IBD : New Therapies, Covid, and Vaccination

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IBD Treatment: Old Drug – New Way

- Budesonide MMX (Cortiment): steroid released specifically in colon and can reach distal colon/rectum – reduced systemic absorption and toxicity.

![Image showing MMX technology release throughout the gastrointestinal tract. The gastro-resistant coating avoids the release of the drug until the tablet is exposed to a pH ≥ 7, normally reached in the terminal ileum. After reaching this site, the activity of the tablet core results in a homogeneous and prolonged exposure of the whole colonic mucosa to the embedded drug.]

IBD Treatment: Old Drug – New Way

• Current Intravenous (IV) Route, will be available with **Subcutaneous (SC)** Route:
  – **Infliximab** (anti-TNF)
  – **Vedolizumab** (anti-integrin)
Stelara (Ustekinumab / IL12-23 inhibitor) for UC

- Previously indicated in Crohn’s
- Approved by FDA for additional indication with Ulcerative Colitis patients Oct 2019
- HSA approved additional indication in UC patients Aug 2020

<table>
<thead>
<tr>
<th>Product Name</th>
<th>STELARA CONCENTRATE FOR SOLUTION FOR INFUSION 130MG/26ML</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>STELARA SOLUTION FOR INJECTION 45MG/ 0.5ML, 90MG/1ML</td>
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<tr>
<td></td>
<td>STELARA SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE 45 MG/0.5ML, 90 MG/1ML</td>
</tr>
<tr>
<td>Active Ingredient</td>
<td>Ustekinumab</td>
</tr>
<tr>
<td>Product Registrant</td>
<td>JOHNSON &amp; JOHNSON PTE. LTD.</td>
</tr>
<tr>
<td>Date of Approval</td>
<td>17/08/2020</td>
</tr>
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</table>

**Indications:**

STELARA® is indicated for the treatment of adult patients with moderately to severely active *ulcerative colitis* who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.
Oral Tofacitinib – HSA approved this year

- JAK (Janus Kinase) Inhibitor
- Significant difference in achieving clinical remission and endoscopic (mucosal) healing in Ulcerative Colitis
- Small molecules (Not Biologics)

Sandborn W. n engl j med 376;18
## Differences: Biologics vs Small Molecules

<table>
<thead>
<tr>
<th>Biologics</th>
<th>Small Molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Complex Structure</td>
<td>Small Simple Structure</td>
</tr>
<tr>
<td>Immunogenic</td>
<td>Non Immunogenic</td>
</tr>
<tr>
<td>Produced in living cell culture</td>
<td>Chemical Synthesis</td>
</tr>
<tr>
<td>Injection (Intravenous or Subcutaneous)</td>
<td>Oral</td>
</tr>
</tbody>
</table>
4-year Safety Data

Table 4. IRs of Adverse Events of Special Interest in the Maintenance and Overall Cohorts

<table>
<thead>
<tr>
<th></th>
<th>Maintenance cohort</th>
<th>Overall cohort (induction + maintenance + OLE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 198)</td>
<td>Tofacitinib 5 mg BID (n = 198)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>IR (95% CI)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>2 (1.0)</td>
<td>1.9 (0.2–7.0)</td>
</tr>
<tr>
<td>HZ</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Ols²</td>
<td>1 (0.5)</td>
<td>1.0 (0.0–5.4)</td>
</tr>
<tr>
<td>Ols (excluding HZ)²</td>
<td>0 (0.0)</td>
<td>0.0 (0.0–3.6)</td>
</tr>
<tr>
<td>Malignancy (excluding NMSC)²</td>
<td>1 (0.5)</td>
<td>0.0 (0.0–3.6)</td>
</tr>
<tr>
<td>NMSC²</td>
<td>1 (0.5)</td>
<td>1.0 (0.0–5.4)</td>
</tr>
<tr>
<td>MACE²</td>
<td>0 (0.0)</td>
<td>0.0 (0.0–3.6)</td>
</tr>
<tr>
<td>GI perforations²</td>
<td>1 (0.5)</td>
<td>1.0 (0.0–5.4)</td>
</tr>
</tbody>
</table>

Safety similar to biologics, except Herpes Zoster (occurring in 5.6% patients)

Sandborn W. Clinical Gastroenterology and Hepatology 2019;17:1541–1550
IBD Treatment Pipeline

- **IL-36 inhibitors**: Speselimab
- **Anti-IL-23 agents**: Risankizumab, Mirikizumab, Brazikumab, Guselkumab
- **Anti-adhesion molecules**: Etrolizumab, Abrilumab, Carotegrast methyl, Ontamalimab
- **PDE inhibitors**: Apremilast
- **S1P receptor modulators**: Ozanimod, Etrasimod
- **JAK inhibitors**: Filgotinib, Upadacitinib, TD-1473, Deucravacitinib

Approved drugs
IBD Treatment Pipeline

- **Selective IL-23 Inhibitors**:
  - Mirikizumab
  - Risankizumab
  - Brazikumab
  - Guselkumab

- **JAK Inhibitors**:
  - **Upadacitinib** (Selective JAK1 inhibitors)
  - **Filgotinib** (Selective JAK1 inhibitors)
  - **Deucravacitinib** (Selective TYK2)
  - **TD-1473** (Gut selective Pan-JAK inhibitor)
IBD Treatment Pipeline

