Progress in Inflammatory Bowel Disease

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Disclosure
Research, Advisory and/or Honorarium

- Abbott
- AbbVie
- Alaven
- Bristol Myers Squibb
- Elan
- Ferring
- Hospira
- Ironwood
- Janssen
- Luitpold / American Regent
- Meda
- Millenium
- Ono
- Pfizer
- Prometheus Laboratories
- Salix Pharmaceuticals
- Santarus
- Shire
- Takeda
- UCB
- Warner Chilcott
Overview

- New agents
  - Moderate to severe disease
    - Vedolizumab (anti-alpha 4 beta 7)
    - Fecal Microbiota Therapy
- Current Management Advances
  - Mucosal Healing
  - Antimetabolite Therapy
    - Safety
    - Efficacy
- AntiTNF Therapy – new data

Biologic Agents for the Treatment of IBD

- **Infliximab**
  - Chimeric monoclonal antibody
  - 75% human
  - IgG1 isotype

- **Adalimumab**
  - Human recombinant antibody
  - 100% human
  - IgG1 isotype

- **Certolizumab Pegol**
  - Humanized Fab’ fragment
  - 95% human
  - IgG1 isotype

PEG, polyethylene glycol.
Limited Benefit of Current Medical Therapy for IBD

UC: Comparing ACT (Infliximab), PURSUIT (Adalimumab) and ULTRA (Golimumab) Clinical Remission

- 6-8 weeks
  - Patients failing 5-ASA / Steroids / IS

- 52-54 weeks

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Low dose</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>10</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>5</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Golimumab</td>
<td>15</td>
<td>35</td>
<td>55</td>
</tr>
</tbody>
</table>
UC SUCCESS study


Early AZA Alone Is Ineffective in CD

Crohn’s Disease

Abbreviation: Tx, transplantation.

Crohn's Disease
Comparing ACCENT I, CHARM and PRECISE 2 Results

Adapted from Danese S Gut 2011;60:998-1008
Vedolizumab: A Humanized, Monoclonal Antibody (mAb) Against α4β7 Integrins

- Targets only α4β7 integrin
- Created by insertion of ACT-1 CDRs into human IgG1 framework
- Two amino acid substitutions abrogate Fc-receptor binding and complement fixation (ADCC)
- IV infusion over 30 – 60 minutes

Ulcerative Colitis: Vedolizumab Phase III: Study Design

**Induction Phase**
- Week 0 – Week 6
- Cohort 1: Blinded Induction N=374
- Placebo N=149
- VDZ N=225
- Week 6: Responder?
- Yes: Week 52 Assessments
- No: Corticosteroid Tapering*

**Maintenance Phase**
- Week 6 – Week 52
- Placebo N=149
- VDZ N=373
- VDZ Q8 wks N=122
- VDZ Q4 wks N=125

*Corticosteroid Tapering*

*Responders began tapering regimen at 6 weeks; others, as soon as a clinical response was achieved.

Ulcerative Colitis: Clinical Response, Clinical Remission, Mucosal Healing at 6 Weeks, ITT Population

![Graph showing clinical response, remission, and mucosal healing at 6 weeks.]


Ulcerative Colitis: Clinical Remission, Durable Clinical Response at 52 Weeks by Prior TNF Antagonist Exposure

![Graph showing clinical remission and durable clinical response at 52 weeks by prior TNF antagonist exposure.]

Mean Δ% vs VDZ/PBO (95% CI):
VDZ/VDZ Q8W: 25.4 (6.1, 43.8)
VDZ/VDZ Q4W: 23.1 (10.3, 47.7)

PBO=placebo; VDZ=vedolizumab
What is the optimal positioning for Vedolizumab in UC?

Therapy is stepped up according to severity at presentation or failure at prior step.

Where are the Gaps for Crohn’s Disease?

Therapy is stepped up according to severity at presentation or failure at prior step.
Vedolizumab for CD Induction and Maintenance

**Vedolizumab for CD Induction and Maintenance**

**Induction Phase**
Week 0 – Week 6

- **Cohort 1**
  - Blinded Induction
  - N=368

- **Cohort 2**
  - Open Label Induction
  - N=747

**Maintenance Phase**
Week 6 – Week 52

- Placebo N=148
- VDZ N=220
- Placebo N=148
- VDZ N=506
- Placebo N=153
- VDZ Q8 wks N=154
- Placebo N=153
- VDZ Q4 wks N=154

**Week 52 Assessments**

*Responders began tapering regimen at 6 weeks; others, as soon as a clinical response was achieved. VDZ=vedolizumab*  

Clinical Remission and CDAI-100 Response at Week 6

**Clinical Remission**

- Placebo
  - 6.8%
  - P=0.02

- Vedolizumab
  - 14.5%

**CDAI-100 Response**

- Placebo
  - 25.7%
  - P=0.23

- Vedolizumab
  - 31.4%

Mean ∆% vs PBO (95% CI)

