Moving Beyond Current IBD Treatment: New Therapies in IBD

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IBD Treatment Approach

- Induce clinical remission
- Maintain clinical remission
- Improve patient quality of life

PLUS

- Achieve mucosal healing
- Decrease overall rates of hospitalization & surgery
- Minimize disease-related & therapy-related complications
IBD Treatment Approach

- “Step-up” or “Bottom-up”
IBD Treatment Approach

- “Top-down” earlier introduction of biologics & immunomodulators
IBD Treatment

- Key - there is NO standard approach for managing all IBD patients.
- Symptoms, severity of disease, & how the disease impacts a patient varies considerably.
IBD Armamentarium

- Aminosalicylates
- Steroids
- Biologics
- Immunomodulators
- Antibiotics
UC Armamentarium

Currently Available

- anti-TNFs
  - Remicade (infliximab)
  - Humira (adalimumab)
  - Simponi (golimumab)
- anti-leukocyte trafficking
  - Entivyo (vedolizumab)

In the Pipeline

- Janus Kinus (JAK) Inhibition
  - Xeljanz (tofacitinib) – approved 3/2018
- anti-Interleukin 12/23
  - Stelara (ustekinumab) - off label use
- Hyperbaric Oxygen
  - Inpatient UC patients
- Sphingosine-1phosphate receptor modulation*
- New anti-leukocyte trafficking
- Phosphodiesterase 4 inhibitors*

*small molecules
Novel targets and new therapies for IBD

**Fecal Microbial Therapy**
- JAK Kinase inhibitors
  - Tofacitinib
  - Filgotinib

**SMAD7 Inhibitor**
- Mongersen

**Anti-IL-12/23 Antibodies**
- Ustekinumab
- MEDI2070

**Spingosine-1-phosphate receptor modulators**
- Ozanimod

**Anti-Leukocyte Trafficking Antibodies**
- Natalizumab
- Vedolizumab
- Etrolizumab
- Anti-MAdCAM

Positioning of Biologics

- When are biologics appropriate for UC?
  - Failure after optimization of 5-ASA or IMM
  - Inability to taper off steroids
  - Moderate to severe active disease

- 1st Line Biologics
  - anti-TNFs- rapidity of onset, immunogenicity
  - Entivyo (vedolizumab)- less rapid onset of action, safety profile

- After failure of anti-TNFs
  - Entivyo (vedolizumab)
  - Discussion with a surgeon
Xeljanz (Tofacitinib)- new kid on the block!

- Approved March 2018
- Inhibits JAK1, JAK2, and JAK3 in vitro
- Functional cellular specificity JAK1 & JAK3 over JAK2
- Modulates signaling for an important subset of pro-inflammatory cytokines: IL-2, -4, -7, -9, -15, & -21
- Induction 10mg twice daily oral/Maintenance 5mg or 10mg twice daily oral
OCTAVE- Xeljanz (tofacitinib) Registration Trials

Xeljanz (tofacitinib)- Adverse Events

- **Infections**
  - Herpes zoster (up to 5% in higher maintenance dose)

- **Cancer**
  - Non-melanoma skin cancer

- **GI Perforation**
  - Risk not increased over placebo

- **LDL & HDL cholesterol increase**
  - Cholesterol levels should checked 4-8 weeks after starting treatment

- **Serum creatinine kinase increase**

- **Elevations in liver aminotransferase** (rare)

- **Lymphocytopenia, neutropenia, & low hemoglobin** (rare events)
Herpes Zoster & Herpes Simplex Incidence Rates Associated with anti-TNF & tofacitinib in RA

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>Person-Years</th>
<th>Incidence Rate*</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>330</td>
<td>6832.8</td>
<td>4.83 (4.34-5.38)</td>
<td>0.89 (0.77-1.03)</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>161</td>
<td>2940.7</td>
<td>5.47 (4.69-6.39)</td>
<td>1.00 (0.83-1.19)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>89</td>
<td>1670.8</td>
<td>5.33 (4.33-6.56)</td>
<td>1.01 (0.80-1.27)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>492</td>
<td>8201.4</td>
<td>6.00 (5.49-6.55)</td>
<td>1.06 (0.93-1.21)</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>74</td>
<td>972.9</td>
<td>7.61 (6.06-9.55)</td>
<td>1.40 (1.09-1.81)</td>
</tr>
</tbody>
</table>

*Per 100 person-years.

