New Medications In IBD: What’s Coming?

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DISCLOSURES

BG Levesque has received consulting fees from Santarus Inc, Prometheus Labs, Abbvie, Takeda, and Nestle Health Sciences
What is our target if we want to prevent disease progression?

SYMPTOMS
What is our target if we want to prevent disease progression?

Mucosal Healing Relevance?

- Normal
- Mild
- Moderate
- Severe
Efficacy
Endoscopic healing – ACCENT I

Week 0
Baseline

Week 10
Following induction regimen (IFX 5 mg/kg) at weeks 0, 2, and 6

Week 54
Following infusions (IFX 5 mg/kg) every 8 weeks after induction regimen

Efficacy
IN04616

Surgery Rates at 10 years by Mucosal Healing Status One Year After Diagnosis

Ulcerative colitis

Crohn’s disease

HR 0.34 (0.14-0.86) p<0.02

HR 0.42 (0.20-0.89) p=0.027

PREDEFINED TIMEFRAME

BASELINE ASSESSMENT

HIGH RISK OF PROGRESSION

TARGET THERAPY ACCORDING TO RISK AND TARGET

CONTINUE THERAPY TARGET SURVEILLANCE

LOW RISK OF PROGRESSION

AVOIDANCE OF LONG-TERM BOWEL DAMAGE AND SUBSEQUENT DISABILITY

TARG ET


OPTIMIZE

Limited shoulder motion during all phases of swing
Limited cervical rotation during backswing
Limited torso rotation or slow rotation during backswing
Limited hip motion during all phases of the swing
Lateral torso flexion to right during backswing
Lower extremity motion from foot to hip.
Time to Initiation of Treatments

**A** Corticosteroids
- HR = 0.97 (0.77, 1.21)
- P = 0.78
- ECI 21.0%
- CM 21.2%

**B** Antimetabolites
- HR = 1.84 (1.39, 2.44)
- P < 0.001
- ECI 26.7%
- CM 15.6%

**C** TNF-Antagonists
- HR = 1.72 (1.34, 2.22)
- P < 0.001
- ECI 27.4%
- CM 17.4%

**D** Combination Therapy with Antimetabolites and TNF-Antagonists
- HR = 2.29 (1.73, 3.04)
- P < 0.001
- ECI 19.7%
- CM 9.6%

Outcomes at 24 Months

**A** Surgery
- HR = 0.69 (0.50, 0.97)
- P = 0.03
- CM 9.5%
- ECI 6.6%

**B** Serious Complication
- HR = 0.73 (0.61, 0.87)
- P < 0.001
- CM 30.9%
- ECI 24.3%

**C** Hospitalization
- HR = 0.84 (0.65, 1.08)
- P = 0.16
- CM 15.6%
- ECI 12.9%

**D** Hospitalization, Surgery or Serious Disease-Related Complication
- HR = 0.73 (0.62, 0.86)
- P < 0.001
- CM 34.7%
- ECI 27.4%
### Serious Disease and Drug-Related Complications and Mortality

<table>
<thead>
<tr>
<th></th>
<th>Early Combined Imunosuppression N (%)</th>
<th>Conventional Management N (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Worsening Crohn’s disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>32 (3.0)</td>
<td>33 (3.7)</td>
<td>0.36</td>
</tr>
<tr>
<td>Fistula</td>
<td>29 (2.7)</td>
<td>39 (4.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stricture/bowel obstruction</td>
<td>67 (6.2)</td>
<td>82 (9.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Serious worsening disease</td>
<td>98 (9.0)</td>
<td>96 (10.7)</td>
<td>0.65</td>
</tr>
<tr>
<td>Serious extra-intestinal</td>
<td>47 (4.3)</td>
<td>50 (5.6)</td>
<td>0.37</td>
</tr>
<tr>
<td>manifestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious drug-related complications</td>
<td>10 (0.9)</td>
<td>10 (1.1)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2 (0.2)</td>
<td>5 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>3 (0.3)</td>
<td>2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Total Mortality</strong></td>
<td>7 (0.7)</td>
<td>10 (1.1)</td>
<td>0.33p</td>
</tr>
</tbody>
</table>

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### Optimizing TNF Antagonist Therapy

