Future therapies for Inflammatory Bowel disease

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  - Professor of Medicine
  - University of Louisville School of Medicine
  - Division of Gastroenterology, Hepatology and Nutrition
Agenda

- **Ongoing Needs With Current IBD Therapy**
  - Symptom control including pain management.

- **Mechanism of Actions and Progress of New and Emerging Agents**
  - Regulation of T-cell and B-cell trafficking and migration
  - Interleukin inhibitors
  - JAK inhibitors
  - Fecal microbial transplant

- **Summary**
Ongoing Needs With Current IBD Medical Therapy

**Advances**

- Current IBD therapies are effective in some patients\[1,2\]
  - Clinical remission achievable with TNF inhibitors
- Probability of major surgery in UC and CD has decreased\[3\]
- We are learning to optimize current therapy with combination therapy, therapeutic drug monitoring, prognostication and symptom (pain)management.

**Ongoing Needs**

- Incidence of primary and secondary nonresponse with TNF inhibitors is 50%\[1\]
- Some patients still require surgery with IBD\[3\]
- Research on disease treatment is needed and is ongoing

Preclinical and Clinical Efficacy of Olorinab, a Peripherally Acting, Highly Selective Full Agonist of the Cannabinoid Receptor 2, for the Management of Visceral Pain in Inflammatory Bowel Disease

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Abdominal Pain in Crohn’s Disease (CD) and the Role of the Cannabinoid Receptor 2 (CB₂) in Visceral Hypersensitivity

- 41% of patients with CD, pain, bloating, and erratic bowel habits persist despite apparent remission of inflammation³

- Current treatment options for abdominal pain have demonstrated limited efficacy and/or unfavorable adverse event profiles⁴

- CB₂ is mainly expressed in immune cells and peripheral tissues, including the GI tract,⁶-⁸ and is upregulated during disease states, such as inflammation⁷

- CB₁ is widely distributed, highly expressed in the brain, and mediates the psychoactive effects of cannabis⁵

- Increased in the GI tract of patients with IBD⁷,⁸ and IBS ¹⁰ and was shown to modulate visceral sensitivity in animal models

CB₁, cannabinoid receptor 1; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; GI, gastrointestinal tract.

Some Investigational Therapies for IBD in 2020

- Regulation of T-cell and B-cell trafficking and migration
  - Integrin inhibitors and MAdCAM-1 inhibitors
  - S1P receptor modulators
- Fecal microbial transplant

- Inhibition of inflammation
  - Extracellular cytokine inhibitors
    - Interleukin inhibitors
  - Intracellular signaling inhibitors
    - Janus kinase inhibitors
    - PDE4 inhibitors

Slide credit: clinicaloptions.com
## New and Emerging Therapies for IBD Inflammation

<table>
<thead>
<tr>
<th>Class</th>
<th>FDA Approved</th>
<th>Investigational</th>
</tr>
</thead>
</table>
| Integrin inhibitors and MAdCAM-1 inhibitors | Natalizumab (CD)  
Vedolizumab | AJM 300  
Etrolizumab  
SHP 647 |
| S1P modulators               |                                                    | Etrasimod  
Ozanimod |
| Interleukin inhibitors       | Ustekinumab (CD)                                   | Brazikumab  
Guselkumab  
Mirikizumab  
Risankizumab  
Ustekinumab (UC) |
| JAK inhibitors               | Tofacitinib (UC)                                   | Filgotinib  
Upadacitinib  
TD-1473 |
| PDE4 inhibitors              |                                                    | Apremilast |
| Microbiome modifiers         |                                                    | Fecal microbiota therapy |

References in slidenotes

Slide credit: clinicaloptions.com
Inhibition of T-Cell and B-Cell Migration: Integrin and MAdCAM-1 Inhibitors
Integrin and MAdCAM-1 Inhibitors in IBD

MAdCAM-1 adhesion molecule on vascular endothelium

Anti–MAdCAM-1
- SHP 647 (investigational)

α4β7 integrin on lymphocyte

Anti-integrins
- AJM 300 (investigational)
- Etrolizumab (investigational)
- Natalizumab
- Vedolizumab