Adjusted for age, sex, baseline glucocorticoid use, methotrexate, number of biologics used, hospitalization, hospitalized infection, outpatient infection and zoster vaccination.

Where will Xeljanz (tofacitinib) go in IBD treatment approach

- Oral, it’s FAST onset of action (within days!)
- Could it possibly replace steroids?
- Will it be safe in combination therapy?
- Likely payers at first will tell us where to position it, but...
  - Likely start after anti-TNFs & Entivyo failures
  - No reason it can’t be considered at same point as anti-TNFs or Entivyo as first line after 5-ASA, IMM, refractory or steroid dependent
In the Pipeline…

- Janus Kinus (JAK) Inhibition
  - Xeljanz (tofacitinib) – approved 3/2018

- anti-Interleukin 12/23
  - Stelara (ustekinumab)

- Hyperbaric Oxygen
  - Inpatient UC patients

- Sphingosine-1phosphate receptor modulation*

- New anti-leukocyte trafficking

- Phosphodiesterase 4 inhibitors*

*small molecules
Ozanimod (S1P-R agonist) - UC Patients With Mucosal Healing % (Endoscopy score of 0-1) at Week 8

![Graph showing mucosal healing percentages for different treatment groups.]

- **Placebo (N=65)**: 12% mucosal healing
- **Ozanimod 0.5 mg (N=65)**: 28% mucosal healing
- **Ozanimod 1 mg (N=67)**: 34% mucosal healing

Δ = 16% p = 0.03
Δ = 22% p = 0.002

Hyperbaric Oxygen

- Breathing 100% O2 while under increase atmospheric pressure (2.4)
- Blood hyper-oxygenated by dissolving O2 within the plasma
- Inflammatory mechanism related to O2- HIF
- Stimulate these pathways which turn off inflammation by hyper- saturating them with hyperbaric O2
# Hyperbaric Oxygen Treatment Outcomes

<table>
<thead>
<tr>
<th></th>
<th>HBOT + steroids (n=10)</th>
<th>Sham+ steroids (n=8)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 5 Clinical Remission</strong></td>
<td>50%</td>
<td>0%</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Day 10 Clinical Remission</strong></td>
<td>50%</td>
<td>0%</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Day 10 Clinical Response</strong></td>
<td>80%</td>
<td>25%</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Day 10 Endoscopic Remission</strong></td>
<td>50%</td>
<td>13%</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>In-hospital 2nd line therapy (biologics or colectomy)</strong></td>
<td>10%</td>
<td>63%</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>In-hospital colectomy</strong></td>
<td>0%</td>
<td>38%</td>
<td>0.07</td>
</tr>
</tbody>
</table>

What’s on the Horizon for Positioning Drugs in UC

- Small molecules vs biologics as 1st line agents
- Better understanding of how disease burden impacts choice of therapy (e.g., losing proteins with severe colitis)
- Combining drug classes
- Completely steroid-free UC treatment
CD Armamentarium

- **Anti-TNFs**
  - Remicade (infliximab)- CD, UC
  - Humira (adalimumumab)- CD, UC
  - Simponi (golimumumab)- UC
  - Cimizia (certolizumab)- CD

- **Anti-leukocyte trafficking**
  - Entivyo (vedolizumab)- CD, UC

- **Anti IL 12/23**
  - Stelara (ustekimumab)- CD
In the Pipeline…

- Integrin
  - Ertolizumab

- Stem Cells

- IL 23
  - Risankizumab

- JAK Inhibition
  - Upadacitinib
  - Filgotinib
Common- Loss of Response to anti-TNF therapy

Moderate to Severely Active IBD
Most Failing Immune modulators
Long Duration of Disease

ACCENT I\(^1\) Infliximab
CDAI 70 & 25% reduction
5mg/kg q8
54 weeks

CHARM\(^2\) Adalimumab
CDAI 70
40mg eow
56 weeks

PRECISE 2&3\(^3\,4\) Cert pegol
CDAI 100 & HBI
400mg q4
80 weeks

Is it a Dosing Issue??

