Medical therapy of IBD: What’s new in 2015

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Abnormal Mucosal Immune Responses in IBD

Crohn's-like Ulcerative colitis-like
### Treating IBD

Blood vessel → Leukocyte → Diapedesis → Intestinal Cell → TNF-α → Gut Mucosa

### Biologic Agents for CD or UC

<table>
<thead>
<tr>
<th>Biologic Agent</th>
<th>Structure</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td><img src="image" alt="Infliximab" /></td>
<td>Chimeric monoclonal antibody (75% human IgG1 isotype)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td><img src="image" alt="Adalimumab" /></td>
<td>Human recombinant antibody (100% human IgG1 isotype)</td>
</tr>
<tr>
<td>Certolizumab Pegol</td>
<td><img src="image" alt="Certolizumab Pegol" /></td>
<td>Humanized Fab' fragment (95% human IgG1 isotype)</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td><img src="image" alt="Vedolizumab" /></td>
<td>Humanized IgG1</td>
</tr>
</tbody>
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**Maria T. Abreu, MD**

ACG/FGS Spring Symposium - Naples, FL
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Positioning New and Established Medications for IBD

**Induction of Remission/Active Disease**
- Cyclosporine
- Ustekinumab (CD)
- Tofacitinib (UC)
  - Vedolizumab (rapidity of response)
- Anti-TNFs
- Corticosteroids
- Budesonide
- 5-ASA

**Maintenance of Remission**
- Ustekinumab (CD)
- Vedolizumab
- Anti-TNFs
- Methotrexate (CD)
- 6-MP/Azathioprine

**When to start? Which to choose? And when do we need combination therapy?**

**Immunomodulators: Thiopurines MTX**
- Mechanistic synergy
- Higher levels of biologic
- MTX for young men

**Anti-TNFs Anti-adhesion molecules (immunogenic)**
- High inflammatory burden
- Moderate-to-severe disease
- Steroid-refractory disease
- Severe prognostic markers
When to start? Which to choose? And when do we need combination therapy?

**Immunomodulators:**
- Thiopurines
- MTX

**Anti-TNFs**
- Anti-adhesion molecules (immunogenic)

- Steroid-dependent disease (applies to both CD/UC)
- Low inflammatory burden
- Steroid-refractory disease
- Mild course/ prognostic markers
- Hi-risk for complications from combo therapy?

**SONIC**
Combination therapy with infliximab and azathioprine works better than either alone in Crohn’s disease

Clinical Remission Without Corticosteroids at Week 26

<table>
<thead>
<tr>
<th>Proportion of Patients (%)</th>
<th>p&lt;0.001</th>
<th>p=0.009</th>
<th>p=0.022</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA + placebo</td>
<td>30</td>
<td>45</td>
<td>57</td>
</tr>
<tr>
<td>IFX + placebo</td>
<td>52/170</td>
<td>75/169</td>
<td>96/169</td>
</tr>
</tbody>
</table>

**SONIC**

Combination therapy with infliximab and azathioprine works better than either alone in Crohn’s disease

**Mucosal Healing at Week 26**

<table>
<thead>
<tr>
<th>Proportion of Patients (%)</th>
<th>AZA + placebo</th>
<th>IFX + placebo</th>
<th>IFX + AZA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>16/109</td>
<td>30/93</td>
<td>44/107</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p=0.023</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p=0.055</td>
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</tbody>
</table>


**UC SUCCESS**

Combination therapy with infliximab and azathioprine works better than either alone in UC

**Patients (%)**

<table>
<thead>
<tr>
<th>Steroid-free remission</th>
<th>Response</th>
<th>Mucosal Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>22/24</td>
<td>55/37</td>
</tr>
<tr>
<td>*P &lt;0.05 compared to IFX; #P &lt;0.05 compared to AZA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SONIC: IFX Trough Levels at Week 30* are Higher with Concomitant AZA

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

Trough Concentration of Infliximab is Higher With Concurrent Methotrexate

Why Don’t Patients Respond to Anti-TNFs?

