Optimizing the effectiveness of anti-TNF therapy in paediatric IBD

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  Takeda: consultant
* Merck: consultant
  * Products or services produced by these companies are relevant to my presentation.
Treatment goals in paediatric IBD have moved “beyond symptoms”

- Aiming to heal the intestine and thereby alter natural history, and improve outcomes
- Recognition of the discrepancy between symptoms and status of intestine particularly in Crohn’s disease
- Possible because of emergence of therapies with greater potential to achieve healing

Outline: Optimizing effectiveness of anti-TNF therapy in paediatric IBD

- Efficacy in paediatric Crohn’s disease and ulcerative colitis
- Dosing and therapeutic drug monitoring to optimize efficacy
- Avoiding secondary loss of response
- Positioning: when to use
- Balancing safety in paediatric IBD
## Infliximab in paediatric Crohn’s disease: Study Design

<table>
<thead>
<tr>
<th>Visits</th>
<th>All patients</th>
<th>Responders</th>
<th>Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
<td>Infliximab 5 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>Infliximab 5 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 6</td>
<td>Infliximab 5 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 10</td>
<td>Infliximab 5 mg/kg</td>
<td>Infliximab 5 mg/kg</td>
<td>No further infliximab</td>
</tr>
<tr>
<td>Week 14</td>
<td>Infliximab 5 mg/kg q 8 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 22</td>
<td>* LOR ≤8Wk Infliximab 10 mg/kg q 8 weeks</td>
<td>Infliximab 5 mg/kg q 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Week 30</td>
<td>* LOR &gt;8Wk Infliximab 5 mg/kg q 8 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 38</td>
<td>* Infliximab 5 mg/kg q 8 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 46</td>
<td>* Infliximab 5 mg/kg q 8 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Infusions

**Hyams J, Gastroenterology 2007**

### Initial response to infliximab in paediatric Crohn’s disease

**Clinical Response at 10 weeks**

- **ACCENT I**
  - 573 adults
  - Longer duration of disease (median 7 years)
  - Response defined by CDAI drop of ≥ 70 points

- **REACH**
  - 112 children
  - Shorter duration of disease (mean 2.0 years)
  - Response defined by PCDAI Drop of ≥ 15 points

**Hyams et al, Gastroenterology 2007; 132(3):863-873**

Real world effectiveness of infliximab: response to 3-dose induction in luminal inflammatory pediatric Crohn’s disease

Single-centre experience: 195 patients

Significant covariates

<table>
<thead>
<tr>
<th>Covariate</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from diagnosis to IFX induction (Years)</td>
<td>0.79 (0.68 - 0.91)</td>
</tr>
<tr>
<td>Early IFX (&lt;18mo from diagnosis)</td>
<td>7.01 (1.56 - 31.56)</td>
</tr>
<tr>
<td>Male</td>
<td>2.24 (1.09 – 4.60)</td>
</tr>
</tbody>
</table>

Covariate OR (95% CI)
- Time from diagnosis to IFX induction (Years): 0.79 (0.68 - 0.91)
- Early IFX (<18mo from diagnosis): 7.01 (1.56 - 31.56)
- Male: 2.24 (1.09 – 4.60)

Significant covariates: 9%

11%

80%

Therapeutic drug monitoring to individualize infliximab regimens in paediatric IBD

<table>
<thead>
<tr>
<th>Crohn's Disease</th>
<th>Ulcerative Colitis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of post-induction through level (weeks post dose 3)</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Induction dose mg/kg median (QI)</td>
<td>6.2 (3.4-9.5)</td>
<td>6.0 (4.4-8.8)</td>
</tr>
<tr>
<td>Inflammation high, median (QI)</td>
<td>7 (4.3-12.6)</td>
<td>10.2 (4.8-14.0)</td>
</tr>
<tr>
<td>Inflammation level &gt;3g/cm2, N (%)</td>
<td>6 (20.0)</td>
<td>4 (15.1)</td>
</tr>
<tr>
<td>Inflammation level &gt;3g/cm2, N (%)</td>
<td>6 (20.0)</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td>Inflammation level &gt;3g/cm2, N (%)</td>
<td>7 (26.3)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
**IMAGINE study: adalimumab in paediatric Crohn disease**

Hyams J et al  

**Open-label induction**

<table>
<thead>
<tr>
<th>Screening</th>
<th>Baseline</th>
<th>Week 2</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>&lt;40 kg: 80/40</td>
<td>≥40 kg: 160/80</td>
<td></td>
</tr>
</tbody>
</table>

**Double-Blind Maintenance**

<table>
<thead>
<tr>
<th>Week 26</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint *</td>
<td></td>
</tr>
</tbody>
</table>

