Novel Therapeutic Options for the Management of Inflammatory Bowel Disease

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4/27/2017
Disclosures

• Abbvie – grant
• Takeda - grant
Outline

Targeting mechanisms similar to approved drugs

- Anti-TNF therapies
- Anti-Adhesion therapies
- Targeting the IL-12/23 pathway

Targeting Novel Mechanisms in IBD

- SMAD7 inhibition
- Sphingosine-1 phosphate receptor modulators
- JAK inhibitors
- Modified release phosphatidylcholine
- Anti-NKG2D monoclonal antibody
What we will not discuss today

• Therapies targeting IL-13 signaling: Tralokinumab, Anrakinzumab, QAX576 (Current studies do not demonstrate benefit or have not been completed)

• Selective FFA2 antagonist: GLPG0974 (lack of benefit in 4wk trial)

• Eotaxin-1 antibody: Bertolimumab (trials not completed)

• Anti IL-6 antibody: PF-04236921 (Phase II trial results not released)

• Anti IL-21 antibodies: ATR-107 had a very high rate of antibody formation and, NNC0114-006 has been completed although results have not been released.

• Tyrosine Kinase inhibitor: Mastinib (no data); Anti-CD40 Monoclonal antibody: FFP104

• Andrographis Paniculata: HMPL-004 (Phase III trials terminated due to lack of efficacy)

• Novel immunomodulators: Vidofludimus and Laquinimod

• CCR9 inhibitor: Vercirnon (Large phase 3 study negative)

• IP10 monoclonal antibody: Eldelumab

• MMP-9 inhibitor GS-5745 (studies terminated)
Crohn’s Disease
Natural History of Crohn’s Disease

Cosnes et al. Inflamm Bowel Dis 2002; 8: 244
Why Treat?

- Symptom improvement
- Improve nutritional status
- Minimize risks of short-term complications
  - Corticosteroid use
  - Extraintestinal manifestations
  - Venous Thromboembolism
  - Flares of disease
- Minimize risks of long-term complications
  - Surgery
  - Colon cancer
  - Bowel obstruction
  - Short bowel syndrome (from extensive bowel resections)
Defining Disease Activity in Crohn’s Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td># liquid or soft stools each day for 7 days</td>
<td>x2</td>
</tr>
<tr>
<td>Abdominal pain (0-3) each day for 7 days</td>
<td>x3</td>
</tr>
<tr>
<td>General well being (0-4) each day for 7 days</td>
<td>x4</td>
</tr>
<tr>
<td>Presence of complications</td>
<td>x20</td>
</tr>
<tr>
<td>Taking lomotil or opiates for diarrhea</td>
<td>x3</td>
</tr>
<tr>
<td>Abdominal mass (0 no, 2 questionable, 5 definite)</td>
<td>x10</td>
</tr>
<tr>
<td>Hematocrit &lt;0.47 or &lt;0.42 for women</td>
<td>x6</td>
</tr>
<tr>
<td>Percent change from standard weight</td>
<td>x1</td>
</tr>
</tbody>
</table>

Typically used cut-offs
- Remission <150
- Mild-moderate 150-220
- Moderate-severe 220-450
- Severe-fulminant >450

Poor correlation between symptoms and mucosal inflammation in CD

Figure 1. Correlation of CDAI vs. CDEIS at D0 (n = 142).

Early Mucosal Healing as a Predictor of Disease Course in CD

Froslie et al. Gastroenterology 2007;133:412-422
Hospitalization and Surgery Rate by Mucosal Healing with Infliximab

- No Mucosal Healing (n=74)
- Mucosal Healing at 1 visit (week 10 or week 54) (n=16)
- Mucosal Healing at both visits (week 10 and week 54) (n=9)

Mucosal healing predicts long-term outcome in patients with CD on infliximab maintenance therapy

