Importance of bowel barrier function in IBD

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Conflicts of interest

Jean-Frederic Colombel has served as consultant, advisory board member or speaker for AbbVie, Amgen, Boehringer-Ingelheim, Celgene Corporation, Celltrion, Enterome, Ferring, Genentech, Immunic, Janssen and Janssen, Lilly, Medimmune, Merck & Co., Pfizer, Protagonist, Second Genome, Seres, Shire, Takeda, Theradiag, Theravance Biopharma.

**Speaker for**
AbbVie, Ferring, Pfizer, Takeda, Shire

**Speaker’s bureau for**
Amgen

**Stock options:**
Intestinal Biotech Development, Genfit

**Research Grants:**
AbbVie, Takeda, Janssen and Janssen
The care of IBD: what did we achieve?
Progress over last two decades

**SONIC**
Colombel et al, NEJM 2010

**CALM**
Colombel et al, Lancet 2018

**GEMINI**

**UNITI**

**GEMINI**

**PURSUIT**

**OCTAVE**

- **Infliximab**
- **Adalimumab**
- **Golimumab**
- **Vedolizumab**
- **Ustekinumab**
- **Tofacitinib**
- **Adalimumab**
- **Golimumab**
- **Vedolizumab**
- **Ustekinumab**
- **Tofacitinib**

**Targan et al, NEJM 1997**

**CALM**
Sandborn et al, NEJM 2018

**UNITI**

**CALM**
We are plateauing
Pivotal Crohn’s Disease Trials: Anti-TNF Naïve Population with anchoring

CHARM – Adalimumab

<table>
<thead>
<tr>
<th>Week 4 Response</th>
<th>Week 54 Remission</th>
<th>Overall Remission Week 54</th>
</tr>
</thead>
<tbody>
<tr>
<td>60,0%</td>
<td>42,0%</td>
<td>25,2%</td>
</tr>
</tbody>
</table>

ACCENT I – Infliximab

<table>
<thead>
<tr>
<th>Week 2 Response</th>
<th>Week 54 Remission</th>
<th>Overall Remission Week 54</th>
</tr>
</thead>
<tbody>
<tr>
<td>58,5%</td>
<td>28,5%</td>
<td>16,7%</td>
</tr>
</tbody>
</table>

GEMINI II – Vedolizumab

<table>
<thead>
<tr>
<th>Week 6 Response</th>
<th>Week 52 Remission</th>
<th>Overall Remission Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>37,5%</td>
<td>47,2%</td>
<td>17,7%</td>
</tr>
</tbody>
</table>

UNITI-2 – Ustekinumab*

<table>
<thead>
<tr>
<th>Week 8 Response</th>
<th>Week 50 Remission</th>
<th>Overall Remission Week 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>58,0%</td>
<td>62,5%</td>
<td>36,3%</td>
</tr>
</tbody>
</table>

• VDZ Q4W or Q8W for maint.

• 130 mg with 47% and 6 mg/kg with 58% response rate
• 50 weeks 90 mg/Q12 at 56.9% and Q8 at 62.5%

Ungaro R et al. DDW 2019
IBD childhood mortality: 2019

Mortality in childhood-onset inflammatory bowel disease (IBD)

Deaths in childhood-onset IBD and matched general population reference individuals during 20 years of follow-up

Olen O et al. Gastroenterology 2019
Risk of lymphoma in IBD
Nation wide French cohort of 189289 patients

<table>
<thead>
<tr>
<th>Lymphoma Type</th>
<th>Exposed to Thiopurine Monotherapy vs Unexposed to Thiopurines or Anti-TNF Agents</th>
<th>Exposed to Anti-TNF Monotherapy vs Unexposed to Thiopurines or Anti-TNF Agents</th>
<th>Exposed to Combination Therapy vs Unexposed to Thiopurines or Anti-TNF Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
<td>Crude HR (95% CI)</td>
</tr>
<tr>
<td>All Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All lymphoma</td>
<td>2.06 (1.58-2.70)</td>
<td>2.60 (1.96-3.44)</td>
<td>1.57 (1.08-2.28)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>2.78 (1.45-5.33)</td>
<td>2.83 (1.37-5.84)</td>
<td>2.21 (0.92-5.35)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1.95 (1.45-2.62)</td>
<td>2.57 (1.90-3.49)</td>
<td>1.47 (0.97-2.22)</td>
</tr>
<tr>
<td>Patients With Incident IBD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All lymphoma</td>
<td>1.58 (0.84-3.00)</td>
<td>2.35 (1.16-4.75)</td>
<td>0.98 (0.39-2.48)</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

a Multivariable Cox model adjusted for baseline characteristics including sex, age, affiliation to Complementary Universal Health Insurance, IBD diagnosis and duration, exposure to methotrexate and aminosalicylates, comorbidities and time-dependent covariates including exposure to corticosteroids, and IBD-related hospitalizations and surgical procedures.
Main Risk of Novel JAK-Inhibitors
4-in-100 Treatment Years Zoster Reactivation