PBO=placebo; VDZ=vedolizumab  
Primary and Secondary Outcomes at 52 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (%)</td>
<td></td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>21.6</td>
<td>26.4†</td>
</tr>
<tr>
<td>CDAI-100 Response</td>
<td>30.1</td>
<td>43.8</td>
</tr>
<tr>
<td>CS-Free Remission</td>
<td>15.9</td>
<td>31.7‡</td>
</tr>
<tr>
<td>Durable Remission</td>
<td>14.4</td>
<td>21.4</td>
</tr>
</tbody>
</table>

Mean Δ% vs VDZ/PBO

1P<.01 vs placebo; †P<.05 vs placebo
CS=corticosteroid; VDZ=vedolizumab

Clinical Remission, CDAI-100 Response at 52 Weeks by Prior TNF Antagonist Exposure

<table>
<thead>
<tr>
<th>Maintenance ITT Population*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients With Prior Anti-TNFα Exposure (n=253)</td>
</tr>
<tr>
<td>100 Patients (%)</td>
</tr>
<tr>
<td>Clinical Remission</td>
</tr>
<tr>
<td>VDZ/PBO</td>
</tr>
<tr>
<td>VDZ/VDZ Q8W</td>
</tr>
<tr>
<td>VDZ/VDZ Q4W</td>
</tr>
<tr>
<td>17.1</td>
</tr>
<tr>
<td>29.5</td>
</tr>
<tr>
<td>27.7</td>
</tr>
<tr>
<td>Mean Δ% vs VDZ/PBO (95% CI)</td>
</tr>
<tr>
<td>VDZ/VDZ Q8W:</td>
</tr>
<tr>
<td>VDZ/VDZ Q4W:</td>
</tr>
</tbody>
</table>

VDZ=vedolizumab
Efficacy of Vedolizumab Induction Therapy in Patients With Crohn’s Disease Who Have Experienced Tumor Necrosis Factor Antagonist Failure or Are Tumor Necrosis Factor Antagonist Naive

Sands B et al. Abstract no. 864

Background and Methods

- **Background**
  - Vedolizumab is an anti-α4β7 integrin monoclonal antibody
  - Evaluated in 2 phase 3 studies (GEMINI 2 and GEMINI 3)

- **Methods**
  - Induction data were pooled from the randomized GEMINI 2 and 3 studies of patients with moderately to severely active CD who received placebo or vedolizumab 300 mg by intravenous infusion at weeks 0, 2, and 6
  - Proportions of patients in clinical remission and with a CDAI-100 response (≥100-point decrease from baseline in CDAI score) were assessed at weeks 6 and 10 for the TNF antagonist failure and TNF antagonist–naive subgroups
Results

<table>
<thead>
<tr>
<th>End Point</th>
<th>TNF Antagonist Failure</th>
<th>TNF Antagonist Naive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VDZ (n=263)</td>
<td>PBO (n=227)</td>
</tr>
<tr>
<td>Week 6 clinical remission, No. patients (%)</td>
<td>35 (13.3) 0.157</td>
<td>22 (9.7)</td>
</tr>
<tr>
<td></td>
<td>57 (21.7) 0.0008</td>
<td>25 (11.0)</td>
</tr>
<tr>
<td>Week 6 CDAI-100 response, No. patients (%)</td>
<td>87 (33.1) 0.005</td>
<td>51 (22.5)</td>
</tr>
<tr>
<td></td>
<td>103 (30.2) 0.0001</td>
<td>51 (22.5)</td>
</tr>
</tbody>
</table>

Data are from post hoc analyses; *P*-value versus PBO and based on the Cochran-Mantel-Haenszel chi-square test.

Take-home Messages

- Vedolizumab is effective in patients who experienced failure of prior TNF antagonist therapy and those who were TNF antagonist naive.
- In clinical practice it may take 10 weeks or more to see a clinical effect in some patients.
A Randomized, Placebo-Controlled Trial of Fecal Microbiota Therapy in Active Ulcerative Colitis

Moayyedi P et al.
Abstract no. 929c

Rationale and Methods

• Rationale
  – Fecal microbiota therapy (FMT) has been successful in treated *C difficile* colitis
  – Small case series suggest it may be effective in active UC

• Methods
  – Randomized, placebo-controlled clinical trial
  – Enrolled patients with active UC
  – Patients (n=63) randomized to 6 weeks of once weekly treatment with:
    • FMT (50 mL retention enema)
    • Placebo (50 mL water enema)
  – Primary outcome: Remission of UC (Mayo score ≤2 with endoscopic score = 0) at Week 7
**Results**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FMT (n=27)</th>
<th>Placebo (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-week Mayo score</td>
<td>6.81 ± 3.72</td>
<td>6.19 ± 3.36</td>
<td>0.52</td>
</tr>
<tr>
<td>6 week IBDQ</td>
<td>148.4 ± 41.9</td>
<td>146.4 ± 33.3</td>
<td>0.82</td>
</tr>
<tr>
<td>Primary end point met</td>
<td>4 (15%)</td>
<td>2 (8%)</td>
<td>0.41</td>
</tr>
<tr>
<td>30% improvement in Mayo score</td>
<td>7 (26%)</td>
<td>8 (31%)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

- **No statistically significant effect of FMT in active UC**

**Conclusions**

This is the first randomized placebo controlled trial of FMT in UC and shows there was no statistically significant effect of FMT in active UC.