• Dose not high enough:
  – Dose of anti-TNF proportional to extent and severity of inflammation
  – Tissue versus serum levels of drug

• Different mechanism driving inflammation:
  – Could be different cytokines
  – Could be epithelial dysfunction
  – Microbial dysbiosis
Assessing loss of response

*If history compatible with early response then loss, I would still try higher dose of biologic in spite of “therapeutic” levels

Adalimumab Trough Levels Correlate With Mucosal Healing

Tissue levels of the anti-TNF may be insufficient for the amount of TNF in the tissue

Factors that affect anti-TNF concentrations

- **Increased (good)**
  - Concomitant immunomodulator

- **Decreased (bad)**
  - Hi CRP
  - Low albumin
  - Anti-drug Abs
  - Hi levels of TNF
  - Hi BMI (waist-to-hip ratio)
  - Male gender

ADA=adalimumab


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### Immunogenicity of Monoclonal Biologics in IBD

<table>
<thead>
<tr>
<th></th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episode Maintenance</td>
</tr>
<tr>
<td></td>
<td>IMS-</td>
</tr>
<tr>
<td>Infliximab¹</td>
<td>CD 5 mg/kg</td>
</tr>
<tr>
<td></td>
<td>CD 10 mg/kg</td>
</tr>
<tr>
<td>Infliximab²</td>
<td>UC 5 mg/kg</td>
</tr>
<tr>
<td></td>
<td>UC 10 mg/kg</td>
</tr>
<tr>
<td>Certolizumab³</td>
<td>(PRECISE I)</td>
</tr>
<tr>
<td>Certolizumab⁴</td>
<td>(PRECISE II)</td>
</tr>
<tr>
<td>Adalimumab⁵</td>
<td>(RA, all doses)</td>
</tr>
<tr>
<td>Adalimumab⁶ (CLASSIC II)</td>
<td>No data</td>
</tr>
<tr>
<td>Golimumab⁷ (PURSUIT)</td>
<td>No data</td>
</tr>
<tr>
<td>Vedolizumab⁸</td>
<td>No data</td>
</tr>
<tr>
<td>Ustekinumab⁹ (CERTIFI)</td>
<td>No data</td>
</tr>
</tbody>
</table>

* v/v=vedolizumab induction followed by vedolizumab maintenance; v/p=vedolizumab induction followed by placebo maintenance

IMS- immunosuppressant; IMS+ immunomodulator

Patients with Higher CRP Do Better with Higher Doses of Adalimumab: CHARM Study

- CRP ≥10 mg/L
- CRP <10 mg/L

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline CRP</th>
<th>Adalimumab Every Other Week</th>
<th>Adalimumab Weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=34)</td>
<td>37 mg/L</td>
<td>32 mg/L</td>
<td>29 mg/L</td>
</tr>
<tr>
<td>ADA 40mg every week</td>
<td>4.4 mg/L</td>
<td>2.5 mg/L</td>
<td></td>
</tr>
</tbody>
</table>

Remission

- Week 26
  - 29 patients
  - 79 patients
- Week 56
  - 41 patients
  - 64 patients

Optimizing levels of anti-TNF may help maintain long-term response

a. Baseline CRP: placebo 37 mg/L; adalimumab every other week 32 mg/L; adalimumab weekly 29 mg/L.

b. Baseline CRP: placebo 4.1 mg/L; adalimumab every other week 4.4 mg/L; adalimumab weekly 2.5 mg/L.

Dose intensification of infliximab in patients with loss of response led to mucosal healing

- Enrolled 52 IBD patients (34 CD and 18 UC) with secondary failure to IFX
- Dose escalation to 10 mg/kg in all patients
- IFX trough, ATI, CRP, and calprotectin measured before dose optimization and at Week 8
- Endpoint: Mucosal healing at Week 8

Active monitoring of anti-TNF levels may ensure durability of response

Prospectively optimized IFX trough concentrations to a target range of 5-10ug/ml

Monoclonal antibody-based therapies (like infliximab, vedolizumab)
- Trough levels, peak levels
- Functional assay:
  - % receptor occupancy
  - Downstream biologic effect

Small molecule inhibitors (like tofacitinib)
- Drug levels
- Functional assays—cytokine inhibition

Impact of Combination Therapy
- Synergy
- Reduced immunogenicity
- Reduced drug clearance
- Higher levels of the biologic
Therapeutic levels of thiopurines may not be necessary for beneficial effect on biologic concentrations

Association Between Clinical Response and 6-TGN in Pediatric Patients with IBD

Levels of 6-TGN correlate with trough infliximab levels

Yarur et al. Clinical Gastroenterology and Hepatology in press 2015

When anti-TNFs don’t work what’s next?

