What’s in the Pipeline?
New Drugs and Treatments for IBD

William J. Sandborn, M.D.
Chief, Division of Gastroenterology
Director, UCSD IBD Center
University of California San Diego,
La Jolla, California
Therapies for IBD: the Pipeline

- Anti-TNF antibodies
  - Adalimumab (Humira) for UC
  - Golimumab (Simponi) for UC
- Anti-Selective Adhesion Molecule
  - Anti-integrin antibodies
    - Vedolizumab (anti-α4β7, MLN-002)
    - Anti-β7
    - Anti-MAdCAM-1
- Chemokine antagonists
  - Antagonist to chemokine receptor 9
    - CCX282-B
  - Anti-IP 10 antibody
- HMPL-004 (*Andrographis paniculata* extract)
- Anti-Interleukin 12/23
  - ABT 874 (J695)
  - Ustekinumab (CNTO 1275, Stelera)
- Anti-Interleukin-17 (AIN457)
- Antagonist to Janus kinase 3 (JAK3)
  - CP-690,550
- Anti-interleukin 6
Adalimumab ulcerative colitis development programme

Phase 3 studies in moderate to severe UC:

M06-826: Randomised, controlled double-blind, 8-week induction study, with open-label maintenance phase through Week 52

M06-827: Randomised, controlled double-blind study – induction and maintenance through Week 52

M10-223: Open-label, long term, extension study

All patients had failed or were intolerant to steroids and/or immunosuppressant therapy
Adalimumab induction and open-label maintenance: clinical remission at week 8 and 52 in ulcerative colitis

Week 8

- Placebo: 9.2% (12/130)
- ADA 80/40: 10.0% (13/130)
- ADA 160/80: 18.5% (24/130)

Week 52

- All randomised:
  - Clinical remission: 29.5% (115/390)

Adalimumab induction and maintenance of clinical remission at week 8 and 52 in ulcerative colitis

ITT analysis set: non-responder imputation (NRI) i.e missing data or switch to OL imputed as not achieving remission
Clinical remission: Mayo score ≤2 with no individual subscore >1

Adalimumab induction and maintenance of clinical response at week 8 and 52 in ulcerative colitis

ITT analysis set: NRI
Response: decrease in Mayo Score ≥ 3 points and decrease ≥ 30% and RBS of 0 or 1 or decrease of RBS ≥ 1

Gastroenterology 2011 Abstract
Endothelial And Leukocyte Adhesion: 
A4 Integrins

- Leukocyte membrane glycoproteins
- β1 and β7 subunits
- Interact with endothelial ligands VCAM-1 and MAdCAM-1, and mediate leukocyte adhesion and trafficking
- Interact with extracellular ligands fibronectin, osteopontin, and thrombospondin

Anti-Beta 7 Mechanism of Action: Adhesion Molecule Inhibition as an IBD Therapy

Leukocyte Infiltration and Gut Inflammation

Reduced Leukocyte Infiltration and Gut Inflammation

Blocked
ENACT-2 Natalizumab in Active Crohn’s Disease (Naïve + Experienced): Maintenance of Clinical Remission with Steroid Withdrawal over 15 Months in Week 12 Responders Receiving Steroids at Baseline

Start ENACT-2

P=0.014  P=0.009  P≤0.003

Natalizumab 300 mg (n=67)
Placebo (n=76)

Sandborn NEJM 2005
Progressive multifocal leukoencephalopathy (PML)

- Rare, progressive infection of the CNS
  Often fatal within 6 months of diagnosis

- Lytic infection of oligodendrocytes by JC virus, a human polyomavirus

- Reported with
  - Natalizumab
  - Rituximab (antiCD20)
  - Efalizumab (antiCD11a)
Anti integrins have shown clinical activity in IBD

anti Beta7 shares some of the same MoA and more

Natalizumab
anti α4

Approved for treatment of MS and CD

MLN0002
anti α4β7

Phase II clinical activity in UC

rhuMAb Beta7
anti β7

In Phase I in UC

Anti MAdCAM

Confirmed cases of PML

Gut-specific

Mucosal Epithelium
Intra-epithelial lymphocytes
(Gut, skin, lung)

Broad expression:
CNS
Peripheral B and T cells

VCAM

α4 β1

E-cadherin

αE β7
Vedolizumab (MLN-0002) For Active Ulcerative Colitis Remission at Week 6

- 181 patients with active ulcerative colitis [ulcerative colitis clinical score (UCSS) $\geq 5$ and modified Baron score (MBS) $\geq 2$] receiving a stable dose of 5-ASA or no medical therapy
- Randomized to receive IV doses of placebo, 0.5 mg/kg, or 2.0 mg/kg vedolizumab on days 1 and 29
- The primary endpoint was % clinical remission (UCSS score 0 or 1, MBS 0 or 1, and no blood) at day 43