There is a possibility that FMT may be effective when administered longer than 6 weeks.

Possibly administer by different methods
- NG tube
- Colonoscopic infusion

Future studies should evaluate FMT over longer time periods, possibly with more intensive therapy but this approach should only be offered to UC patients in the context of a clinical study.
Overview

- New agents
  - Moderate to severe disease
    - Vedolizumab (anti-alpha 4 beta 7)
- Current Management Advances
  - Mucosal Healing
  - Antimetabolite Therapy
    - Safety
    - Efficacy
- AntiTNF Therapy – new data
- Deep remission and treat to target

Case History

- 32 year-old
- UC x 16 years-pancolitis
- Maintenance
  - mesalamine 1.6 g/d
- Asymptomatic
- Surveillance colonoscopy
  - Moderate activity
  - Some normal areas
Case Continued

- Colon biopsies
  - Patchy minimally active chronic colitis, some areas of inactive colitis, some normal biopsies. No dysplasia

- CRP = 9.0 normal < 8.0

Case: Management Options

1. Status Quo
2. Dose Escalate Mesalamine
3. Check TPMT
   - Initiate Azathioprine / 6-Mercaptopurine
4. Add an Anti-TNFα Antibody
Randomized Controlled Trial of Mesalamine Dose Escalation for Ulcerative Colitis in Remission

Lewis J et al. Abstract no. 862

Purpose and Methods

- **Purpose**
  - In quiescent UC, lower fecal calprotectin concentration is associated with lower relapse rates
  - Examined whether higher-dose mesalamine can reduce FC concentration among patients with quiescent UC

- **Methods**
  - Randomized controlled trial
  - Patients: UC in remission (N=52) taking no more than 3 g/day mesalamine
  - Patients not taking MMX mesalamine switched to 2.4 g/d for 6 weeks prior to randomization
  - Treatments
    - Continue current mesalamine dose
    - Increase dose by 2.4 g/day for 6 weeks
  - Primary outcome: continued remission with FC concentration <50mcg/g at 6 weeks
Results and Conclusions

- Primary outcome achieved by 3.8% of control patients and 26.9% of patients randomized to dose escalation ($P=0.0496$).
- More patients in the dose escalation group achieved reduction in FC concentration below 100 mcg/g (52.6% vs 15.8%, $P=0.04$) and 200 mcg/g (76.9% vs. 16.7%, $P=0.005$)

Take-home Messages

- Mesalamine dose escalation is associated with reductions in FC concentrations to levels associated with lower relapse rates
Overview

- New agents
  - Moderate to severe disease
    - Vedolizumab (anti-alpha 4 beta 7)
    - Fecal Microbiota Therapy
- Current Management Advances
  - Mucosal Healing
  - Antimetabolite Therapy
    - Safety
    - Efficacy
- AntiTNF Therapy – new data

Potential Adverse Events of IBD Therapy
Meta-analysis of duration of exposure to thiopurines in association with development of lymphoma in patients with Inflammatory Bowel Disease: population cohort analysis.

Kotlyar D et al. Abstract no. 1109

Rationale and Methods

• Rationale
  – The issue of whether increased duration of exposure to thiopurines increases lymphoma risk remains a highly clinically relevant yet poorly characterized issue.
  – No meta-analysis of population based studies has yet been performed evaluating if there is a relationship between the time of exposure and development of lymphoma.

• Methods
  – Meta Analysis: evaluated Lymphoma as an outcome, and pts. received AZA and/or 6-MP.
  – Pooled standardized incidence ratios (SIRs) were generated and confidence intervals were based on the Poisson distribution.
  – Pooled standardized incidence ratios (SIRs) were generated and confidence intervals were based on the Poisson distribution.
Results

• There were 4,383 citations in total.
• Two citations - Khan 2013, Chaparro 2010- were included.
• In those with less than 1 year of thiopurine exposure, the SIR=1.39 (95% CI= 0.60-3.24),
• in those with 1-2 years of exposure, SIR=4.31 (95% CI=1.85-10.1),
• In those with 2-3 yrs of exposure SIR=3.08 (95% CI=1.05-9.00))
• In those with >3 yrs of exposure SIR=4.84 (95% CI= 2.88-8.11). (Table 1).
• Other than one case of lymphoma which developed within 2 months of treatment, which may have been concurrent, there was a lag time of at least 8 months prior to onset of lymphoma.
• Of the cases, 5 (23%) were <1 yr, 5 (23%) between 2-3 yrs, and 12 (55%) greater than 3 yrs.