**Emerging Concepts**

- Objective evidence of the presence of inflammation should drive clinical decision making not the presence of symptoms in isolation
- Combining antimetabolite therapy and a TNF antagonist results in optimal efficacy and protects the latter against sensitization
- The pharmacokinetics of TNF antagonists are complex and therapy should be optimized for individual patients
- Therapeutic drug monitoring is a useful guide for clinical decision making
The ACT Studies: Proportions of Patients with Clinical Remission by Serum IFX Concentration Quartiles

Reinisch W. et al DDW 2012

Colectomy Rate According to the Presence and Absence of a Detectable Trough Serum Infliximab Concentration

Seow CH. et al. Gut 2010;59:49-54
**UC SUCCESS: Mucosal Healing Week 16**

\[
\begin{array}{ccc}
\text{AZA (N=76)} & \text{IFX (N=77)} & \text{IFX/AZA (N=78)} \\
37 & 55^* & 63^* \\
n=38 & n=53 & n=60 \\
\end{array}
\]

*\text{p}<0.05 vs. AZA alone

* Mayo endoscopy sub-score 0 or 1

Panaccione et al. ECCO 2011. Abstract OP13

**ULTRA 1: Clinical Remission at Week 8**

\[
\begin{array}{ccc}
\text{Placebo} & \text{ADA 80/40 mg} & \text{ADA 160/80 mg} \\
9.2\% & 10.0\% & 18.5\% \\
N=130 & N=130 & N=390 \\
\end{array}
\]

* \text{p}=0.031, ADA 160/80 vs placebo

ITT: A3 analysis set (NRI)
Clinical remission: Mayo score \leq 2 with no individual subscore >1

Cyclosporine vs Infliximab in UC


ULTRA 2: Remission- Weeks 8 and 52

PURSUIT-SC Induction: Clinical Response† at Week 6

Randomized Patients in Phase 3 After the Dose Selection

**Proportion of patients (%)**

- Placebo (n=256)
  - 28.7%
- 200 mg → 100 mg (n=257)
  - 51.8%
- 400 mg → 200 mg (n=258)
  - 55.0%

* p<0.0001 vs. placebo

Sandborn WJ et al. DDW 2012

PURSUIT-SC Induction: Secondary Endpoints at Week 6

Randomized Patients in Phase 3 After the Dose Selection

**Proportion of patients (%)**

- Clinical Remission†
  - Placebo (n=256)
    - 6.3%
  - 200 mg → 100 mg (n=257)
    - 16.7%
  - 400 mg → 200 mg (n=258)
    - 17.8%
- Mucosal Healing‡
  - Normal/Inactive Mucosal Disease
    - Placebo (n=256)
      - 26.5%
    - 200 mg → 100 mg (n=257)
      - 43.2%
    - 400 mg → 200 mg (n=258)
      - 45.3%

* p=0.0001 vs. placebo
** p<0.001 vs. placebo
* p=0.043 vs. placebo
** p=0.001 vs. placebo

†‡ Sandborn WJ et al. DDW 2012
Recruitment of Neutrophils Into Inflamed Tissue

Van Deventer. Gut. 2002

Endothelial and Leukocyte Adhesion: $\alpha_4$ Integrins

- Leukocyte membrane glycoproteins
- $\beta_1$ and $\beta_7$ subunits
- Interact with endothelial ligands VCAM-1, fibronectin, and MAdCAM-1
- Mediate leukocyte adhesion and trafficking

Clinical Efficacy: 3 Point Improvement in UCSS Score

Overall p=.001
p=.001
p=.010


Vedolizumab & Mucosal Healing Through 52 Weeks, ITT Population

Primary and Secondary Outcomes Through 52 Weeks

Maintenance ITT Population

- Placebo
- VDZ Q8 wks
- VDZ Q4 wks

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Week 6</th>
<th>Week 10</th>
<th>Week 6</th>
<th>Week 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Remission</td>
<td>41.8%</td>
<td>44.8%</td>
<td>23.0%</td>
<td>26.3%</td>
</tr>
<tr>
<td>Durable Clinical Response</td>
<td>52.0%</td>
<td>56.8%</td>
<td>19.0%</td>
<td>20.6%</td>
</tr>
<tr>
<td>Mucosal Healing</td>
<td>61.0%</td>
<td>64.0%</td>
<td>8.7%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Durable Clinical Remission</td>
<td>11.8%</td>
<td>15.3%</td>
<td>17.6%</td>
<td>28.5%</td>
</tr>
<tr>
<td>CS-Free Remissions</td>
<td>46.2%</td>
<td>72.0%</td>
<td>73.3%</td>
<td>72.0%</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, ***P<0.0001