Ulcerative Colitis

A proctitis

B left-sided colitis

C pancolitis
### Defining Disease Activity in Ulcerative Colitis

**Mayo Endoscopy Scoring**

<table>
<thead>
<tr>
<th>Score</th>
<th>Rectal Bleeding</th>
<th>Stool Frequency</th>
<th>Endoscopy</th>
<th>Physician Global Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>normal</td>
<td>inactive</td>
<td>normal</td>
</tr>
<tr>
<td>1</td>
<td>Streaks &lt;50% of time</td>
<td>1-2&gt;normal</td>
<td>mild</td>
<td>mild</td>
</tr>
<tr>
<td>2</td>
<td>Obvious Blood with stool</td>
<td>3-4&gt;normal</td>
<td>moderate</td>
<td>moderate</td>
</tr>
<tr>
<td>3</td>
<td>Blood alone</td>
<td>&gt;5 above normal</td>
<td>severe</td>
<td>severe</td>
</tr>
</tbody>
</table>

Images From Pineton de Chambrun et al. Nat Rev Gast Hepatol 2010;7:15-29
25% of patients achieve clinical remission without endoscopic remission

Early Mucosal Healing with Corticosteroids Predicts Long-Term Outcomes in Patients with UC

A (Clin and Endo Remission)
B (Clin Remission Only)
C (Neither Clin or Endo Remission)

Early Mucosal Healing as a Predictor of Disease Course in UC

Froslie et al. Gastroenterology 2007; 133:412-422
Medications in development that target similar pathways to currently available FDA therapies for IBD

• Anti-TNF\(\alpha\) therapies
• Anti-integrin therapies
• IL-12/23 inhibitors
Anti-TNF antibodies

Biosimilars

• Definition:
  – Highly similar to FDA-approved biological product
  – No clinically meaningful difference in potency, purity and safety to original biologic (interchangeable)

• In 2014 (USA)
  – Remicade® sales $8.1 billion
  – Humira® sales $11.8 billion

• 6 Remicade and 6 Humira biosimilars in development

• FDA-approval: demonstrate structural and functional biosimilarity without difference in clinical outcomes between the biosimilar and biologic

[Diagram showing the hierarchy of clinical and nonclinical studies]
Oral Anti-TNF Therapy (AVX-470)

- Polyclonal antibody generated from purifying the antibody from the colostrum of cows immunized with recombinant anti-TNF.
- In vitro, has similar neutralizing capabilities as infliximab
- Effective in murine models of colitis.
- Phase 1b study in 30 patients with UC:

<table>
<thead>
<tr>
<th></th>
<th>Placebo (9)</th>
<th>0.2g/day (8)</th>
<th>1.6g/d (12)</th>
<th>3.5g/day (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Response</td>
<td>11.1%</td>
<td>37.5%</td>
<td>16.7%</td>
<td>26.8%</td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14.3%</td>
</tr>
<tr>
<td>Endoscopic Response</td>
<td>0</td>
<td>0</td>
<td>8.3%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Endoscopic Remission</td>
<td>0</td>
<td>0</td>
<td>8.3%</td>
<td>14.3%</td>
</tr>
</tbody>
</table>

- No immunogenicity
- Decrease in CRP in 3.5g/day group
- Bovine IgG in tissue and stool not in serum
- TNF in colon tissue decreased

Harris M et al. United European Gastroenterology Journal;2014:S1
Why integrins are an attractive target for IBD?

Anti-Integrin Therapies

Lobaton T et al. Aliment Pharmacol Ther 2014;
Vedolizumab induction and maintenance therapy in patients with ulcerative colitis

Vedolizumab induction and maintenance in patients with Crohn’s disease

**Week 6**

- Clinical Remission: Placebo (N=148) 6.8%, Vedolizumab (N=220) 14.5%
- CDAI-100 Response: Placebo 25.7%, Vedolizumab 31.4%

**Week 52**

- Clinical Remission: Placebo (N=153) 21.6%, Vedolizumab, every 8 wk 39.0%, Vedolizumab, every 4 wk 36.4%
- CDAI-100 Response: Placebo 30.1%, Vedolizumab, every 8 wk 43.5%, Vedolizumab, every 4 wk 45.5%
- Glucocorticoid-Free Remission: Placebo 15.9%, Vedolizumab, every 8 wk 31.7%, Vedolizumab, every 4 wk 28.8%
- Durable Clinical Remission: Placebo 14.4%, Vedolizumab, every 8 wk 21.4%, Vedolizumab, every 4 wk 16.2%