Conclusion

• Exposure for more than one year of treatment while on active therapy significantly increases the risk of lymphoma.

• While few cases have been seen with less than twelve months of treatment, the SIR for less than one year of therapy may be influenced by patients using the drug for extremely short amounts of time (e.g. 1-2 months, and not tolerating the drug due to adverse effects).

• Thus, the lack of an observed increased risk within one year of initiating therapy may be falsely reassuring.

• The risk of developing lymphoma in patients with IBD exposed to AZA/6-MP is escalated over the general population when exposed to more than 1 year of treatment based on the analysis of two studies and further prospective studies will be critical to better understanding the relationship between duration of exposure to thiopurines and the development of lymphoma.
Risk of Lymphoma in Patients with Inflammatory Bowel Disease Treated with Azathioprine and 6-Mercaptopurine: a Meta-Analysis.


Background

AIMS

- To estimate the relative risk of lymphoma in IBD patients exposed to thiopurines, and to compare relative risks derived from population-based studies with that of referral center-based studies.

- We also inquired if active use engendered a higher risk than past use.

- We also wished to discover if gender, age, or duration of use affected the risk of lymphoma.

Methods

- We searched MEDLINE, EMBASE, and Cochrane databases, as well as conference abstracts and international publications, for the terms 6-MP and lymphoma, 6-mercaptopurine and lymphoma, thiopurines and lymphoma, azathioprine and cancer and IBD, azathioprine and malignancy and IBD, azathioprine and lymphoma, and lymphoproliferative and thiopurines.

- Pooled standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were estimated.

- The deviance statistic from Poisson models was used to calculate heterogeneity.


Results

- Eighteen studies (among 4383 citations) met our inclusion criteria.

- The SIR for lymphoma was
  - Overall- 4.49 (95% CI, 2.81–7.17),
  - 2.43 (95% CI, 1.50–3.92) in 8 population studies
  - 9.16 (95% CI, 5.03–16.7) in 10 referral studies.

- Population studies demonstrated an
  - Increased risk among current users (SIR=5.71; 95% CI, 3.72–10.1) but
  - No increased risk in former users (SIR=1.42; 95% CI, 0.86–2.34).

RESULTS

- **Sex**
  - Men have a greater risk than women (RR=2.05; \( P<.05 \))
  - Both sexes were at increased risk for lymphoma
  - Men: SIR for men = 3.60 (95% CI, 2.68–4.83)
  - Women: SIR for women = 1.76 (95% CI, 1.08–2.87)

- **Age**
  - Patients < 30 years had the highest RR
    - SIR=6.99; CI, 2.99–16.4
  - Younger men had the highest risk
  - The absolute risk was highest in patients > 50 years
    - 1:377 cases per patient–year

**Take Home Message**

- For patients of all ages and genders, the risk of lymphoma needs to be weighed against the potential benefits of therapy.
The impact of age-specific risks of lymphoma on the decision to use combination therapy with infliximab and azathioprine versus infliximab alone: A Markov Model

Scott F et al. Abstract no. 4

Rationale and Methods

• Rationale
  – The impact of age-related risk of NHL and HSTCL has not been addressed in prior studies
  – After accounting for age and treatment-specific risks of lymphoma, the preferred treatment strategy in CD may differ by age

• Methods
  – Markov model constructed to assess age-specific risks and benefits of combination therapy vs anti-TNF monotherapy
  – Expected risk and incremental effectiveness calculated for patients initiating therapy across 25 to 75 age range
  – Baseline case: 35-year-old male with severe CD
Results

• Combination therapy was the preferred strategy in the baseline case (0.7714 vs. 0.7611 QALYs)
• Combination therapy resulted in fewer surgeries (94,888 vs. 144,351), deaths (4133 vs. 4155), and patients with active disease (162,524 vs. 198,191)
• Benefit persisted across all ages in the base model, though the margin of benefit decreased with increasing age

Results

• When accounting for life years lost due to mortality, monotherapy was preferred if the HR of NHL with AZA therapy was >11.5 in those age 65 or >6.9 in those age 75
• For 25-year-old males, accounting for the risk of HSTCL, monotherapy resulted in fewer deaths and was the preferred strategy if the incidence of HSTCL was greater than 24 per 100,000
Take-home Messages

• From ages 35 to 65, combination therapy is the preferred strategy
• For those who are >65, and particularly those >75, monotherapy may be a more beneficial strategy due to the increased risk of NHL and NHL-related mortality with combination therapy
• Due to HSTCL risk, combination therapy in young males may result in more deaths without providing substantially greater QALYs