Immunogenicity Reduces Clinical Efficacy

Percent of Patients in Clinical Remission on Day 43 by Treatment & HAHA Status

<table>
<thead>
<tr>
<th>HAHA Status</th>
<th>Placebo</th>
<th>MLN0002</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAHA Negative</td>
<td>15%</td>
<td>42%</td>
</tr>
<tr>
<td>HAHA Positive Low Titer (&lt;= 125)</td>
<td></td>
<td>41%</td>
</tr>
<tr>
<td>HAHA Positive High Titer (&gt; 125)</td>
<td></td>
<td>12%</td>
</tr>
</tbody>
</table>
Vedolizumab (MLN-0002) For Active Ulcerative Colitis Remission at Week 6

- Secondary endpoint was % endoscopic remission (MBS 0) at day 43
- Secondary endpoint was % of patients with decrease ≥ 3 UCSS points from baseline
- Serious adverse events 8% for MLM-02 and 5% for placebo, one patient with angioedema after MLN-02

Vedolizumab (MLN-0002) For Active Crohn’s Disease Response and Remission at Week 8

- 185 patients with active Crohn’s disease receiving a stable dose of 5-ASA or antibiotics or no medical therapy
- Randomized to receive IV doses of placebo, 0.5 mg/kg, or 2.0 mg/kg MLN-02 on days 1 and 29
- The primary endpoint was % clinical response (decrease in CDAI of ≥70 points) at day 57
- Secondary endpoint was % remission (CDAI < 150) at day 57
- Saturation of α4β7 on peripheral blood lymphocytes was not consistently achieved

Feagan Clinical Gastroenterology & Hepatology 2008
Vedolizumab (MLN-0002) For Active Crohn’s Disease Response and Remission at Week 8

MLN0002 induced a significantly greater clinical remission rate in patients with Crohn’s disease compared to placebo (2 mg/kg group) at days 15, 29, and 57.

Feagan Clinical Gastroenterology & Hepatology 2008
Anti-MAdCAM 1 Antibody (PF-00547,659) for active ulcerative colitis

- 80 patients with active UC [Mayo score ≥ 6 and endoscopic subscore ≥ 2] receiving a stable dose of 5-ASA, steroids or Aza

- Randomized to receive placebo (n=20) or IV or sc increasing doses of PF-00547,659 given as simple dose (n=30) or multiple doses (n=50)

- The primary endpoint was safety and tolerability

Vermeire S et al. Gut 2011
Anti-MAdCAM 1 Antibody (PF-00547,659) for active ulcerative colitis

Vermeire S et al. Gut 2011
Selective anti-adhesion molecules

Rutgeerts P et al. Gastroenterology 2009
CCX282-B (Traficet-EN™) for active Crohn’s disease

- 436 patients with active Crohn’s disease

- Randomized to receive oral doses of placebo (bid), 250mg/d, 500mg/d or 250mg bid CCX282-B

- The primary endpoint was
  - Induction period: response 70 at wk8
  - Maintenance period: CDAI 70 pts response at wk8 and maintenance at 1yr

Keshav S et al. DDW 2009
CCX282-B (Traficet-EN™) for maintaining remission in Crohn’s disease: Protect-2

Remission (CDAI ≤ 150)

CCX282-B well tolerated and safe, and maintained remission in CD over 36 weeks

Keshav S. DDW 2010
**Interferon Gamma Inducible Protein 10 (IP-10 or CXCL-10)**

- Belongs to CXC family of chemokine ligands
- Induced by IFN-γ and produced by various cell types including hematopoietic & stromal cells
- Mechanism of action
  - CXCR3-*mediated* recruitment of T cells to inflamed tissues
  - CXCR3-*independent* (or dependent) modulation of functions of other cells including epithelial, endothelial and islet β cells

---

**IP-10**

- **CXCR3**
- **Unidentified receptor**
- **Heparan sulfate**
- **TLR4 (?)**

**T cell** → ↑ Trafficking

**Epithelial** → ↓ Proliferation & Migration

**Endothelial** → ↓ Proliferation

**Islet β cell** → ↑ Apoptosis

Clinical Response, Remission and Mucosal Healing Rates
Pre-Specified (SAP)

Response and Remission Rates
By Day 57 Trough Concentration Tertiles

Placebo (n = 54)
Low tertile (n = 17): 26.4 - 78.6 ug/ml
Mid tertile (n = 16): 79.2 - 105 ug/ml
Top tertile (n = 16): 108 - 235 ug/ml

Proportion of Responders

Note: This result is from a post-hoc analysis with re-derived Mayo score after unblinding the data.
Mayo Score was re-derived by following conventional rules in the literature.