What is the unmet need
Unmet need: mucosal healing with anti-TNF +/- immunomodulator

Unmet need with anti-TNFs

- For both diseases
  - Patients with co-morbidities, e.g. MS, cancer
  - Older age
  - Previous malignancy (vedolizumab probably ok)
  - High attrition of anti-TNF effect (immunogenicity + mechanistic escape)
    - 10-20% per year not counting need to increase dose
Unmet need: what have we filled in so far (editorial comments)

- UC
  - Vedolizumab big advance
  - Jak inhibitors
- CD
  - Ustekinumab (modest)
  - Vedolizumab better than clinical trial data belies
  - Jak inhibitors need another chance

Genetic Associations in the IL-12/23 Pathways

IL-12 and IL-23 Cytokines and Receptors Are First Cousins

**IL-12**

**IL-23**


Intracellular Signaling (eg, STAT-P)

Anti-p40 Mechanism of Action

**IL-12**

**IL-23**


Ustekinumab
Briakinumab

No Signal
Ustekinumab for Crohn’s Disease: Blocks IL-12/IL-23


Normal Host: Leukocyte Surveillance
Immune Defect in IBD: Increased Leukocyte Migration and Activation

Diapedesis in IBD
Minimizing Diapedesis

**Key Adhesion Molecule Interactions**

- **α4-Integrins**: required for firm adhesion to and migration across endothelium
- **Natalizumab**
- **Vedolizumab**
- **Upregulated by cytokines**
- **PF-00547,659 (Anti-MAdCAM)**

MAdCAM-1 = mucosal addressin cell adhesion molecule-1; VCAM-1 = vascular cell adhesion molecule-1

**Vedolizumab: A Monoclonal Antibody For IBD**

- Humanized IgG1
- Targets only α4β7 integrin
- 30 min IV infusion
- No Fc-receptor binding or complement fixation (ADCC)

**GEMINI I: Vedolizumab in Ulcerative Colitis Induction Phase: Outcomes at Week 6**

<table>
<thead>
<tr>
<th>Induction ITT population</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO (n=146)</td>
<td>VDX (n=225)</td>
</tr>
<tr>
<td>Clinical Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.5</td>
<td>47.1</td>
<td>p &lt; 0.051</td>
</tr>
<tr>
<td>(95% CI: 16.6 - 31.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>11.5 (4.7, 18.3)</td>
<td>16.3</td>
</tr>
<tr>
<td>p &lt; 0.051</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucoanal Healing</td>
<td>16.1 (6.4, 26.9)</td>
<td>24.8</td>
</tr>
<tr>
<td>p &lt; 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PBO, placebo; VDX, vedolizumab; Mean ± SD (95% CI). *p* < 0.05 indicates significance. Vedolizumab is superior to placebo (95% confidence interval).

GEMINI I: Vedolizumab in Ulcerative Colitis Maintenance Phase: Outcomes at Week 52

Vedolizumab Response Based on Trough Levels: UC Week 6

GEMINI II: Vedolizumab in Crohn’s Disease

**Induction Phase: Outcomes at week 6**

**Primary endpoints**

- **Clinical Remission**
  - PBO (n=148): 6.8%
  - VDZ (n=200): 14.5%

- **CDAI-100 Response**
  - PBO (n=148): 25.7%
  - VDZ (n=200): 31.4%

Mean ±2% (95% CI) VDZ vs PBO
- Clinical Remission: 7.8 (12.143)
- CDAI-100 Response: 5.7 (-36.15.0)

**Maintenance Phase: Outcomes at week 52**

**Maintenance ITT Population**

- **Clinical Remission**
  - PBO: 21.6%
  - VDZ Q8 wks: 39%
  - VDZ Q4 Wks: 36.4%

- **CDAI-100 Response**
  - PBO: 30.1%
  - VDZ Q8 wks: 43.5%
  - VDZ Q4 Wks: 45.4%

*p<0.05  **p<0.01

Vedolizumab works in CD patients that have been on anti-TNF previously

Clinical remission at week 10

PF-00547,659 (anti-MAdCAM IgG2 antibody) in active ulcerative colitis

Finding the Right Mechanism for the Right Patient