Potential Benefit of Antimetabolite Therapy
### ATI Formation Is Lower in Patients on Concomitant IM Therapy

**ACCENT 1 Subanalysis**

Percent ATI(+) Patients According to Treatment Regimen

- **Episodic strategy**
  - No immunomodulators (n=362)
  - With immunomodulators (n=152)
  - ATI (+) Patients (%): 38, 11

- **5 mg/kg Maintenance**
  - No immunomodulators (n=362)
  - With immunomodulators (n=152)
  - ATI (+) Patients (%): 16, 7

- **10 mg/kg Maintenance**
  - No immunomodulators (n=362)
  - With immunomodulators (n=152)
  - ATI (+) Patients (%): 8, 4

\[ P = 0.003 \]
\[ P = 0.42 \]


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### AAA Formation Lowers Adalimumab Trough Serum Levels

- 92% of the patients with a trough serum concentration measured below the threshold for detection were positive for AAA

<table>
<thead>
<tr>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 54</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA TR (μg/mL)</td>
<td>AAA TR (μg/mL)</td>
<td>AAA TR (μg/mL)</td>
<td>AAA TR (μg/mL)</td>
<td>AAA TR (μg/mL)</td>
</tr>
<tr>
<td>2.1 (n=9)</td>
<td>0.6 (n=8)</td>
<td>0.1 (n=8)</td>
<td>0.02 (n=3)</td>
<td>0.05 (n=10)</td>
</tr>
<tr>
<td>6.1 (n=58)</td>
<td>8.9 (n=53)</td>
<td>8.8 (n=37)</td>
<td>11.1 (n=46)</td>
<td>5.8 (n=30)</td>
</tr>
</tbody>
</table>

Discontinuation

**SONIC**

**IFX Trough Levels at Week 30***

Patients who had 1 or more PK samples obtained after their first study agent administration were included in the analysis.


- **Median Serum Trough Levels** (mg/ml) (n=97) (n=109)
  - **IFX + placebo**
    - 0 2 4 6 8 10
    - 1.6 (n=97)
  - **IFX + AZA**
    - 3.5 (n=109)

**Drug Levels Predict Immunogenicity:**

**Serum IFX at Week 4 After an Infusion Predicts Eventual Appearance of ATI’s in Episodic Dosing**

- **Week 4 serum level and subsequent ATI titre**
  - **P = ns**
  - **P<0.001**
  - **P<0.001**

- **ATI <8**
  - **ATI >8**
  - **ATI ??**

- **“an IFX level of <4 μg/ml measured 4 weeks after the first infusion had a PPV of 81% to detect the development of high ATIs during the later course of treatment”**

- **“an IFX level of >15 μg/ml measured 4 weeks after the first infusion was 80% predictive for the absence of ATIs during later follow-up.”**

"Therefore, IFX levels measured early after the first infusion of IFX (at 4 weeks) are a good prognostic parameter for development of immunogenicity."

Vermeire et al. Gut 2007;56;1226-1231
**SONIC**

Azathioprine + IFX Combination Therapy

Could it improve the safety of infliximab?

Addition of an Immunomodulator to IFX Therapy Eliminates Antidrug Antibodies in Serum and Restores Clinical Response of Patients With IBD

**Methods**

- Chart review of IFX-treated IBD patients to identify patients who:
  - Developed a loss of response* to IFX in the presence of anti-IFX antibodies
  - Have undetectable trough levels of IFX
- Patients were treated with IFX + immunomodulators after the loss of response was identified
- IFX and ATIs in the serum were measured by ELISA

* Loss of response – re-emergence of IBD symptoms coupled with a decision of the treating physician to alter the therapy, that is, to increase the dose, switch anti-TNF, add an immunomodulator, or refer the patient for CD surgery


**Results**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex, age</th>
<th>Disease location</th>
<th>Prior treatments</th>
<th>No. infusions until LOR</th>
<th>Immuno-modulator introduced</th>
<th>Subsequent course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M, 26</td>
<td>CD Small bowel &amp; perianal 8 years</td>
<td>AZA, MTX, ADA</td>
<td>5 infusions 5 mg/kg/6 wk</td>
<td>MTX</td>
<td>Clinical remission 12 months</td>
</tr>
<tr>
<td>2</td>
<td>F, 18</td>
<td>CD Small bowel &amp; upper GI 3 years</td>
<td>AZA, MTX</td>
<td>7 infusions 5 mg/kg/4 wk</td>
<td>6-MP</td>
<td>Clinical remission 10 months</td>
</tr>
<tr>
<td>3</td>
<td>M, 22</td>
<td>CD Small bowel &amp; perianal 2 years</td>
<td>None</td>
<td>14 infusions 5 mg/kg/4wk</td>
<td>AZA</td>
<td>Clinical response 8 months</td>
</tr>
<tr>
<td>4</td>
<td>M, 37</td>
<td>UC Left-sided 2 years</td>
<td>AZA</td>
<td>9 infusions 5mg/kg/6 wk</td>
<td>AZA</td>
<td>Clinical remission 13 months</td>
</tr>
<tr>
<td>5</td>
<td>F, 34</td>
<td>UC Left-sided 3 years</td>
<td>AZA</td>
<td>3 infusions, induction regimen</td>
<td>MTX</td>
<td>Clinical remission 10 months</td>
</tr>
</tbody>
</table>