- Questions we are asking is if we use higher doses of biologics would there be better efficacy and will there be less immunogenicity and longer duration of response???
CD (Gemini II): Entivyo (vedolizumab) Efficacy Summary

- **Induction Primary Endpoint**
  - Clinical Remission
  - CDAI-100 Response

- **Maintenance Primary Endpoint**
  - Clinical Remission Q8w
  - Clinical Remission Q4w

- **Maintenance Secondary Endpoint**
  - CDAI-100 Response Q8w
  - CDAI-100 Response Q4w
  - Corticosteroid-free Clinical Remission Q8w
  - Corticosteroid-free Clinical Remission Q4w
  - Clinical Remission at 80% Visits Q8w
  - Clinical Remission at 80% Visits Q4w

Risk Difference (%)

CD (Gemini II): Week 52 Remission & CDAI-100 Response by Prior anti-TNF Failure
Etrolizumab: Clinical Remission in All Comers & by anti-TNF status - Primary Endpoint at Week 10
Entivyo (vedolizumab) vs anti-TNFs: Differentiated Indications & Populations?

<table>
<thead>
<tr>
<th>anti-TNFs</th>
<th>Entivyo (vedolizumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe acute colitis</td>
<td>Anti-TNF refractory</td>
</tr>
<tr>
<td>Severe EIMs</td>
<td>Risk or with history opportunistic infection</td>
</tr>
<tr>
<td>Perianal CD</td>
<td>Risk or with history of malignancy</td>
</tr>
<tr>
<td></td>
<td>Elderly population</td>
</tr>
<tr>
<td></td>
<td>PSC ?</td>
</tr>
</tbody>
</table>
Cx601 Mesenchymal Stem Cells
Safe & Effective Treatment of
Complex Perianal Fistulas in CD

Aim
- To determine efficacy/safety of a single injection of Cx601 for complex perianal fistulas in CD observed at week 24 is maintained over 52 weeks

Methods
- Phase 3, randomized, double blind, placebo-controlled study
  - Single injection of Cx601 (n=70) vs. placebo (n=61)
  - All patients treated with 2 surgical procedures prior to randomization
- Primary endpoint: combined remission at week 24 (closure of external openings; absence of collections > 2cm of treated perianal fistulas (MRI)
- Secondary endpoints
  - Clinical remission and response at week 24
  - Combined remission at week 52

Results
- Cx601 vs. controls
  - Higher maintenance of combined remission at week 52 (56.3% vs. 38.6%; P=0.010)
  - Of those who achieved combined remission at week 24, greater proportion without relapse at week 52 (75.0% vs. 55.9%; P=0.052)
  - Higher clinical remission at week 52 (52.9 vs. 41.6%; P=0.013)

Stelara (ustekinumab) - Anti-IL 12/23

- FDA approved September 2016
- For moderate to severe CD
- **Dose**
  - **Initial weight-based IV dose:**
    - ≤ 55kg : 260mg IV
    - >55kg to 85kg: 390mg IV
    - >85 kg: 520mg IV
  - **Maintenance dose:**
    - 8 weeks after initial
    - 90mg SQ q 8 wks
Stelara (ustekinumab) Induces Clinical Response (CR-100) Through Week 8

**Clinical Response** *(≥ 100 Point CDAI Reduction)*

- **PBO**
- **UST 130 mg**
- **UST ~6 mg/kg**

- **UNITI-1**
  - Fraction of patients (%)
  - Time (Weeks)
  - Fraction of patients (%)
  - Time (Weeks)

- **UNITI-2**
  - Fraction of patients (%)
  - Time (Weeks)
  - Fraction of patients (%)
  - Time (Weeks)

*All p-values < 0.05, any UST vs. PBO

Stelara (ustekinumab) Induces Clinical Remission Through Week 8

**Clinical Remission** (CDAI < 150)

**UNITI-1**
- PBO
- UST 130 mg
- UST ~6 mg/kg

**UNITI-2**
- PBO
- UST 130 mg
- UST ~6 mg/kg

**All p-values < 0.05 except 130 mg dose at Week 3, any UST vs. PBO**

Primary Endpoint- Clinical Remission at Week 44 (52 Weeks of Treatment)