- High-Dose
  - ≥40 kg: 40 mg eow
  - <40 kg: 20 mg eow
- Low-Dose
  - ≥40 kg: 20 mg eow
  - <40 kg: 10 mg eow

Randomization stratified by:
- Week 4 body weight
- Week 4 responder status
- Prior infliximab use

Dose escalation for flare or non-response beginning at Week 12

* Potential dose adjustment by body weight

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**Multicenter pediatric clinical trial data with anti-TNF therapy in Crohn’s disease**

<table>
<thead>
<tr>
<th>Infliximab (REACH)</th>
<th>Adalimumab (IMAGINE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=112 (mean age 13.3 years)</td>
<td>188 (mean age 13.5 years)</td>
</tr>
</tbody>
</table>

Prior anti-TNF treatment
- None (all anti-TNF naïve)
- Included 83 pts with secondary Loss of response /intolerance to infliximab

Concomitant IM during study
- 99% throughout (thiopurines usually)
- 62% from start to week 26

Response rate (drop in PCDAI ≥15) after induction
- 88% at week 10
- 87% of anti-TNF naïve patients

Remission rate at week 26
- 60% of week 10 responders randomized to 5 mg/kg q 8 weekly maintenance
- 63% of anti-TNF naïve week 4 responders randomized to high dose for body weight q 2 weeks
Corticosteroid-free remission with adalimumab at weeks 26 and 52: by prior infliximab use

Adalimumab: Clinical remission at week 52 with alternate weekly dosing

Hyams JS et al, Gastroenterology 2012
Real world effectiveness of adalimumab in luminal inflammatory paediatric Crohn’s disease

Single centre experience January 2007 to April 2015: n = 106

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Cohort (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, N (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>67 (63.2)</td>
</tr>
<tr>
<td>Age at ADA induction, Median (IQR)</td>
<td>14.3 (12.8-15.8)</td>
</tr>
<tr>
<td>Time to ADA, Months, Median (IQR)</td>
<td>14.4 (12.7-15.8)</td>
</tr>
<tr>
<td>ADA as First Anti-TNF, N (%)</td>
<td>64 (60.4)</td>
</tr>
<tr>
<td>Primary treatment indication for adalimumab, N (%)</td>
<td></td>
</tr>
<tr>
<td>Treatment of active disease</td>
<td>96 (90.6)</td>
</tr>
<tr>
<td>Maintenance of remission</td>
<td>10 (9.4)</td>
</tr>
<tr>
<td>Concomitant IM</td>
<td>37 (34.9)</td>
</tr>
</tbody>
</table>

Popalis C, ESPGHAN 2016

Real world effectiveness of adalimumab: response to induction in active luminal inflammatory paediatric Crohn’s disease

Single-centre experience: 96 patients

Anti-TNF naïve
N=59

Prior Infliximab
N=37

P=0.02

Paediatric-onset ulcerative colitis is extensive in 75% of patients

Toronto data

Children aged <10 years at diagnosis
- E4 pancolitis 73%
- E3 7%

Children aged >10 years at diagnosis
- E4 pancolitis 67%
- E3 11%

Similar to Scottish (Edinburgh) data
Van Limbergen J et al, Gastroenterology 2008;135: 1114-1122

Infliximab as rescue therapy for steroid-refractory pediatric ulcerative colitis


Total short term colectomy rate 11/128 (8.6%)
Infliximab in ambulatory paediatric ulcerative colitis

PedUC


Real world effectiveness of infliximab: response to 3-dose induction in paediatric ulcerative colitis

Single-centre experience: 125 patients

Ho S, et al, DDW 2016
Who were the patients?

<table>
<thead>
<tr>
<th>Patients (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Age at UC diagnosis, median (IQR)</td>
</tr>
<tr>
<td>Age at infliximab initiation, median (IQR)</td>
</tr>
<tr>
<td>Duration of UC diagnosis prior to infliximab, median (IQR)</td>
</tr>
<tr>
<td>Extent of UC:</td>
</tr>
<tr>
<td>- Pancolitis (E4), n (%)</td>
</tr>
<tr>
<td>- Extensive UC (E3), n (%)</td>
</tr>
<tr>
<td>- Left-sided UC (E2), n (%)</td>
</tr>
<tr>
<td>Indication – Steroid refractory: steroid dependent, n (%)</td>
</tr>
<tr>
<td>PUCAI, median (IQR)</td>
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</tbody>
</table>

Steroid-refractory: active UC non-responsive to IV steroids
Steroid-dependent: clinical remission achievable with steroids but unable to stop