Vedolizumab Phase 3 Induction Trial in CD CDAI-100 Response

CDAI-100 Response

- ITT Population
  - Anti-TNFα Failure Population (n=315)
  - Overall Population (n=416)

<table>
<thead>
<tr>
<th>Week 6</th>
<th>Week 10</th>
<th>Week 6</th>
<th>Week 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>VDZ</td>
<td>PBO</td>
<td>VDZ</td>
</tr>
<tr>
<td>22.3%</td>
<td>39.2%</td>
<td>24.8%</td>
<td>48.6%</td>
</tr>
<tr>
<td>22.7%</td>
<td>39.2%</td>
<td>24.2%</td>
<td>47.8%</td>
</tr>
</tbody>
</table>

*P<0.0011 vs placebo; †P<0.0001 vs placebo; ‡P<0.0002 vs placebo

Sandborn, NEJM 2014
Budesonide MMX for Active Ulcerative Colitis Clinical and Endoscopic Remission at Week 8

Remission (%)

Placebo
MBEX 9 mg
Mesalamine CR 2.4 g
Budesonide CR 8 mg

*Statistically significant (P<0.025)
+Statistically significant (P<0.05)


Cytokine Signaling of Janus Kinase (JAK)

Tofacitinib (CP-690,550) is a novel, small-molecule, oral JAK inhibitor that is being investigated as a targeted immunomodulator for several inflammatory diseases including ulcerative colitis (UC) and Crohn’s disease.1,2

Tofacitinib inhibits JAK1, JAK2, and JAK3 in vitro with functional cellular specificity for JAK1 and JAK3 over JAK2.3 Importantly, tofacitinib directly or indirectly modulates signaling for an important subset of pro-inflammatory cytokines including IL-2, -4, -7, -9, -15, and -21.4

Cytokine Effects on the immune system

- IL-2: Stimulate the proliferation and differentiation of Th, Tc, and natural killer (NK) cells
- IL-4: Induce the differentiation of Th0 to Th2
- IL-7: Induce immunoglobulin switching
- IL-9: Promote the development, proliferation and survival of T, B, and NK cells
- IL-15: Promote the proliferation, cytotoxicity and cytokine production of NK cells
- IL-21: Enhance T and B cell function

1. ADIS. Drugs 2010; 10(4): 271-274;
3. Li X et al. Presented at the 15th IIRA Conference, Chantilly, Virginia, September 21-24, 2008;

Courtesy of Dr. William Sandborn
Rates of Primary and Major Secondary Endpoints at 8 Weeks in the Modified Intention-to-Treat Population According to Study Group

Ustekinumab (Anti-Interleukin 12/23 p40) for Active Crohn’s Disease: Clinical Response at Week 6

Number of Subjects in Clinical Remission at Week 22; Subjects Randomized as Responders to UST Induction
Ustekinumab (Anti-Interleukin 12/23 p40) for Active Crohn’s Disease: Clinical Remission at Week 22

Number of Subjects in Clinical Remission\textsuperscript{a,b} at Week 22; Subjects Randomized as Responders to UST Induction

![Graph showing clinical remission at Week 22](image)

Sandborn W. Gastroenterology 2011 Abstract

Etrolizumab vs Placebo – Eucalyptus Phase II Randomized Induction Study in Active UC – Clinical Remission at Wk 10

- Humanized monoclonal antibody to the B7 subunit of the heterodimeric integrins $\alpha_4\beta_7$ and $\alpha E\beta 7$ in patients with mod-sev active UC
- N=124
- Randomized to 2 dose groups vs placebo

![Graph showing clinical remission at Wk 10](image)

Sphingosine 1-Phosphate Receptor 1 Modulation: Mechanism of Action

- S1P1R agonism induces receptor internalization, lymphocytes lose response to S1P gradient
- Become trapped in lymph nodes causing peripheral lymphopenia
- Upon drug withdrawal receptor expression is restored and lymphocytes leave nodes reversing lymphopenia

Anti Smad 7 GED-0301

Marafini, Monteleone, JCCI 2014
On the Horizon?

• Bacterial Release Oral Anti-TNF Therapy?
• Cow’s Milk Clostrum Oral Anti-TNF therapy?
• Phosphatidyl Choline (oral Therapy) for UC?
• Andrographis Paniculata (oral therapy) For UC?
• Nutritional Therapies?

Conclusions