Number of subjects in clinical remission\textsuperscript{a,b} at Week 44; randomized subjects

- Placebo SC\textsuperscript{c} (N=131): 35.9%
- 90 mg SC q12w (N=129): 48.8% (P=0.040)
- 90 mg SC q8w (N=128): 53.1% (P=0.005)
- Combined (N=257): 51.0% (P=0.005)

Selective IL-23 Inhibitor BI 655066 (Risankizumab) Moderate to Severe CD

Clinical remission (CDAI <150) at Wk 12
94% exposure to ≥1 TNF antagonist

P-values vs PBO

P=0.31

P=0.025

Primary endpoint

P=0.049

<table>
<thead>
<tr>
<th>% patients</th>
<th>PBO</th>
<th>RKZ 200 mg</th>
<th>RKZ 600 mg</th>
<th>Pooled RKZ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15.4</td>
<td>24.4</td>
<td>36.6</td>
<td>30.5</td>
</tr>
<tr>
<td></td>
<td>6/39</td>
<td>10/41</td>
<td>15/41</td>
<td>25/82</td>
</tr>
</tbody>
</table>

- AEs were similar between RKZ and PBO
  - Fewer severe and serious AEs with RKZ 600 mg vs PBO (7% and 7% vs 23% and 31%, respectively)

Conclusions: Risankizumab was more effective than PBO for inducing clinical and endoscopic remission at 12 weeks and was well tolerated in patients with active CD.

AEs, adverse events; CD, Crohn’s disease; CDAI, Crohn’s Disease Activity Index; CDEIS, Crohn’s Disease Endoscopic Index of Severity; PBO, placebo; pts, patients; RKZ, risankizumab; TNF, tumor necrosis factor; wk, week; yrs, years

Upadacitinib (ABT-494)

- Safe & effective in induction of CD remission
- JAK-1 inhibitor selective

Methods:
- **Inclusion**-
  - CDAI 240-450 (moderate to severe)
  - Stool Frequency ≥ 2.5 daily
  - Abdominal pain ≥ 2
  - SES-CD ≥ 6 (>4 for ileal only disease)
  - 16 week induction
- **Clinical Remission**-
- **Endoscopic remission 12/16wk**-
  - SES-CD ≤4 & ≥2 pt decrease
- **Results**-
  - 220 randomized pts
  - Significant endoscopic remission at doses- 3-, 12- & 24 mgbid
  - Significant clinical remission at 6mg bid
  - AE w/JAK inh 1 case of VZV, 2 GI perforation, 2 CV events, 1 NMSC

![Graphs showing endoscopic and clinical remission at specified weeks](image-url)
Efficacy of Filgotinib, Selective JAK1 Inhibitor, Independent of Prior Anti-TNF Exposure

**Aims:**
- 20-week Phase 2 study evaluating efficacy and safety of filgotinib in patients with active Crohn’s disease
- Exploratory subgroup analysis of the first 10 weeks based on previous TNF exposure

**Methods:**
- Study Design

**Results:**
- Clinical remission (CDAI < 150) was induced at Week 10 in 47% of filgotinib patients versus 23% on placebo ($P=0.0077$)
- CDAI remission and response were higher in the filgotinib group irrespective of prior anti-TNF therapy
- Quality of life improved more in both filgotinib subgroups compared to placebo
- Filgotinib was safe and well-tolerated

**Conclusions:**
- Efficacy of filgotinib was shown in CD patients independently of their prior anti-TNF exposure
- Safety profile was also similar

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1 Responder status based on investigator calculation of CDAI score at week 10; non-responder = CDAI reduction of <100 points from baseline; responder = CDAI reduction of ≥100 points from baseline.

More data is needed…

- Head to head studies
- Biomarkers of response- serologic & mucosal
- New drugs
- Treat to target strategies
- Predicators of disease outcome i.e. Personalized Medicine
Final Thoughts…

- Very exciting time in the IBD world as our armamentarium expands.
- It is important to know that your treating GI MD will work with you to help find the right medication for you.
- Remember it may take some time for medications to take effect or even sometimes a medication may stop working.
- Management of IBD is a team approach it involves open communication with your GI MD and dedication to take your medications as prescribed working towards common goal of remission and an improved QOL.
Thank You