Patient Characteristics at Baseline

<table>
<thead>
<tr>
<th>Patients (n=125)</th>
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</thead>
<tbody>
<tr>
<td>Concurrent corticosteroid, n (%)</td>
</tr>
<tr>
<td>Prior immunomodulator treatment, n (%)</td>
</tr>
<tr>
<td>Hemoglobin, median (IQR)</td>
</tr>
<tr>
<td>C-reactive protein, median (IQR)</td>
</tr>
<tr>
<td>Serum albumin, median (IQR)</td>
</tr>
</tbody>
</table>
Real world effectiveness: Response to 3-dose Infliximab Induction in paediatric ulcerative colitis

No significant difference in response and steroid free clinical remission rates in steroid-refractory versus steroid-dependent patients

Rapid anti-TNF clearance in acute severe UC?

No significant difference in response and steroid free clinical remission rates in steroid-refractory versus steroid-dependent patients

Low albumin and high CRP associated with decreased IFX exposure in UC


An Accelerated Infliximab Induction Regimen Reduces the Need for Early Colectomy in Patients With Acute Severe Ulcerative Colitis

David J. Gibson, Zaid S. Heetun, Ciaran E. Redmond, Kavin S. Nanda, Denise Keegan, Kathryn Byrne, Hugh E. Mulcahy, Garret Cullen, and Glen A. Doherty

Clinical Gastroenterology and Hepatology 2015
Infliximab induction dosing regimen in paediatric ulcerative colitis

Dosing (mean mg/kg over 3 induction doses)

Interval (weeks between dose 1 and dose 3)

Intensified: ≥7 mg/kg and/or 3 induction doses given within 5 weeks
Induction Dose Regimens

- **Intensified**: ≥7 mg/kg and/or 3 induction doses within 5 weeks (n=52, 41%)
- **Standard**: 5 mg/kg at weeks 0, 2, 6 (n=73, 59%)

Results: Response to Infliximab Induction Based on Regimen Used

- Intensification of infliximab induction regimen was associated with higher response rate in steroid-refractory patients, but did not improve outcomes when used in steroid-dependent patients (P=0.01, P=0.02)

![Graph showing response rates](image)

Results: Response to Infliximab Induction Based on Regimen Used (N=74)

- Steroid-Refractory
  - Standard (N=36): Clinical Response 64%, Clinical Remission 50%, Primary Non-response 36%
  - Intensified (N=38): Clinical Response 90%, Clinical Remission 76%, Primary Non-response 10%

P<0.01, P<0.02
Results: Response to Infliximab Induction Based on Regimen Used

Intensification of infliximab induction regimen was associated with higher response rate in steroid-refractory patients, but did not improve outcomes when used in steroid-dependent patients.

Induction infliximab levels among patients with acute severe ulcerative colitis compared with patients with moderately severe ulcerative colitis

<table>
<thead>
<tr>
<th></th>
<th>Acute severe colitis</th>
<th>Moderately severe colitis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D14</td>
<td>7.15 ± 5.3</td>
<td>14.4 ± 11.2</td>
<td>0.007</td>
</tr>
<tr>
<td>W6</td>
<td>3.25 ± 10.5</td>
<td>8.2 ± 8.3</td>
<td>0.14</td>
</tr>
<tr>
<td>W14</td>
<td>4.3 ± 5</td>
<td>5.3 ± 3.1</td>
<td>0.48</td>
</tr>
</tbody>
</table>
Therapeutic drug monitoring to individualize regimens: early post-induction

<table>
<thead>
<tr>
<th>Timing of post-induction trough level (weeks post dose 3)</th>
<th>Crohn’s Disease (n=30)</th>
<th>Ulcerative Colitis (n=21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks post induction</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>6 weeks post induction</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

- Induction dose (mg/kg, median [IQR]):
  - NC (n=30): 5.2 [4.1-6.1] vs. 9.6 [6.4-8.9] (p=0.001**)

- Infliximab trough levels (µg/ml, median [IQR]):
  - NC (n=30): 9.7 [6.4-13.6] vs. 9.9 [4.8-14.5] (p=0.8)

Clinical status following infliximab induction (CD vs UC)

- 24/28 CD vs. 9/21 UC patients achieved steroid-free clinical remission post induction
- Of patients not in remission, 9/12 UC and 2/4 CD patients had continuing active disease despite trough levels >3µg/ml

* Fisher’s exact test
Outline: Optimizing effectiveness of anti-TNF therapy in paediatric IBD

- Efficacy in Crohn’s disease and ulcerative colitis
- Dosing and therapeutic drug monitoring to optimize efficacy
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- Positioning: when to use
- Balancing safety in pediatric IBD
Durability of clinical response to infliximab in paediatric luminal CD

Individualization of regimen (dose escalation or interval shortening) was common especially in first 1-2 years of maintenance therapy (standard of care).