P-values:

- Week 6: P=0.02, P=0.23
- Week 52:
  - Clinical Remission: P<0.001, P=0.004, P=0.005
  - CDAI-100 Response: P=0.01, P=0.02
  - Glucocorticoid-Free Remission: P=0.04
Etrolizumab

Phase 2 Trial
- 124 patients with UC
- Mayo Endoscopy score ≥2

**Primary End Point**
- MCS≤2
- No subscore >1

**Key Points**
- Anti-TNF naïve patients appeared to do better
- Mucosal αE expression at baseline associated with response

Vermeire S et al. Lancet 2014;384;309-318
Etrolizumab results in decreased CD8+ cells homing to the gut compared to vedolizumab

PF-00547659; MAdCAM-1 monoclonal antibody in UC

- RCT of SC 7.5mg, 22.5mg, 75mg, 225mg or placebo q4 weeks x 3 doses
- 357 patients with ulcerative colitis (TURANDOT)
- All had total Mayo score >6 with a Mayo endoscopy subscore ≥ 2
- Endpoints Assessed at 12 weeks

**Clinical Remission**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>7.5mg</th>
<th>22.5mg</th>
<th>75mg</th>
<th>225mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>0</td>
<td>6.4</td>
<td>15.4</td>
<td>22.4</td>
<td>24.4</td>
</tr>
</tbody>
</table>

**Clinical Response**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>22.5mg</th>
<th>75mg</th>
<th>225mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>0</td>
<td>27.8%</td>
<td>35.8%</td>
<td>42.8%</td>
</tr>
</tbody>
</table>

27.8% of patients receiving 22.5mg vs. 8.2% of placebo achieved mucosal healing

Reinisch et al. Gastroenterology 2015; 148;S1:S-1193
PF-00547659; MAdCAM-1 monoclonal antibody in Crohn’s Disease

• Randomized Placebo Controlled Trial (OPERA)
• 267 subjects with moderate to severe Crohn’s disease (CDAI 220-450) + CRP>3mg/L and ulcers on colonoscopy
• All failed or intolerant to anti-TNF or immunsuppressants

<table>
<thead>
<tr>
<th>Week 12 Outcome</th>
<th>Placebo</th>
<th>22.5mg</th>
<th>75mg</th>
<th>225mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response (70pt)</td>
<td>59%</td>
<td>62%</td>
<td>65%</td>
<td>58%</td>
</tr>
<tr>
<td>Remission (100pt)</td>
<td>23%</td>
<td>27%</td>
<td>28%</td>
<td>29%</td>
</tr>
<tr>
<td>Remission with CRP&gt;18</td>
<td>14%</td>
<td>37%</td>
<td>24%</td>
<td>39%</td>
</tr>
</tbody>
</table>

Therapies Targeting IL-12 and IL-23 signaling

![Diagram showing IL-12 and IL-23 signaling pathways](image)

- IL-23 signaling leads to IL-17A, IL-17F, IL-22 production and Th17 stabilization.
- IL-12 signaling leads to IFN-γ and Th1 development.
Ustekinumab induces early remission

Ustekinumab is effective at maintaining remission

AMG-139 (MEDI2070): p19 monoclonal antibody

**BI655066**

- Monoclonal antibody to p19
- Effective in early phase trials in psoriasis (87% response at 12 weeks) with sustained response after a single infusion (66 wks)
- In Phase II studies for Crohn’s disease

Sands BE et al. J Crohn’s and Colitis; 2015:S15
Therapies Targeting Novel Mechanisms in IBD Treatment

- SMAD7 inhibition
- Sphingosine-1 phosphate receptor modulators
- JAK Kinase inhibitors
- Modified release phosphatidylcholine
- Anti-NKG2D monoclonal antibody
- PDE4 inhibitor (apremilast)
Anti-SMAD7 oligonucleotide

