New Therapeutic Agents in IBD

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Therapies for IBD: the Pipeline

- Budesonide
  - Oral MMX budesonide
  - Rectal budesonide foam
- Anti-TNF antibodies
  - Adalimumab (Humira) for UC
  - Golimumab (Simponi) for UC
- Anti-Selective Adhesion Molecule
  - Anti-integrin antibodies
    - Vedolizumab (anti-α4β7)
    - Etrolizumab (anti-β7)
    - Anti-MAdCAM-1
- Chemokine antagonists
  - Antagonist to chemokine receptor 9
    - Vircirmon (CCX282-B)
    - Anti-IP 10 antibody
- HMPL-004 (Andrographis paniculata extract)
- Anti-Interleukin 12/23
  - Briakinumab (ABT 874, J695)
  - Ustekinumab (CNTO 1275, Stelara)
- Anti-Interleukin-17
  - Secukinumab
- Antagonist to Janus kinase 3 (JAK3)
  - Tofacitinib
- Anti-Interleukin 6
- Trichuris suis
- S1P1 Receptor modulator (RPC1063)
Oral Forms of Budesonide

Controlled ileal-release (CIR): Entocort EC
- Enteric-coated granules that release at pH >5.5
- Majority absorbed in ileum and cecum (69%, 95% CI: 50–84%)
- Indication: Treatment of acute mild-to-moderate CD, involving ileum and / or ascending colon, maintenance of clinical remission for up to 3 months

pH-modified release: Budenofalk
- Dissolves at pH >6.4
- Maximal release in distal small intestine
- Not approved in US

Extended release tablets (MMX): Uceris
- Releases budesonide throughout colon
- Enteric coat dissolves at pH 7
- Proposed indication: Induction of remission of active mild-to-moderate UC in adults


Budesonide MMX Comparative Pharmacokinetics
- Bioavailability profile of budesonide MMX (6 and 9 mg tablets) compared to a controlled ileal-release formulation, budesonide CIR (Entocort EC) 9 mg (3 x 3 mg) capsules in healthy volunteers. Single oral dose.

Concentration (pg/mL)

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Budesonide CIR 3 mg x 3 caps</th>
<th>Budesonide MMX 9 mg</th>
<th>Budesonide MMX 6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2000</td>
<td>1500</td>
<td>1000</td>
</tr>
<tr>
<td>2</td>
<td>1500</td>
<td>1000</td>
<td>500</td>
</tr>
<tr>
<td>4</td>
<td>1000</td>
<td>500</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>500</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Budesonide MMX not bioequivalent to Budesonide CIR

Budesonide MMX for Active Ulcerative Colitis
Clinical and Endoscopic Remission at Week 8

Remission (%)

US Trial

EU Trial

Placebo
MMX 9 mg
Mesalamine DR 2.4 g
Budesonide CIR 9 mg

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

Golimumab

- Subcutaneous fully human anti-tumor necrosis factor IgG1 monoclonal antibody
- FDA approved for ulcerative colitis, rheumatoid arthritis (in combination with methotrexate), psoriatic arthritis (alone or in combination with methotrexate), ankylosing spondylitis (alone or in combination with methotrexate)
- Comes as 50 mg and 100 mg autoinjector or syringe
- Approved dose for ulcerative colitis is 200 mg at week 0 and 100 mg at week 2 for induction and 100 mg every 4 weeks for maintenance
Golimumab for Induction in Moderate to Severe Ulcerative Colitis: Clinical Response† at Week 6

†Defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1

Proportion of patients (%)

Placebo (n=256) 200 mg → 100 mg (n=257) 400 mg → 200 mg (n=258)

* p<0.0001 vs. placebo


Golimumab for Induction in Moderate to Severe Ulcerative Colitis: Secondary Endpoints at Week 6

Major Secondary endpoint defined as Mayo score ≤ 2 points, with no individual subscore >1

Major secondary endpoint defined as Mayo endoscopy subscore of 0 or 1

Normal/Inactive Mucosal Disease

p<0.0001

p<0.0005

p<0.0001

p=0.043 vs. placebo

p<0.001 vs. placebo

Clinical Golimumab for Maintenance in Moderate to Severe Ulcerative Colitis: Remission and Mucosal Healing at Both Week 30 and 54

† Defined as Mayo score ≤ 2 points, with no individual subscore >1
‡ Defined as Mayo endoscopy subscore of 0 or 1

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=156)</th>
<th>50 mg GLM (n=153)</th>
<th>100 mg GLM (n=154)</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical Remission</strong></td>
<td>15.4</td>
<td>23.5</td>
<td>28.6</td>
</tr>
<tr>
<td><strong>Mucosal Healing</strong></td>
<td></td>
<td>26.9</td>
<td>41.8</td>
</tr>
</tbody>
</table>