Concentration of IFX and ATI Levels Before and After Immunomodulator Treatment

![Graphs showing concentration of IFX and ATI before and after treatment.]

IFX levels closed squares
ATI open squares


Factors that Influence the PK of TNF Antagonists

<table>
<thead>
<tr>
<th>Factor</th>
<th>Impact on TNF antagonist PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of ADAs</td>
<td>Decreases drug concentration&lt;br&gt; Increases clearance&lt;br&gt; Worse clinical outcomes</td>
</tr>
<tr>
<td>Concomitant use of Immunosuppressives</td>
<td>Reduces ADA formation&lt;br&gt; Increases drug concentration&lt;br&gt; Decreases drug clearance&lt;br&gt; Better clinical outcomes</td>
</tr>
<tr>
<td>Low serum albumin concentration</td>
<td>Increases drug clearance&lt;br&gt; Worse clinical outcome</td>
</tr>
<tr>
<td>High baseline CRP concentration</td>
<td>Increase drug clearance</td>
</tr>
<tr>
<td>High baseline TNF concentration</td>
<td>May decrease drug concentration by increasing clearance</td>
</tr>
<tr>
<td>High body size</td>
<td>May increase drug clearance</td>
</tr>
<tr>
<td>Sex</td>
<td>Males have higher clearance</td>
</tr>
</tbody>
</table>

Higher 6-Thioguanine Nucleotide Concentrations Are Associated With Higher Trough Levels Of Infliximab In Patients On Combination Therapy

Yarur A et al. Abstract no. 788

Rationale and Methods

• Objective
  – Assess if there is a correlation between 6-thioguanine (6-TGN), IFX trough level, and antibodies to IFX (ATI)

• Methods
  – Cross-sectional study of IBD patients receiving maintenance therapy with IFX with a thiopurine (AZA or 6-MP) for ≥4 months
  – Primary outcome: IFX trough level and the presence of ATI
Results

- Significant positive correlation between 6-TGN levels and IFX levels (rho: 0.477 \(P<.0001\))
- 6-TGN \(\geq125\) pmol/8X10^8 RBC best predicted higher anti-TNF levels (ROC: 0.82, \(P=.002\))
- Only 6-TGN level was predictive of IFX measurements (\(P<.001\))
- Patients with 6-TGN levels <125 pmol/8X10^8 had a 1.3-fold higher chance of having detectable ATI (OR: 1.3 \([P<.01]\))

Take-home Messages

- 6-TGN metabolite levels rather than weight-based dosing may assist in optimizing treatment when using thiopurines in combination with IFX
- Therapeutic levels of 6-TGN (>232 pmol/8X10^8 RBC) are not necessary to achieve higher trough levels of IFX
- Lower target 6-TGN levels (125 pmol/8X10^8 RBC) may maximize IFX levels while minimizing toxicity
Azathioprine decreases the risk of adalimumab primary non-response and secondary loss of response but only if adequately dosed

Kariyawasam V et al. Abstract no. 343

Purpose and Methods

• Purpose
  – Assess the impact of concomitant immunomodulators and drug monitoring to confirm compliance on ADA efficacy

• Methods
  – All patients treated with adalimumab at a single center included (N=118)
  – Treatment periods assessed in 6-month semesters
Results

• Complete clinical response to induction was achieved in 78% (92/118)
  – Thiopurines 3 months prior to starting ADA associated with significantly higher likelihood of response (84.2% vs 66.7%, \( P=0.028 \))

• Reclassifying according to TGN levels improved this association (87.3% vs 65.9%, \( P=0.011 \))

Figure 1. Time to Adalimumab failure according to therapeutic levels of azathioprine for 3 months prior to starting therapy.
Results

• 169 semesters in 81 patients were analyzed for the effect of concomitant immunomodulators

• Semesters with concomitant immunomodulators when classified according to TGN showed significantly lower flare (16.4% vs 24.6%) and failed (9.2% vs 2.7%) semesters ($P=.019$)

• Not seen when TGN levels were not considered ($P=.074$)

Take-home Message

• Thiopurine use adjusted with drug monitoring may increase rate of successful induction of remission and reduce numbers of flares and failure during maintenance
Early Combined Immunosuppression for the Management of Crohn's Disease: a Community-Based Cluster Randomized Trial