Lymphocyte migrating through vascular endothelium to gut


Slide credit: clinicaloptions.com
Integrin and MAdCAM-1 Inhibitors

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Current Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>α4β7- and α4β1-integrin</td>
<td>Natalizumab[1,2]</td>
<td>FDA approved 2008</td>
</tr>
<tr>
<td>α4β7-integrin</td>
<td>Vedolizumab[2,3]</td>
<td>FDA approved 2014</td>
</tr>
<tr>
<td>MAdCAM-1</td>
<td>SHP 647[8]</td>
<td>Phase III in CD,[9] UC[1101]</td>
</tr>
</tbody>
</table>

Integrin and MAdCAM-1 inhibitors block lymphocyte migration through the vascular endothelium to the gut

AJM 300: α4-Integrin Inhibitor in UC

- Randomized, double-blind, placebo-controlled, multicenter, phase IIa study of adults with moderate to severe active UC (N = 102)
  - Patients had inadequate response or intolerance to mesalamine or corticosteroids, no TNF in previous 12 wks

- AJM 300 well tolerated

Etrolizumab: α4β7- and αEβ7-Integrin Inhibitor in UC

- Randomized, double-blind, placebo-controlled, multicenter phase II study in adults with moderate to severe UC (N = 119)
  - Patients had no previous response to conventional therapy

- Etrolizumab well tolerated

*100 mg at Wks 0, 4, and 8 with placebo at Wk 2. †Loading dose: 420 mg at Wk 0, then 300 mg at Wks 2, 4, 8.

TURANDOT: SHP 647 (MAdCAM-1 Inhibitor) in UC

- Randomized, double-blind, placebo-controlled phase II study of adults with moderate to severe UC (N = 357)
  - 57% of patients anti-TNF experienced

- SHP 647 well tolerated, no association with increased risk of infection

Regulation of T-Cell and B-Cell Trafficking: S1P Receptor Modulators
S1P Receptor Modulators in IBD

- S1P gradient promotes egress of activated **lymphocytes** from lymph nodes\(^1,2\)

- S1P receptor modulators induce S1P receptor internalization, temporarily trapping **lymphocytes** in lymph nodes

- **S1P receptor modulators\(^1,3\):**
  - Etrasimod (investigational)
  - Ozanimod (investigational)

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# S1P Receptor Modulators

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Current Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1PR1/4/5</td>
<td>Etrasimod[^1]</td>
<td>Phase II in patients with UC[^2,3]</td>
</tr>
<tr>
<td>S1PR1/5</td>
<td>Ozanimod[^4]</td>
<td>Phase III in UC, CD[^5,6]</td>
</tr>
</tbody>
</table>


**STOP**

**S1P receptor modulators block lymphocyte egress from lymph nodes**

Slide credit: [clinicaloptions.com](http://clinicaloptions.com)
OASIS: Etrasimod (S1P Modulator) in UC

- Randomized, double-blind, placebo-controlled phase II study in patients with moderate to severe UC (N = 156)

- Etrasimod well tolerated

TOUCHSTONE: Ozanimod (S1P Modulator) in UC

- Randomized, double-blind, placebo-controlled, multicenter phase II study in adults with moderate to severe UC (N = 197)
  - 15% to 20% of patients anti-TNF experienced, depending on treatment arm
- Larger studies needed to establish clinical efficacy and safety


Slide credit: clinicaloptions.com
Inhibition of Inflammation: Extracellular Interleukin Inhibitors
Interleukin Inhibitors in IBD

- activated antigen-presenting cell

Proinflammatory cytokines
- IL-12
- IL-23

Interleukin Inhibitors
- Brazikumab (anti–IL-23, investigational)
- Gusekumab (anti–IL-23, investigational)
- Mirikizumab (anti–IL-23, investigational)
- Risankizumab (anti–IL-23, investigational)
- Ustekinumab (anti–IL-12/23)

Interleukin Inhibitors

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Current Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-12/23</td>
<td>Ustekinumab</td>
<td>FDA approved in CD (2016), phase III in UC</td>
</tr>
<tr>
<td>IL-23</td>
<td>Brazikumab</td>
<td>Phase II in UC</td>
</tr>
<tr>
<td>IL-23</td>
<td>Gusekumab</td>
<td>Phase II/III in CD</td>
</tr>
<tr>
<td>IL-23</td>
<td>Mirikizumab</td>
<td>Phase III in UC</td>
</tr>
<tr>
<td>IL-23</td>
<td>Risankizumab</td>
<td>Phase II in CD and phase III in UC</td>
</tr>
</tbody>
</table>

Interleukin inhibitors block extracellular signals that activate and differentiate lymphocytes.


