What’s in the Pipeline?  
An Update on IBD Medications

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Outline

• Version 2.0 Anti-Adhesion Molecules
• Biologics with New Mechanisms of Action
• New Small Molecule Medications
• Fecal Microbial Transplantation
• Clinical Trials
Version 2.0 Medications

• Version 1.0: Entyvio (α4β7 inhibitor)
  – Block inflammatory cells from getting to GI tract
  – Gut specific anti-adhesion molecule

• Version 2.0:
  – AMG181 = α4β7 inhibitor, Subcutaneous dosing
  – Anti-MadCAM-1, Subcutaneous dosing
  – Etrolizumab (β7 inhibitor), Subcutaneous dosing
    • Should not have risk of PML (brain infection) but may be more effective
Anti-adhesion Pipeline in IBD

- CCL25/TECK
- T cell
- AMG181-Amgen
- Anti-MAdCAM1-Pfizer
- Anti-β7-Genentech

Intestine
Anti-Adhesion Side Effects

- Vary based on precise medications
- Infusion, injection reaction
- Gastrointestinal infections
- Nasopharyngitis

- **Gut specific medications have not been associated with rare brain infection (PML)**
Version 3.0 “Anti-Adhesion”

• Sphingosine 1-phosphate (S1P1) R modulator
  – S1P1 molecules facilitate migration of T cells out of lymph nodes to travel to areas of inflammation
  – “Trap” T cells in the lymph nodes

• Oral Medication
• Similar effect as vedolizumab
• Phase 3 clinical trials
Interleukin(IL) 12 and 23 Inhibitors

• Monoclonal antibodies (humanized)
  – Focused on Crohn’s disease & psoriasis
  – Ustekinumab (stelera) – coming soon
  – Briakinumab
  – Next generation: IL-23 (p19) Inhibitors

• How does it work?
  – Blocks inflammatory cytokine signaling ex. IL-12 and IL-23
  – Blocks development of T cells (Th1 and Th17 Cells)
  – Specific to IBD pathogenesis
Interleukins 12 and 23

Antigen Presenting Cell

Stimulus TLR?

IL-12

p35, p40

Anti-IL-12/23

IL-17 (Th17)

IL-12Rβ1

β2

IL-23R

IL-12/23

IFNg (Th1)

Anti-IL-12/23

Inflammatory T cells contributing to IBD, esp Crohn’s

CD4+

Ag

MHCII

TCR

Stimulus

TLR?

p40

p35

IL-12

p40

p35

IL-23

β2

IL-12Rβ1

Anti-IL-12/23
Ustekinumab for Maintenance of Moderate to Severe Crohn’s Disease

Janus Kinase (JAK) inhibitors:

• Small molecule (NOT biologic)
  – Oral medications
  – Tofacitinib (Xeljanz) – approved for RA, coming soon for UC
  – Many more in development

• Mechanism of action:
  – Blocks signaling in inflammatory cytokine signaling pathways in inflammation
  – Used in multiple diseases
JAK inhibitor Mechanism

Adapted from www.mdanderson.org
Tofacitinib & Ulcerative Colitis

A. Proportion of patients achieving clinical response

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion of patients (%)</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>41.7</td>
</tr>
<tr>
<td>0.5 mg BID</td>
<td>32.3</td>
</tr>
<tr>
<td>3 mg BID</td>
<td>48.5</td>
</tr>
<tr>
<td>10 mg BID</td>
<td>60.6</td>
</tr>
<tr>
<td>15 mg BID</td>
<td>77.6</td>
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</tbody>
</table>

B. Proportion of patients achieving clinical remission

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10.4</td>
</tr>
<tr>
<td>0.5 mg BID</td>
<td>12.9</td>
</tr>
<tr>
<td>3 mg BID</td>
<td>33.3</td>
</tr>
<tr>
<td>10 mg BID</td>
<td>48.5</td>
</tr>
<tr>
<td>15 mg BID</td>
<td>40.8</td>
</tr>
</tbody>
</table>

P-values:

- A. Placebo vs. 0.5 mg BID: P=0.417
- A. Placebo vs. 10 mg BID: P=0.085
- A. Placebo vs. 15 mg BID: P<0.001
- B. Placebo vs. 0.5 mg BID: P=0.750
- B. Placebo vs. 10 mg BID: P=0.011
- B. Placebo vs. 15 mg BID: P<0.001

# JAK Inhibitor Summary

## Benefits
- Oral medication
- No risk of antibodies
- Developing more specific versions of this medications
- Only for UC (for now)

## Side effects
- Blocks other signaling pathways
- Infections
- Low white blood cell count
- Anemia
- Rise in lipid (ex. LDL)
- Rare lymphoma
Microbiome in IBD

• What is the microbiome?
  – Many micro-organisms sharing our body space
  – 10x as many bacterial v. human cells in the gut
  – Generally, beneficial effects for our health

• Microbiome & Health
  – Many abnormalities have been found in many diseases
    • IBD, diabetes, obesity, autism, liver disease
Microbiome in IBD

• Changes in microbiome of patients with IBD
  – Less diverse bacteria
  – More of “bad bacteria”
  – Less of “good bacteria”

• Cause or Effect?
  – Consequence of inflammation?
  – Or, causing disease?
  – If we change the microbiome, may be able to alter the disease
Fecal Microbial Transplantation

• Replace an individual’s microbiome with a healthy individual’s microbiome

• Infuse donor “healthy” stool into a patient during colonoscopy

• Effective for Recurrent C difficile
MANY clinical trials examining FMT in IBD
- Different strategies
  - Infusion with colonoscopy, endoscopy, OR enema
  - Single v. serial FMT, early v. late IBD
- So far, most have NOT shown lasting effect
- Currently not an effective therapy, but may change!

May learn how to alter the microbiome in a more targeted manner
Clinical Trials for Ulcerative Colitis

- Adalimumab high v. standard dosing
- Etrolizumab (anti-B7)
- Anti - MMP-9
  - Inhibitor of Matrix Metalloproteinase 9 (MMP9)
  - MMP9 released in response to inflammation, causing more inflammation

- Chronic, antibiotic refractory pouchitis
  - Enema blocking production of cell adhesion molecule
  - Blocks inflammatory cells from entering the pouch
Clinical Trials for Crohn’s Disease

- Adalimumab high v. standard dosing
- Etrolizumab (Anti-B7)
- Vedolizumab (open label)
- S1P1 modulator (Ozanimod) – oral
- MMP9 inhibitor
- JAK inhibitor - oral
- Rifaximin (gut specific antibiotic) – oral
Summary

• Many new types of drugs coming
• Newer anti-adhesion medications
• Completely different biologics
  – IL-12/IL-23 inhibitors
• New oral medications
  – Jak inhibitors
• Fecal Microbial Transplantation – work in progress
• Many more drugs in clinical trials
Thank you

Questions??