Crude incidence rates of herpes zoster (HZ) in the Tofacitinib Rheumatoid Arthritis (RA) Development Program (left of broken line) and in published studies of patients with RA treated with nonbiologic and biologic disease-modifying agents (right of broken line).

Impaired Response to Vaccines During IBD Therapy with Immunosuppressants

<table>
<thead>
<tr>
<th></th>
<th>Controlsa</th>
<th>Azathioprine</th>
<th>Infliximab</th>
<th>Combinedb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (N)</td>
<td>35</td>
<td>19</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>Dose/duration before baseline</td>
<td>N/A</td>
<td>2-2.5 mg/kg for at least 24 wk</td>
<td>5 mg/kg for at least 16 wk</td>
<td>Same</td>
</tr>
<tr>
<td>Response rate (P-value)</td>
<td>88.6% (N/A)</td>
<td>78.9% ($P = .43$)</td>
<td>57.7% ($P = .008$)</td>
<td>62.5% ($P = .02$)</td>
</tr>
<tr>
<td>Average antibody titer vs. baseline</td>
<td>5.71-fold increase</td>
<td>3.25-fold increase</td>
<td>2.69-fold increase</td>
<td>2.84-fold increase</td>
</tr>
</tbody>
</table>

*Control: anti-inflammatory, but not immunosuppressant therapy (e.g., mesalamine).
*Combined: azathioprine plus infliximab, same doses.
N/A: not applicable; IBD: inflammatory bowel disease (Crohn's disease and ulcerative colitis).
Source: Reference 7.

Reference: Gupta et al. Incidence and Risk Factors for Herpes Zoster Among Patients With Inflammatory Bowel Disease. Clinical Gastroenterology and Hepatology, Volume 4, Issue 12, 1483 - 1490
Update on Impact of COVID-19 in Inflammatory Bowel Disease Patients

Erica Brenner, MD (University of North Carolina at Chapel Hill)
Ryan Ungaro, MD MS (Icahn School of Medicine at Mount Sinai, New York)
Jean-Frederic Colombel, MD (Icahn School of Medicine at Mount Sinai, New York)
Michael Kappelman MD, MPH (University of North Carolina at Chapel Hill)

Brenner E et al. Gastroenterology in press.
## Multivariable Analysis

<table>
<thead>
<tr>
<th>Variable (Referent group)*</th>
<th>ICU/Vent/Death</th>
<th>Hospitalization or Death</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>(n = 517)</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.04 (1.01-1.06)</td>
<td>0.002</td>
<td>1.03 (1.01-1.04)</td>
</tr>
<tr>
<td>Male (Female)</td>
<td>1.20 (0.55-2.60)</td>
<td>0.65</td>
<td>1.38 (0.89-2.15)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease (ulcerative colitis/IBD unspecified)</td>
<td>0.76 (0.31-1.85)</td>
<td>0.54</td>
<td>0.84 (0.51-1.38)</td>
</tr>
<tr>
<td>Disease severity (remission)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active disease</td>
<td>1.14 (0.49-2.66)</td>
<td>0.76</td>
<td>1.96 (1.23-3.11)</td>
</tr>
<tr>
<td>Systemic corticosteroid (none)</td>
<td>6.87 (2.30-20.51)</td>
<td>&lt;0.001</td>
<td>6.46 (2.74-15.23)</td>
</tr>
<tr>
<td>TNF antagonist (none)</td>
<td>0.90 (0.37-2.17)</td>
<td>0.81</td>
<td>0.60 (0.38-0.96)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.55 (0.06-4.94)</td>
<td>0.59</td>
<td>2.38 (0.92-6.16)</td>
</tr>
<tr>
<td>BMI ≥ 30</td>
<td>2.00 (0.72-5.51)</td>
<td>0.18</td>
<td>1.18 (0.61-2.31)</td>
</tr>
<tr>
<td>Comorbidities (none)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.22 (0.45-3.26)</td>
<td>0.70</td>
<td>1.29 (0.76-2.20)</td>
</tr>
<tr>
<td>≥2</td>
<td>2.87 (1.05-7.85)</td>
<td>0.04</td>
<td>4.42 (2.16-9.06)</td>
</tr>
<tr>
<td>5-ASA/sulfasalazine (none)</td>
<td>3.14 (1.28-7.71)</td>
<td>0.01</td>
<td>1.77 (1.00-3.12)</td>
</tr>
</tbody>
</table>
What gastroenterologists want!