Secondary Loss of Responsiveness
- Complete loss of benefit from IFX after significant benefit had been obtained, despite adjustment of dose and/or dosing interval

“Substantial” mucosal healing in 75% of children re-examined when doing well clinically

Durability of response: mono vs combo with infliximab in pediatric Crohn’s disease

*Controlling for previous IM use, and response to induction
Durability of responsiveness in pediatric UC among complete responders continuing therapy (n=86)

Hepatosplenic T-cell lymphoma occurrences

Estimated Risks:
- Males <35 yrs on Thiopurines: 1/7404
- Males <35 yrs on Thiopurines + Anti-TNF: 1/3534


- 37 cases in IBD (35 male)
- 18 on anti TNF therapy + thiopurine (17 male)
- 19 on thiopurine therapy alone
- Age 12-58 (mean 26)
- 1-24 infusions (8 had <3 infusions)
Risk of HSTCL: Monotherapy with anti-TNF vs. Combination therapy anti-TNF + thiopurine


Duration of Thiopurine Exposure In Relation to Development of HSTCL

≥2 yrs of exposure in most but even less possible

**Immunomodulator and other biologic exposure in patients who had received infliximab (n=47)**

![Bar chart showing number of cases for different medications](chart1.png)

*Note: Medication categories are not mutually exclusive*

Data courtesy of Janssen, 2014

**Overall survival of peripheral T-cell lymphoma (PTCL) subtypes**

![Survival curve for different PTCL subtypes](chart2.png)

“*If there are modifiable risk factors that may impact disease incidence, their manipulation should be considered*”

(pediatric oncologist’s viewpoint)

*Savage KJ. Hematology Am Soc Hematol Educ Program 2008:280–8*
Anti-TNF Monotherapy vs combination therapy with an immunemodulator in paediatric IBD

- Combination therapy clearly important with infliximab;
  - For Crohn’s disease: methotrexate at least in boys rather than thiopurines

- Adalimumab?
  - No SONIC equivalent
  - Real world experience
  - Antibodies develop.....?neutralizing

Subcutaneously administered anti-TNFs: less variability in drug levels

Adapted from Tracey D, et al. *Pharmacol Ther* 2008;117:244–79
Meta-analysis: anti-TNF mono- or combination therapy

6 months clinical remission and concomitant IMM use

Adalimumab

Certolizumab

Infliximab

OR: 0.88 (0.58-1.35)

OR: 0.93 (0.65-1.34)

OR: 1.79 (1.06-3.01)

Favours anti-TNF mono

Favours anti-TNF combo

Sensitivity Analysis Including ACCENT 2
Systematic review of 11 RCTs in patients with luminal and/or fistulising CD who received anti-TNF therapy with/without concomitant IMM therapy

Durability of adalimumab responsiveness among complete responders to induction (n=81)
Durability of adalimumab responsiveness among complete responders to induction (n=81)

Prior infliximab loss of response n=27

Anti-TNF naive n=54
Outline: Optimizing effectiveness of anti-TNF therapy in paediatric IBD

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Treatment goals in paediatric IBD have moved “beyond symptoms”

- Aiming to heal the intestine and thereby alter natural history, and improve outcomes
- Recognition of the discrepancy between symptoms and status of intestine particularly in Crohn’s disease
- Possible because of emergence of therapies with greater potential to achieve healing

STRIDE “Selecting therapeutic targets in Inflammatory Bowel Disease”
Peyrin-Biroulet et al, Am J Gastro 2015
Efficacy and Safety: consider together in planning and positioning

For steroids (or exclusive enteral nutrition in CD) + immunomodulator maintenance

For anti-TNF induction therapy + continued maintenance

Positioning of anti-TNF in luminal inflammatory CD: exposure to immunomodulators prior to infliximab

Single-centre experience: 195 patients

Church P, Inflamm Bowel Dis 2014
Positioning of anti-TNF in paediatric UC

CONSENSUS STATEMENT

Clinical Practice Guidelines for the Medical Management of Nonhospitalized Ulcerative Colitis: The Toronto Consensus

Brian Bressler,1,6 John K. Marshall,1,6 Charles N. Bemstein,2 Alain Bitton,3 Jennifer Jones,3 Grigoris I. Leontiadi,1 Remo Panaccione,5 A. Hillary Steinhardt,7 Francis Tse,7 and Brian Feagan,6 on behalf of the Toronto Ulcerative Colitis Consensus Group