HMPL-004
Andrographis paniculata extract

- Herbal mixture is anti-inflammatory; inhibits TNF-\(\alpha\), IL-1\(\beta\) and NF-\(\kappa\)B
- Effective in chemically induced colitis in rats
- The marker compound composes only 1-2\% of the mixture
- No single component is as effective as the mixture; components probably synergistic

Marker Compound, one of a series of closely related diterpene lactones
HMPL-004 in Active Ulcerative Colitis
Response, Remission, Mucosal Healing at Week 8

Sandborn WJ. Gastroenterology 2010 (Abstract)
Biology of Interleukins 12 and 23

Stimulus: TLR?

Antigen Presenting Cell

IL-12

Anti-IL-12/23

p35

p40

IFNγ (Th1)

CD4+

β2

Ag

Ag

MHCII

TCR

IL-12Rβ1

IL-23R

IL-12Rβ1

IL-17 (Th17)

Biology of Interleukins 12 and 23

Ant-IL-12/23

• CNTO 1275 (ustekinumab) and ABT 874 (briakinumab) are fully human IgG1 monoclonal antibodies
• Bind the p40 subunit of human IL-12/23
• Prevent IL-12 and IL-23 from binding IL-12Rβ1
• Normalize IL-12 and IL-23 mediated signaling, cellular activation, and cytokine production
• In development in Crohn’s disease and psoriasis

IL-17

p19

p40

p19

p40

IL-23R

IL-23

Anti-IL-12/23

p40

p35

p40

p35

IL-12Rβ1

β2
Ustekinumab (CNTO 1275) for Active Crohn’s Disease: Clinical Response Through Week 8

Response: ↓CDAI scores of ≥25% & ≥70 points

<table>
<thead>
<tr>
<th></th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC and IV placebo (N=53)</td>
<td>32</td>
<td>41</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>SC and IV Ustekinumab 1275</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>40</td>
</tr>
</tbody>
</table>

Primary Endpoint

Proportion of patients (%)
Ustekinumab (CNTO 1275) for Active Crohn’s Disease: Subgroup Analysis in Patients with Prior Infliximab Experience

Clinical Response Through Week 8

Response: ↓CDAI scores of $\geq 25\%$ & $\geq 70$ points

Sandborn
Gastroenterology 2008
Ustekinumab (CNTO 1275) for Active Crohn’s Disease: Clinical Response at Week 6

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

<table>
<thead>
<tr>
<th></th>
<th>Proportion of Subjects (%)</th>
<th>Placebo</th>
<th>1mg/kg</th>
<th>3mg/kg</th>
<th>6mg/kg</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>23.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1mg/kg</td>
<td>36.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3mg/kg</td>
<td>34.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6mg/kg</td>
<td>39.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>36.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N=132, N=131, N=132, N=131, N=394

\textsuperscript{p=0.021, p=0.057, p=0.005, p=0.005}

Sandborn W. Gastroenterology 2011 Abstract
Ustekinumab (CNTO 1275) 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

- **Placebo**
  - 20/73 (27.4%)
  - p=0.029

- **SC Ustekinumab**
  - 30/72 (41.7%)

\textsuperscript{a}Subjects who discontinued study agent due to lack of efficacy, had a prohibited CD-related surgery, or had prohibited concomitant medication changes after Week 8 are considered not to be in clinical remission, regardless of their CDAI score.

\textsuperscript{b}Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical remission.

Sandborn W. Gastroenterology 2011 Abstract
Tofacitinib (CP-690,550), an Oral Janus Kinase (JK) Inhibitor

- Tofacitinib (CP-690,550) is a novel, small-molecule, oral JAK inhibitor
- Tofacitinib inhibits JAK1, JAK2, and JAK3 in vitro with functional cellular specificity for JAK1 and JAK3 over JAK2. Importantly, tofacitinib directly or indirectly modulates signaling for an important subset of pro-inflammatory cytokines including IL-2, -4, -7, -9, -15, and -21

Sandborn W et al. DDW 2011
Phase 2 Study of Tofacitinib (CP-690,550), an Oral Janus Kinase Inhibitor, in Active Ulcerative Colitis

Primary Efficacy Endpoint: Model-fitted Clinical Response Rate at Week 8

- Difference from placebo (90% CI) in estimated clinical response rate:
  - Tofacitinib 10 mg BID treatment group: 26.9% (17.0, 36.8)
  - Tofacitinib 15 mg BID treatment group: 38.2% (25.3, 51.2)

Sandborn W et al. DDW 2011
Tocilizumab (Humanized Monoclonal Antibody Interleukin-6 Receptor – Previously Atlizumab or MRA) For Active Crohn’s Disease

- 36 patients with active Crohn’s disease (CDAI > 150, ↑ CRP)
- Randomized to receive IV placebo, tocilizumab (previously atlizumab, MRA) 8 mg/kg every 2 weeks, or atlizumab 8 mg/kg every 4 weeks for 12 weeks
- The endpoints were % response (decrease in CDAI ≥ 70) and remission (CDAI ≤ 150) at week 12
- Frequency of adverse events similar in all groups

Ito Gastroenterology 2004