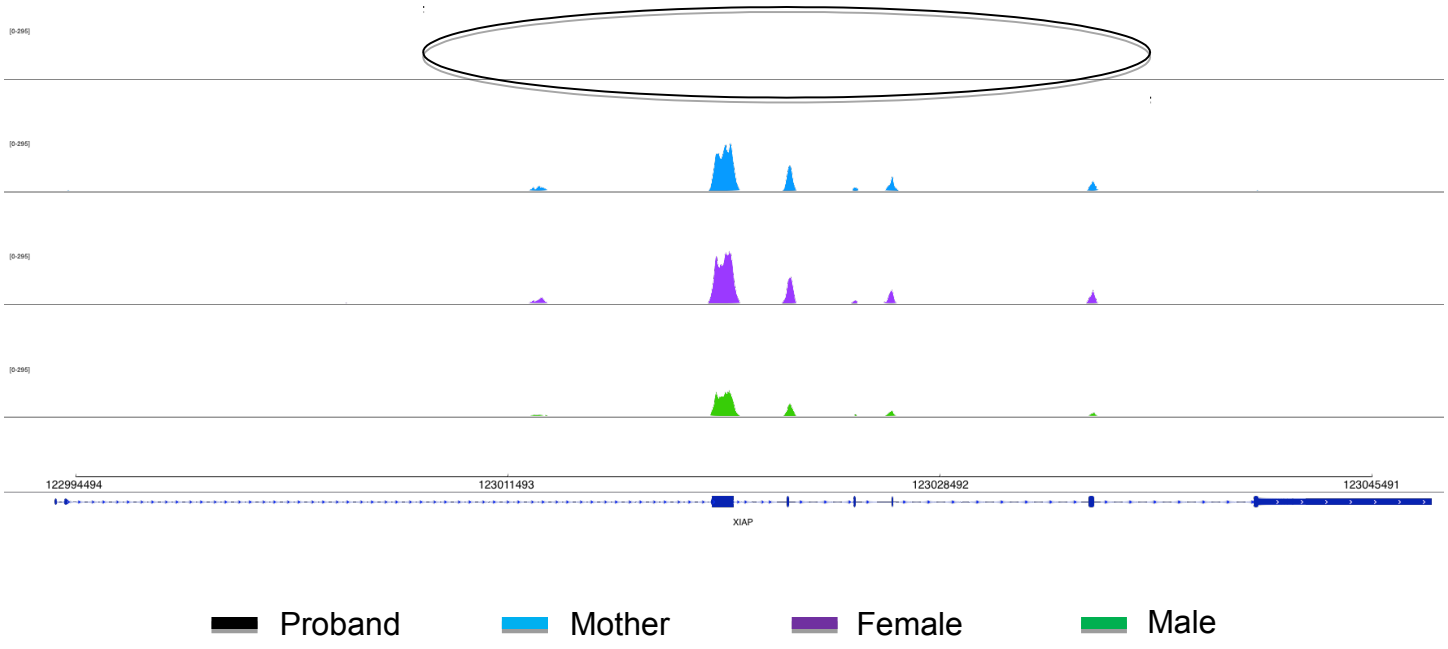
Case 5

- Male: neonatal onset bloody diarrhea
- Severe refractory course complicated by:
  - FTT and TPN/G-tube dependence
  - Pathological vertebral fracture
  - No oral intake until 12-year old
  - Rectal stricture→ colonic perforation and diverting ileostomy
  - Colectomy

Case 5

  - Duodenal stenosis
  - Recurrent abscess (skin and intestinal)
- Laboratory evaluation: decreased NK cells, poor B cell maturation

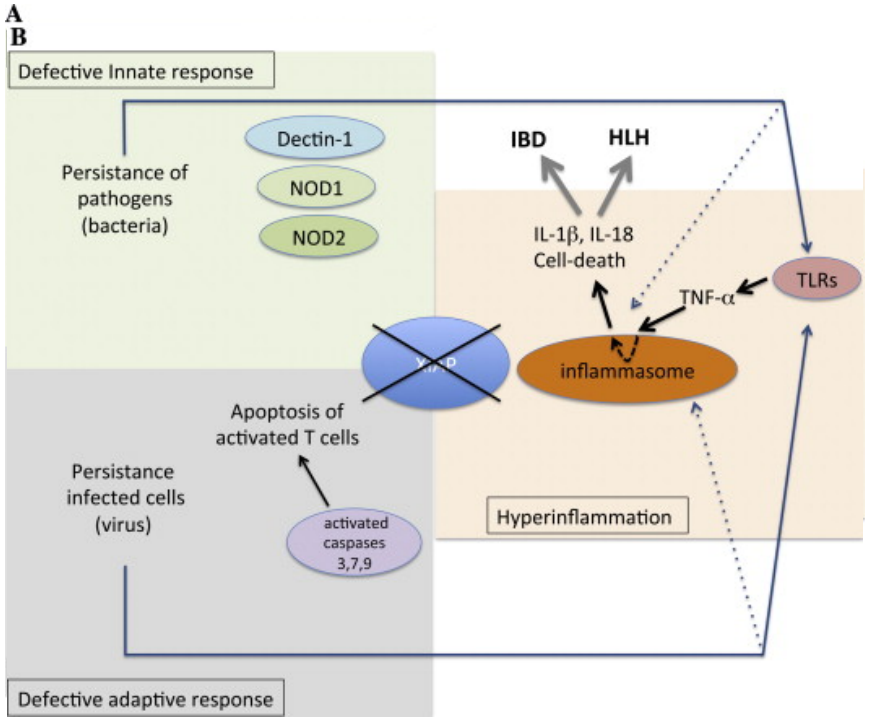
XIAP: De Novo Whole Gene Deletion



XIAP Expression

Population	XIAP: %positive	Reference
• CD4 0%	>92	
• CD8 0%	>93	
• CD56 0%	>94	
• CD19 0%	>89	

XIAP is the Causal Gene in X-linked Lymphoproliferative Disease 2



Latour S, Aguilar C., **XIAP deficiency syndrome in humans,** Seminars in Cell & Developmental Biology, 2015

Follow up

- Patient underwent HSCT
- Now in complete remission

Thank you