Slide credit: clinicaloptions.com
UNITI-1, -2, and -IM: Ustekinumab (IL-12/23 Inhibitor) in CD

- 3 randomized, double-blind, placebo-controlled, multicenter phase III studies in adults with moderate to severe CD

- Ustekinumab well tolerated

Brazikumab: IL-23 Inhibitor in CD

- Randomized, double-blind, placebo-controlled phase II study in adults with moderate to severe CD (N = 119)
  - Patients with inadequate response or intolerance to anti-TNF

![Bar chart showing primary outcome at Wk 8](chart.png)

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients With Clinical Response (%)</th>
<th>n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>7/16 (43.75%)</td>
<td>16/60</td>
</tr>
<tr>
<td>Brazikumab 700 mg IV Q4W</td>
<td>2/29 (6.9%)</td>
<td>29/59</td>
</tr>
</tbody>
</table>

*P = .01*

Mirikizumab: IL-23 Inhibitor in CD

- Randomized, double-blind, placebo-controlled, multicenter phase II study in adults with moderate to severe CD (N = 249)
  - 63% of patients biologic experienced

![Primary Outcome at Wk 12](https://clinicaloptions.com)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Patients in Clinical Remission (%)</th>
<th>n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3/63</td>
<td>4.8</td>
</tr>
<tr>
<td>Mirikizumab 50 mg IV Q4W</td>
<td>10/63</td>
<td>15.0</td>
</tr>
<tr>
<td>Mirikizumab 200 mg IV Q4W</td>
<td>14/62</td>
<td>22.0</td>
</tr>
<tr>
<td>Mirikizumab 600 mg IV Q4W</td>
<td>7/61</td>
<td>11.0</td>
</tr>
</tbody>
</table>

Risankizumab: IL-23 Inhibitor in CD

- Randomized, double-blind, placebo-controlled, multicenter phase II study in adults with moderate to severe CD (N = 121)
  - 79% of patients with anti-TNF failure

Primary Outcome at Wk 12

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients in Clinical Remission (%)</th>
<th>n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>6/39</td>
</tr>
<tr>
<td>Risankizumab 200 mg IV Q4W</td>
<td></td>
<td>10/41</td>
</tr>
<tr>
<td>Risankizumab 600 mg IV Q4W</td>
<td></td>
<td>15/41</td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com
Inhibition of Inflammation: Intracellular JAK Inhibitors
Diverse Signaling Pathways in Immune Cells: JAK

Slide credit: clinicaloptions.com
JAK Inhibitors

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Current Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK1/2/3</td>
<td>Tofacitinib[^1]</td>
<td>FDA approved in UC[^2]</td>
</tr>
<tr>
<td>JAK1</td>
<td>Upadacitinib[^7]</td>
<td>Phase III in CD, UC[^8][^9]</td>
</tr>
<tr>
<td>JAK1/2/3</td>
<td>TD-1473[^10]</td>
<td>Phase II in CD[^11][^12]</td>
</tr>
</tbody>
</table>

JAK inhibitors block intracellular signals that activate and differentiate lymphocytes.