<table>
<thead>
<tr>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 10-40% of moderate-severe patients do not respond to any remission induction therapy</td>
<td>1. ~30% patients are primary non-responders (PNR) to anti-TNF biologics</td>
</tr>
<tr>
<td>2. 24–46% develop secondary loss of response within the first year after drug-induced remission or surgery</td>
<td>2. ~15-30% lose response (LOR) over time or become intolerant to anti-TNFs</td>
</tr>
<tr>
<td>3. ~10% stop maintenance treatment due to adverse drug reactions or tolerability issues</td>
<td>3. PNR patients are less likely to respond to 2nd-line therapy as compared to patients with prior loss of response or intolerance</td>
</tr>
</tbody>
</table>

**Physician ranked unmet needs in CD:**
1. Agents to maintain remission without immunosuppression
2. An effective treatment for fistulizing disease
3. Predicting response to biologic therapy
4. An effective cost-saving nonbiologic
5. Better activity measures in clinical trials
6. Drugs targeted for the mild patient population

**Physician ranked unmet needs in UC:**
1. A well-tolerated treatment for inducing remission quickly
2. Effective treatments for refractory patients
3. A non-steroid oral maintenance drug
4. Disease-modifying drugs
5. An effective cost-saving nonbiologic
6. Simple blood tests that indicate disease activity

Reference: Datamonitor, Gastroenterologist survey 2016
The expanding IBD pipeline: most targeting immune system!
Need for new therapeutic options in IBD

That allow the long-term treatment of gastrointestinal diseases without impairing the immune system

Concept of bowel permeability is central to many gastrointestinal diseases

Impaired bowel barrier function allows the microbiome to interact with the immune system
Dysfunction in each of these physiological components (dysbiosis, leaky gut, and inflammation) contributes in a mutually interdependent manner to IBD onset and exacerbation. (Vindigni et al. 2016)
Crohn’s disease – patient with increased bowel permeability have higher probability for relapse

Wyatt et al. Lancet 1993
CD/UC– high bowel permeability correlates with symptoms

Chang et al. Gastroenterology 2017
Early events in IBD: dysbiosis, altered IP?

Sartor B et al. Gastroenterology 2017
Presumed Trigger for IBD: Bacterial penetration through weakened tight junctions causes immune overstimulation

Enhanced *E. coli* LF82 Translocation through the Follicle-associated Epithelium in Crohn’s Disease is Dependent on Long Polar Fimbriae and CEACAM6 expression, and Increases Paracellular Permeability

Åsa V. Keita, Lina Yakymenko Alkaissi, Elin B. Holm, Stéphanie D. S. Heil, Benoit Chassaing, Arlette Darfeuille-Michaud, Derek M. McKay, Johan D. Söderholm
First degree relatives IBD patients have increased intestinal permeability

CD - Crohn’s disease (CD)
CDR - first degree relatives
CD-NR - non-blood relatives

The rationale: IBD as other immune-mediated diseases have a preclinical period that can be targeted
Crohn’s disease: Anti-microbial markers are elevated many years before diagnosis

Time-varying trajectory of antimicrobial antibodies*

Univariate analysis

* Derived using functional PCA in training data and evaluated in the testing data
Torres J et al. Gastroenterology 2020

Selected markers (multivariate analysis)

Multivariate analysis
The GEM project

Find 75 healthy subjects who go on to develop disease and compare with healthy subjects

75 new cases and 300 controls

Risk of Crohn’s in FDR = 0.3% per year

5000 healthy Sibs and Offspring

Completed

Being from multiplex family, intestinal permeability and microbiome diversity may be risk factors for development of CD

Courtesy K Croitoru
Increased IP precedes development of Crohn’s disease

Follow up of 1420 FDRs – 50 developed IBD

Risk of developing CD

LMR test

Courtesy K Croitoru

HR : 3.03 CI (1.94-5.63)
Discussion: Potential use in Crohn’s Disease

01 Mild CD disease
• The “mesalazine” of CD?

02 Post-operative setting
• Endpoint: avoid recurrence of local disease

03 Maintenance of remission in CD
• Monotherapy in remission
• Combination therapy in active disease

04 Prevention?