1Division of Gastroenterology, Department of Medicine, St Paul’s Hospital, Vancouver, British Columbia; 2Department of Medicine, McMaster University, Hamilton, Ontario; 3IBD Clinical and Research Centre, University of Manitoba, Winnipeg, Manitoba; 4Department of Medicine, McGill University Health Centre, Montreal, Quebec; 5Department of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan; 6Department of Medicine, University of Calgary, Calgary, Alberta; and 7Robarts Research Institute, Western University, London, Ontario, Canada

Approach to new onset (or established) IBD

- Careful phenotypic characterization
  - Risk assessment

- Selection of initial and maintenance treatment plan that is endorsed by family and patient
  - Agree upon targets

- Implementation of chosen therapies optimally

- Monitoring of outcomes including assessment of intestinal healing
Thank you for listening and for this invitation to the Summit
Patients

<table>
<thead>
<tr>
<th>Grohn’s Disease (n=30)</th>
<th>Ulcerative Colitis (n=21)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, N male (%)</td>
<td>20 (66.7)</td>
<td>9 (42.9)</td>
</tr>
<tr>
<td>Age at induction, yrs, median (IQR)</td>
<td>14.2 (12.9-16.0)</td>
<td>15.4 (12.4-16.4)</td>
</tr>
<tr>
<td>Disease Duration, yrs, median (IQR)</td>
<td>0.22 (0.1-2.4)</td>
<td>0.69 (0.3-2.1)</td>
</tr>
<tr>
<td>PGA of disease activity at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild, N (%)</td>
<td>12 (40.0)</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>Moderate, N (%)</td>
<td>14 (46.7)</td>
<td>3 (19.1)</td>
</tr>
<tr>
<td>Severe, N (%)</td>
<td>4 (13.3)</td>
<td>14 (66.7)</td>
</tr>
<tr>
<td>Receiving steroids at baseline, N (%)</td>
<td>12 (40.0)</td>
<td>21 (100.0)</td>
</tr>
<tr>
<td>Administered concomitant immunomodulator during induction N (%)</td>
<td>29 (96.7)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Body Mass Index, kg/m², median (IQR)</td>
<td>18.1 (16.8-20.5)</td>
<td>18.7 (18.2-23.6)</td>
</tr>
<tr>
<td>Baseline serum albumin, median (IQR)</td>
<td>38.0 (33.0-42.0)</td>
<td>33.0 (30.0-39.9)</td>
</tr>
<tr>
<td>Baseline serum hsCRP, median (IQR)</td>
<td>8.1 (2.5-27.3)</td>
<td>13.0 (2.8-31.0)</td>
</tr>
</tbody>
</table>

Infliximab in paediatric ulcerative colitis: Induction Dosing Regimen (n=118)
CCFA RISK Stratification Study
New Onset Pediatric Crohn’s Disease

Walters TD, Gastroenterology 2014

Crohn’s disease: 552 children with complete data and 1 yr f/u

TREATMENT in first 3 months

- Anti-TNFα only n = 68
- Early IM only n=248
- No early immunotherapy n = 236

Propensity Score Matching

- Anti-TNFα only n = 68
- IM only n = 68
- No early immunotherapy n = 68

Crohn’s disease RISK cohort: 12 Month Outcomes for the three early therapy approaches

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Achieved steroid-free, surgery-free remission by 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-TNF by 3 months</td>
<td>85%</td>
</tr>
<tr>
<td>IM by 3 months</td>
<td>60%</td>
</tr>
<tr>
<td>No immune therapy by 3 months</td>
<td>54%</td>
</tr>
</tbody>
</table>

Propensity score matching of cohorts

Walters TD et al, Gastroenterology 2014

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Absolute Risk Reduction</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF vs IM</td>
<td>25%</td>
<td>4</td>
</tr>
</tbody>
</table>

Chi squ p = 0.0003
Fecal loss of infliximab predicts clinical response


Absence of response in UC may be associated with low early IFX exposure

Brandse JF et al Clin Gastro Hepato 2015; 14: 251-258
IFX trough levels in Acute severe UC vs Moderately Severe UC?

ASUC n=16 → 3 primary non-responders
MSUC n=16 → 4 primary non-responders

IFX levels:
D14  9.8 ±9  vs.  12.1 ±10.6  P = 0.3
W6   3.75 ±2.2 vs.  9 ±9.9     P = 0.045

ATI levels:
D14  71%  vs.  32%  Mechanism of primary non-response??
D14  3.4 ±5.7 vs.  1.2 ±4  P = 0.06