*p = 0.003

*p = 0.011

Therapeutic Targets for Lymphocyte Trafficking

Leucocyte Adhesion
NATALIZUMAB

VOLUTIONAB

ETROLIZUMAB

ACTIVATED INTESTINAL MICROVASCULAR ENDOTHELIAL CELLS

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

Vedolizumab (Anti-Alpha 4 Beta 7 Integrin) For Moderately-to-Severely Active Ulcerative Colitis: Results at Week 6 in 374 Patients

- Clinical response: 25.5% vs. 47.1%, P<0.001
- Clinical remission: 5.4% vs. 16.9%, P=0.0009
- Mucosal healing: 24.8% vs. 48.9%, P=0.0012

Vedolizumab (Anti-α4β7 Integrin) For Maintenance of Response in Moderately-to-Severely Active Ulcerative Colitis: Results at Week 52 in 373 Patients


Vedolizumab (Anti-α4β7 Integrin) For Moderately-to-Severely Active Crohn's Disease: Results at Week 6 in 368 Patients

P = 0.02
P = 0.23

Δ 7.8
95% CI: 1.2, 14.3

Δ 5.7
-3.6, 15.0

Induction ITT Population
Vedolizumab (Anti-α4β7 Integrin) For Maintenance of Response in Moderately-to-Severely Active Crohn’s Disease: Results at Week 52 in 461 Patients

**Patients, %**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>VDZ Q8wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ17.4</td>
<td>21.6</td>
<td>39.0 **</td>
</tr>
<tr>
<td>Δ15.9</td>
<td>15.9</td>
<td>28.8</td>
</tr>
<tr>
<td>Δ12.9</td>
<td>14.4</td>
<td>21.4</td>
</tr>
</tbody>
</table>

*Δ* = 17.4 **P**<0.05  **Δ** = 17.4 **P**<0.01  
†CS tapering began in responders at 6 weeks; for others, as soon as a clinical response was achieved.

**Other Drugs in this Class**

- Anti-MAdCAM1 (PF-00547,659)
- Etrolizumab (anti-β7, rhumab beta 7) (Genentech)
- Anti-β7 (AMG181, Amgen)
- Verciron (oral CCR9 antagonist, GSK1605786)
- Oral S1P1 receptor modulator (RPC1063)
**Anti-MAdCAM1 Antibody for Active UC**

- Placebo controlled dose escalation RCT
- 3 doses against placebo
- Pooled analysis
- Total n=80

- Humanized monoclonal antibody to the B7 subunit of the heterodimeric integrins α4β7 and αEβ7 in patients with mod-sev active UC
- N=124
- Randomized to 2 dose groups vs placebo

Vermeire S. et al. Gut 2011;60:1068-1075

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**Etrolizumab for Moderate to Severe Ulcerative Colitis: Clinical Remission at Week 10**

- 100 mg
- 300 mg + LD
- Placebo

- P=0.004
- P=0.049

Vermeire S. et al. Gastroenterology 2013 Late Breaking Abstract
Virciron (GSK1605786: An Oral CCR9 Antagonist)

- Potent and selective CCR9 receptor antagonist
- Orally administration
- No significant toxicity has been observed in pre-clinical studies
- Safety profile in Crohn’s patients is similar to placebo in > 500 subjects who have received GSK1605786 in clinical trials
- Gut-specific targeted therapy may avoid safety limitations of generalized immunosuppressants

Gut-homing activated T cells

Verciron (Oral CCR9 Antagonist for Moderate to Severe Crohn’s Disease: CDAI 100 Response at Week 12)

Keshav S et al, PLOS 2013

![Graph showing CDAI 100 response at Week 12 for different treatment groups.]

- Placebo (N=144)
- 250 mg QD (N=98)
- 250 mg BID (N=96)
- 500 mg QD (N=97)

P = 0.029
Vercirnon (Oral CCR9 Antagonist for Moderate to Severe Crohn’s Disease: Maintenance of Remission Over 36 Weeks)

Placebo (N=95)
GSK1605786 250mg BID (N=145)

Primary endpoint: Maintenance of response not achieved

Keshav S et al, PLOS 2013

Vercirnon (Oral CCR9 Antagonist for Moderate to Severe Crohn’s Disease: CDAI 100 Response at Week 12)

% of Subjects (95% CI)
p-value vs. placebo: 0.546 0.648

Placebo (n=203) Vercirnon 500mg OD (n=203) Vercirnon 500mg BID (n=202)
25.1 27.6 27.2

**Vercirnon (Oral CCR9 Antagonist for Moderate to Severe Crohn’s Disease: CDAI 100 Response at Week 12)**

% of Subjects (95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% of Subjects</th>
<th>95% CI</th>
<th>p-value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=203)</td>
<td>15.3</td>
<td>7.1-23.5</td>
<td>0.592</td>
</tr>
<tr>
<td>Vercirnon 500mg QD (n=203)</td>
<td>13.3</td>
<td>5.8-20.8</td>
<td>0.475</td>
</tr>
<tr>
<td>Vercirnon 500mg BID (n=202)</td>
<td>12.9</td>
<td>5.6-20.2</td>
<td></td>
</tr>
</tbody>
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**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