- **Anti Trafficking Agents**:
  - **Anti Adhesion Therapies**:
    - **Etrolizumab** ($\alpha_4\beta_7$ and $\alpha E\beta_7$ inhibitor)
    - AIM 300 (alpha 4 inhibitor)
    - PF-00547659 (MAD-CAM-1 inhibitor)
  - **S1P Receptor Modulators**:
    - **Etrasimod** (S1P1, S1P4, S1P5)
    - **Ozanimod** (S1P1, S1P5)
Covid-19 and GI symptoms

- Meta-analysis of 78 studies and >12,000 patients

- Prevalence of GI symptoms:
  - Diarrhea was 12.4% (95% CI, 8.2% to 17.1%)
  - Nausea and/or vomiting, 9.0% (95% CI, 5.5% to 12.9%)
  - Loss of appetite, 22.3% (95% CI, 11.2% to 34.6%)
  - Abdominal pain, 6.2% (95% CI, 2.6% to 10.3%)

• ACE2 and TMPRSS2 is also expressed in GI tract.
• However, ACE2 is not increased in patients with IBD and with immunosuppressants/biologics
Risk of contracting Covid-19

- Studies from China, Italy, Spain, France, and USA did not find increased risk for contracting Covid-19 in IBD patients.
- Adherence with hygienic, distancing, or shielding measures in IBD patients
- More recent population based study from Sweden showed increased Covid-19 in IBD patients compared to general population: 1.21% vs 0.97%; HR (95% CI 1.13-1.33)
Outcome IBD patients with Covid

Italian Group Study: Covid infection in IBD patients

Outcomes comparable with general population

Figure 1 Negative outcomes of COVID-19 in the overall IBD cohort, and for patients with Crohn’s disease (CD) and UC. CPAP, continuous positive airway pressure.

Sweden nationwide population based study
Increased hospital admission for Covid-19 in IBD
But risk of getting severe Covid-19 is not increased in IBD patients

Ludvigsson JF. United European Gastroenterol J. 2021;1–16.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N events (%)</th>
<th>Time at risk (years)</th>
<th>Incidence rate (95% CI) per 1000 PY</th>
<th>HR^a (95% CI)</th>
<th>HR^b (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IBD</td>
<td>Comparators</td>
<td>IBD</td>
<td>Comparators</td>
<td>HR^a</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>179 (0.27%)</td>
<td>33,207</td>
<td>3.4 (3.1–3.7)</td>
<td>1.45 (1.22–1.72)</td>
<td>1.43 (1.19–1.72)</td>
</tr>
<tr>
<td>Severe COVID-19^c</td>
<td>65 (0.10%)</td>
<td>33,329</td>
<td>1.2 (1.1–1.4)</td>
<td>1.24 (0.92–1.66)</td>
<td>1.11 (0.81–1.52)</td>
</tr>
<tr>
<td>Intensive care admission</td>
<td>18 (0.03%)</td>
<td>33,239</td>
<td>0.5 (0.4–0.7)</td>
<td>0.96 (0.57–1.60)</td>
<td>0.98 (0.54–1.75)</td>
</tr>
<tr>
<td>Death due to COVID-19</td>
<td>53 (0.08%)</td>
<td>33,242</td>
<td>0.8 (0.7–1.0)</td>
<td>1.40 (1.00–1.96)</td>
<td>1.20 (0.83–1.72)</td>
</tr>
</tbody>
</table>
Italian Group: Covid infection in IBD patients

- Risk factors for severe Covid-19 (pneumonia), and related mortality: Old age, multiple co-morbid, Active IBD, Corticosteroids

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>5.87</td>
<td>1.15 to 29.66</td>
<td>0.03</td>
</tr>
<tr>
<td>CCI score &gt;1</td>
<td>2.91</td>
<td>1.06 to 9.21</td>
<td>0.04</td>
</tr>
<tr>
<td>UC diagnosis</td>
<td>2.72</td>
<td>1.06 to 6.99</td>
<td>0.03</td>
</tr>
<tr>
<td>Active IBD</td>
<td>10.25</td>
<td>2.11 to 49.73</td>
<td>0.003</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>4.94</td>
<td>0.95 to 25.55</td>
<td>0.05</td>
</tr>
<tr>
<td>Thiopurines</td>
<td>1.21</td>
<td>0.22 to 6.40</td>
<td>0.82</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>1.18</td>
<td>0.47 to 2.97</td>
<td>0.71</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>0.53</td>
<td>0.16 to 1.73</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Bold indicates p < 0.05.
CCI, Charlson Comorbidity Index; TNF, tumour necrosis factor.

Vaccination in IBD patients with Immunosuppressive therapy may still work – although with reduced efficacy.

ICARUS-IBD Study

- USA Study – just published
- Small number of IBD patients, most were on biologics
- Similar Serological (Antibody) Response in IBD patients compared to non-IBD
International Consensus Statement

- IBD patients should be vaccinated against Covid-19 at the earliest opportunity
- Covid-19 vaccination is unlikely to cause a flare in IBD
- Covid-19 vaccination should not be deferred due to immune-modifying therapies
- Covid-19 vaccine efficacy may be decreased with steroids, but vaccination should not be deferred
- Messenger RNA, Inactivated virus, and Recombinant Vaccines are safe in IBD patients

IOIBD Consensus. 2021
Thank You