[^1]: Clinicaloptions.com
[^2]: References in slidenotes.
[^3]: References in slidenotes.
[^4]: References in slidenotes.
[^5]: References in slidenotes.
[^6]: References in slidenotes.
[^7]: References in slidenotes.
[^8]: References in slidenotes.
[^9]: References in slidenotes.
[^10]: References in slidenotes.
[^11]: References in slidenotes.
[^12]: References in slidenotes.
JAK Inhibitor Activity and Signaling

Interleukins and other cytokines

- yc family: IL-2, IL-7, IL-15, IL-21
- IFN-γ
- IL-6 family
- IL-12, IL-23
- EPO, GM-CSF

JAK Inhibitors
- Tofacitinib
- Filgotinib (investigational)
- TD-1473 (investigational)
- Upadacitinib (investigational)

OCTAVE: Tofacitinib (JAK Inhibitor) in UC

- 3 randomized, double-blind, placebo-controlled, multicenter phase III studies in adults with moderate to severe UC
  - 46% to 58% of patients' anti-TNF experienced, depending on treatment arm

Slide credit: clinicaloptions.com

FITZROY: Filgotinib (JAK Inhibitor) in CD

- Randomized, double-blind, placebo-controlled, multicenter phase II study in adults with moderate to severe CD (N = 174)[1]
  - 56% to 64% of patients anti-TNF experienced, depending on treatment arm

- In subanalysis, efficacy was independent of prior TNF inhibitor exposure[2]

![Graph showing primary outcome at Wk 10]

- Patients With Clinical Remission (%)
  - Placebo: 23 (10/44)
  - Filgotinib 200 mg PO QD: 47 (60/12)


Slide credit: clinicaloptions.com
CELEST: Upadacitinib (JAK Inhibitor) in CD

- Randomized, double-blind, placebo-controlled, multicenter phase II study in adults with moderate to severe CD with (N = 220)
  - Patients had inadequate response or intolerance to anti-TNF


Slide credit: clinicaloptions.com
Inhibition of Inflammation: Intracellular PDE4 Inhibitor
Diverse Signaling Pathways in Immune Cells: PDE4

Slide credit: clinicaloptions.com
# PDE4 Inhibition in UC

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Current Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE4</td>
<td>Apremilast[1]</td>
<td>Phase II[2,3]</td>
</tr>
</tbody>
</table>

PDE4 inhibitor blocks intracellular signals that activate and differentiate lymphocytes

Apremilast: PDE4 Modulation in UC

- Randomized, double-blind, placebo-controlled, multicenter phase II study in adults with active UC (N = 170)
  - Patients with prior treatment failure and naive to biologic therapy

Bar chart showing:
- Placebo: 13.8% (58 patients) with 6 patients achieving TMS Clinical Remission
- Apremilast 30 mg PO BID: 31.6% (57 patients) with 6 patients achieving TMS Clinical Remission
- Apremilast 40 mg PO BID: 21.8% (55 patients) with 6 patients achieving TMS Clinical Remission

Primary Outcome at Wk 12

Altering the Microbiome
Fecal Microbiota Transplantation in UC

- Randomized, double-blind, placebo-controlled, parallel study in adults with active UC without infectious diarrhea (N = 75)


No difference in adverse events
Fecal Microbiota Transplantation: Endoscopic Remission

- Meta-analysis of 4 randomized controlled trials in patients with active UC

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Endoscopic Remission, n/N</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FMT</td>
<td>Placebo</td>
</tr>
<tr>
<td>Rossen 2015</td>
<td>2/23</td>
<td>2/25</td>
</tr>
<tr>
<td>Moayyedi 2015</td>
<td>9/38</td>
<td>2/37</td>
</tr>
<tr>
<td>Paramsothy 2017</td>
<td>5/41</td>
<td>3/40</td>
</tr>
<tr>
<td>Costello 2017</td>
<td>4/38</td>
<td>0/35</td>
</tr>
<tr>
<td>Total</td>
<td>20/140</td>
<td>7/137</td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com
Fecal Microbiota Transplantation: Unanswered Questions

- Long-term safety?
- Best given by NG tube, colonoscopy, or enema?
- How frequently is maintenance therapy required?
Conclusions

- Significant unmet needs still exist despite currently approved therapies
  - Symptom management also on the agenda (pain)
- Agents in phase III trials include a multitude of novel targets:
  - Integrin inhibitors and MAdCAM-1 inhibitors
  - S1P receptor modulators
  - Anti–IL-12/23 antibodies
  - JAK and PDE4 signaling inhibitors
  - Fecal microbiota therapy
- Algorithms and comparative trials will be essential guiding a wealth of upcoming new therapies