Abstract 1053


Background

• Conventional management (CM) of Crohn's disease (CD) consists of sequential use of corticosteroids, antimetabolites, and tumor necrosis factor (TNF)-antagonists.
• Recent evidence indicates that early combined immunosuppression (ECI) with a TNF-antagonist and an antimetabolite may be more effective than CM.
• We compared the effectiveness of ECI (Figure 1) to CM in community gastroenterology practices
Methods

- In this cluster randomization trial (Randomized Evaluation of an Algorithm for Crohn’s Treatment or REACT; Clinicaltrials.gov NCT01030809; partial support AbbVie), practices in Canada (n=34) or Belgium (n=5) were randomly assigned in a 1:1 ratio to ECI or CM.

- Up to 60 consecutive adult patients (≥18 years of age) with CD in each practice evaluated for 24 months.

- The primary outcome was proportion of patients in remission (Harvey-Bradshaw Score (HBS) ≤4 in the absence of steroids) at 12 months.

Figure 1: Therapeutic algorithm utilized for patients in the ECI group
RESULTS

- Twenty-one centers (1084 patients) assigned to ECI and 18 (898 patients) to CM.
- Mean HBS scores were 4.1 in both groups.
- The proportion of patients in the ECI and CM groups who received combination of antimetabolite / TNF-antagonist by 12 months was 15.1% and 6.5% ($P<.001$) and 19.7% and 9.6% by 24 months ($P<.001$).
- Mean % (SD) remission rates in the ECI and CM groups were 66 (14) and 62 (17) at 12 months ($P=.65$) and 73 (8) and 65 (17) at 24 months ($P=.35$).
- However, highly significant and clinically important differences in the rates of complications, surgeries, and the combined outcome of hospitalizations, complications, and surgeries were observed in favor of ECI over 24 months (Figure 2).
- The 24 month actuarial estimates for the combined outcome were 27.7% and 35.1% in the ECI and CM groups, respectively (hazard ratio adjusted for CD caseload and country: .74 [.62, .87, $P<.001$]).

Figure 2:
Hospitalizations, complications (abscesses, new fistulas, extra-intestinal manifestations of CD, serious adverse events), and surgeries for patients in the ECI and CM groups over 24 months.
Conclusion

Community-based data indicate that
• 1) a symptom based conventional approach to CD management may not be optimal and
• 2) ECI may be more effective in preventing CD-related complications
Usefulness of a rapid test for fecal calprotectin as predictor of relapse in Crohn's disease patients under maintenance treatment with adalimumab

Dominguez-Munoz E et al. Abstract no. 345

Purpose and Methods

- **Purpose**
  - Evaluate predictive value of a rapid test of fecal calprotectin to predict flares in CD patients during ADA maintenance

- **Methods**
  - Prospective, observational cohort study
  - CD patients in clinical remission for ≥6 months with standard dose of 40 mg/every other week adalimumab
  - Calprotectin measured and correlated with relapse over next 4 months
  - “Quantum Blue” rapid 12-15 fecal calprotectin test used for analysis (not available in the US)
Results

- After the four months follow-up, 70.0% patients remained in clinical remission; 30.0% relapsed
- Fecal calprotectin significantly higher in patients who had a relapse during follow-up
- Optimal cutoff to predict remission: 204 µg/g

Serum CRP is a better early marker for response to infliximab induction therapy than fecal calprotectin in patients with moderate to severe ulcerative colitis

Purpose and Methods

- **Purpose**
  - Aimed to define the optimal timing of serum CRP and fecal calprotectin measurement and compare both markers for response to therapy

- **Methods**
  - Multicenter prospective observational study
  - Serum CRP, albumin, and fecal calprotectin measured during the first 6 weeks of induction therapy
  - Absence of response defined as need for higher-dose infusion during induction or colectomy within 3 months
  - Endoscopic response defined as improvement at week 6-8 endoscopy

### Results

Markers that significantly discriminate between absence of response and response or endoscopic response or non-response

<table>
<thead>
<tr>
<th></th>
<th>Absence of response (n=5)</th>
<th>Responders (n=12)</th>
<th>P value</th>
<th>Predictive value cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CRP (mg/l)</td>
<td>124 (95-128)</td>
<td>9 (2-31)</td>
<td>P=0.04</td>
<td>OR: 3.4 (95% CI:1.76-6.7)</td>
</tr>
<tr>
<td>Day 1 CRP (mg/l)</td>
<td>95 (60-123)</td>
<td>7 (2-29)</td>
<td>P=0.04</td>
<td>OR: 3.4 (95% CI:1.76-6.7)</td>
</tr>
<tr>
<td>Day 4 CRP (mg/l)</td>
<td>91 (30-936)</td>
<td>3.8 (1.7-11.3)</td>
<td>P=0.01</td>
<td>OR: 1.5 (95% CI:1.25-10.36)</td>
</tr>
<tr>
<td>Day 4 Albumin (g/l)</td>
<td>20 (20-22)</td>
<td>40 (27-46)</td>
<td>P=0.02</td>
<td>OR: 0.4 (95% CI:1.76-6.7)</td>
</tr>
</tbody>
</table>