Courtesy Dr. Alan Olsen
Fingolimod for Multiple Sclerosis

- Interferon (N=431)
  - Adjusted Annualized Relapse Rate: 0.33
- Fingolimod 0.5 mg (N=429)
  - Adjusted Annualized Relapse Rate: 0.16
- Fingolimod 1.25 mg (N=420)
  - Adjusted Annualized Relapse Rate: 0.20

P<0.001


HMPL-004
Andrographis paniculata extract

- Herbal mixture is anti-inflammatory; inhibits TNF-α, IL-1β and NF-κB
- 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**

- **Clinical Response**
  - Placebo: 41
  - 1200 mg/day: 50
  - 1800 mg/day: 55
  - HMPL-004: 64

- **Remission**
  - Placebo: 27
  - 1200 mg/day: 35
  - 1800 mg/day: 43
  - HMPL-004: 59

- **Mucosa Healing**
  - Placebo: 33
  - 1200 mg/day: 38
  - 1800 mg/day: 43
  - HMPL-004: 64

**Biology of Interleukins 12 and 23**

- **Anti-IL-12/23**
  - Ustekinumab and 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

- **CD4+ T cells**
  - IL-17 (Th17) pathway
  - Anti-IL-12/23 targets p40 subunit
  - IFNγ (Th1) pathway

**Ustekinumab and briakinumab**

- Fully human IgG1 monoclonal antibodies
- Bind 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
- Psoriasis
Ustekinumab (anti-IL 12/23p40) for Induction of Clinical Response in Moderate to Severe Crohn's Disease


Ustekinumab Placebo

- Placebo
- Ustekinumab

2 4 6 8 0 20 40 60 80 100
0

Weeks

Patients (%)

\( P = .02 \)  \( P = .019 \)  \( P = .337 \)

Ustekinumab vs Placebo

2 4 6 8 0 20 40 60 80 100
0

Weeks

Patients (%)

\( P = .046 \)  \( P = .001 \)  \( P = .004 \)  \( P = .022 \)

Previously Treated with Infliximab

0.2 0.4 0.6 0.8 1.0

CRP in All Patients

\( P = .335 \)  \( P = .02 \)  \( P = .019 \)  \( P = .022 \)

Week 0 vs. Week 8

Infliximab-Experienced

- Placebo
- Ustekinumab

Median CRP (mg/dL)

Week 8

Week 0

All Patients

Previously Treated with Infliximab

Clinical Response

Clinical Remission

\(* P < 0.05 \)

\(* P > 0.05 \) vs. PBO by CMH test

0 5 10 15 20 25 30 35 40 45 50

Clinical Response (%)
Ustekinumab (Anti-IL-12/23p40) for Maintenance of Moderate to Severe Crohn’s Disease

- Placebo: 69.4%
- UST SC: 42.5%
- p<0.001

- Placebo: 41.7%
- UST SC: 27.4%
- p=0.029

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.

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

Tofacitinib (JAK Inhibitor) for Induction of Moderate to Severe Ulcerative Colitis: Response and Remission at Week 8

<table>
<thead>
<tr>
<th>Patients (%) achieving:</th>
<th>Placebo (N=48)</th>
<th>0.5 mg BID (N=31)</th>
<th>3 mg BID (N=33)</th>
<th>10 mg BID (N=33)</th>
<th>15 mg BID (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical remission</td>
<td>42%</td>
<td>32%</td>
<td>49%</td>
<td>60%</td>
<td>78%</td>
</tr>
<tr>
<td>Endoscopic response</td>
<td>46%</td>
<td>52%</td>
<td>58%</td>
<td>67%</td>
<td>78%</td>
</tr>
<tr>
<td>Endoscopic remission</td>
<td>2%</td>
<td>10%</td>
<td>18%</td>
<td>30%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Clinical response: decrease in Mayo score ≥3 points and ≥30%; decrease in rectal bleeding subscore ≥1 point or absolute subscore ≤1
Clinical remission: Mayo score ≤2 and no subscore >1
Endoscopic response: decrease in endoscopic subscore ≥1
Endoscopic remission: endoscopic subscore of 0

*A linear-in-dose model was selected as an appropriate fit to the clinical response data. The fitted response rates are predicted values based upon this linear-in-dose model*


Tofacitinib for Induction in Moderate to Severe Crohn’s Disease: Clinical Response and Remission at Week 4

Sandborn W. Gastroenterology 2011 Abstract
Mean percentage change from baseline in log transformed CRP (mg/L) in those patients with baseline CRP ≥5 mg/L (B)

**Conclusions**

• Budesonide and agents targeted against multiple targets including TNF, beta 7 integrin, MAdCAM-1, the p40 subunit of interleukin 12/23, and JAK3, hold great promise for the future