Mongersen

LNA  2'-MOE  Phosphorothioate backbone (PS)
2'-O-methyl  2'-F

Mongersen – phase II trial results

- Randomized placebo control trial
- Moderate to severe CD (CDAI 220-400)
- Disease confined to TI and right colon
- Primary endpoint was remission at 2 weeks (CDAI<150) who stayed in remission for 2 weeks
- 166 patients randomized
- Adverse events similar

Sphingosine-1 Phosphate (S1P) Receptor Modulators

Sphingosine 1 Phosphate 1 Receptor Modulator (Ozanimod, RPC1063)

- Phase II RCT comparing 0.5mg, 1mg, and placebo
  - 197 patients with moderate to severe UC: 8 week induction treatment
  - 103 patients who achieved a clinical response continued treatment for an additional 24 weeks.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Remission (%)</th>
<th>Response (%)</th>
<th>Mucosal Improvement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6.2%</td>
<td>36.9%</td>
<td>12.3%</td>
</tr>
<tr>
<td>0.5mg</td>
<td>13.8%*</td>
<td>53.8%</td>
<td>27.7%*</td>
</tr>
<tr>
<td>1mg</td>
<td>16.4%*</td>
<td>58.2%*</td>
<td>34.3%*</td>
</tr>
</tbody>
</table>

Also in Phase II Studies

- MT-1303: Crohn’s Disease
- APD-334: UC

Sandborn W et al. ECCO 2015
Hanauer SB et al. ACG 2015
JAK Inhibitors

Filgotinib (GLPG 0634)
- Selective inhibitor of JAK1>>>JAK2
- Early phase studies in RA showed benefit (now in phase 3)
- In phase III for CD

ABT-494
- Selective inhibitor of JAK1>>>>JAK2
- Early phase studies in RA showed benefit (now in phase 3)
- In phase II for CD

Peficitinib
- Selective inhibitor of JAK3>JAK1/JAK2
- Early phase studies in psoriasis showed benefit (now in phase 3), less in RA
- In phase II for UC

Neurath MF. Nature Immunology 2014;14:329-42
Tofacitinib in Ulcerative Colitis

Inhibitor of JAK1 > JAK2 or JAK3

Phase II study
194 patients
Moderate to Severe UC
Outcome assessed at 8 weeks

Safety
Dose dependent increases in LDL and HDL
3 cases of neutropenia

Tofacitinib Phase 3 induction and maintenance

OCTAVE Induction 1 and 2 (week 8)

Octave Sustain (Week 52)

Remission - Induction 1  Mucosal Healing Induction 1  Remission - Induction 2  Mucosal Healing Induction 2

Clinical Response  Clinical Remission  Mucosal Healing

Placebo  Tofacitinib 10mg

Placebo  Tofacitinib 5mg  Tofacitinib 10mg
Tofacitinib in Crohn’s disease

Modified release phosphatidylcholine (LT-02)

- Phosphatidylcholine is a component of the mucosal barrier (mucous)
- RCT in patients with mesalamine refractory disease for 12 weeks:
  - Mucosal Healing: 32.5% of Placebo vs. 47% LT-02 (p=0.09)
  - Histologic remission 20% placebo vs. 40.5% LT-02 (p=0.02)
  - Well Tolerated

Anti-NKG2D monoclonal antibody (NNC0142-0002)

• 78 patients with Crohn’s disease
• Active Crohn’s CDAI 220-450 and CRP >9 or endoscopic ulcerations.
• Single 2mg/kg SC dose
• Primary Endpoint: Change in CDAI at week 4 (not met)
• Difference was seen at week 12.
• Patients with elevated calprotectin (>250ug/g) did better

Allez et al. Gut. 2016. published online
Raulet. Nature Reviews Immunology 3, 781-790
Conclusion

• There are many exciting new treatments for IBD in development.

• Keep in mind that many will never reach the clinical arena.

• Response/Remission rates continue to be less than ideal -- there will be continued focus on using our therapies more effectively and developing tools for personalized treatment approach.
Thank You!

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