Day 7 CRP (mg/l), cut-off 3ng/l

<table>
<thead>
<tr>
<th></th>
<th>Absence of response (n=5)</th>
<th>Responders (n=12)</th>
<th>P value</th>
<th>Predictive value cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7 calprotectin (ng/l), cut-off 1300ng/l</td>
<td>15.3 (2-30)</td>
<td>15.6 (3.3-10)</td>
<td>P=0.06</td>
<td>OR: 3.4 (95% CI:1.76-6.7)</td>
</tr>
</tbody>
</table>

Day 10 calprotectin (ng/l), cut-off 750ng/l

<table>
<thead>
<tr>
<th></th>
<th>Absence of response (n=5)</th>
<th>Responders (n=12)</th>
<th>P value</th>
<th>Predictive value cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 10 calprotectin (ng/l)</td>
<td>800 (150-1830)</td>
<td>466 (320-1438)</td>
<td>P=0.02</td>
<td>OR: 5.5 (95% CI:1.88-16.24)</td>
</tr>
<tr>
<td>Day 14 calprotectin (ng/l)</td>
<td>800 (1428-1830)</td>
<td>222 (130-835)</td>
<td>P=0.01</td>
<td>OR: 5.5 (95% CI:1.88-16.24)</td>
</tr>
</tbody>
</table>
Results

Serum CRP during IFX induction

- Absence of response (n=3)
- Responders (n=12)
- Endoscopic non-responders (n=8)
- Endoscopic responders (n=7)

Take-home Messages

- Serum CRP is a better early marker for response to IFX vs fecal calprotectin or serum albumin
- Optimal timing for measuring serum CRP to predict absence of clinical or endoscopic response:
  - Day 4 (cut-off value 2.5 mg/dL)
  - Day 7 (cut-off value 0.5 mg/dL)
Risk of incident cancer in patients with inflammatory bowel disease starting anti-TNF therapy while having prior malignancy within past 5 years

Laharie D et al. Abstract no. 341

Purpose and Methods

- **Purpose**
  - assess survival without incident cancer in a cohort of patients with IBD exposed to anti-TNF therapy while having prior malignancy within past 5 years

- **Methods**
  - Survey conducted that collected all IBD patients with malignancy diagnosed within 5 years prior to starting an anti-TNF
  - Primary objective: Evaluate the cumulative incidence of incident (new or recurrent) cancer
Results

- 79 cases of IBD patients with prior malignancy identified
- Most frequent: breast (n=17), skin (n=15), urinary tract (n=12), and those attributed to chronic inflammation (n=8)
- After median follow up of 21 [1-119] months, 15 (19%) patients developed an incident cancer: 8 recurrent cancers and 7 new cancers, including 5 BCCs
- Survival without incident cancer was 96%, 86% and 72% at 1, 2 and 5 years, respectively
- Two recurrences possibly related to anti-TNF administration

Take-home Messages

- Pending large prospective studies, a case by case joint decision taken with the oncologist is recommended in this situation.

- My Assessment:
  - Melanoma – probably no anti-TNF
  - Early stage malignancy several years out-discuss with oncologist.
Infliximab trough levels are correlated with Infliximab-associated adverse events

Huang V et al.
Abstract no. 3

Rationale and Methods

- **Rationale**
  - To determine the prevalence of infliximab-associated AEs in IBD patients and evaluate their relationship to infliximab trough levels

- **Methods**
  - Cross-sectional study of consecutive patients from a single center (N=75)
  - Infliximab levels obtained before infusion
  - Records reviewed for infliximab-associated AEs
Results

- Median trough levels were significantly higher in patients who reported dermatologic AEs (9.9 μg/mL vs 0.1 μg/mL, \(P=.020\)),
- Median trough levels were significantly lower in patients who reported infusion AEs (0.4 (0-6.3) μg/mL vs 9.9 (0-19.5) μg/mL, \(P=.048\))
- Median trough levels were not significantly different between patients with and without arthralgias or neuropathy AEs (4.1 μg/mL vs. 7.3 μg/mL, \(P=.091\))

Take-home Messages

- High trough levels of infliximab correlated with dermatologic adverse reactions
- Low trough levels correlate with infusion reactions
Conclusion

- Current medical therapy for UC and CD is inadequate
- Novel Emerging Treatments are necessary
- Safe and Better use of current medical therapy is critical
- DDW has advanced our knowledge of the current and future medical therapeutic armamentarium.