IBD : New Therapies, Covid, and Vaccination

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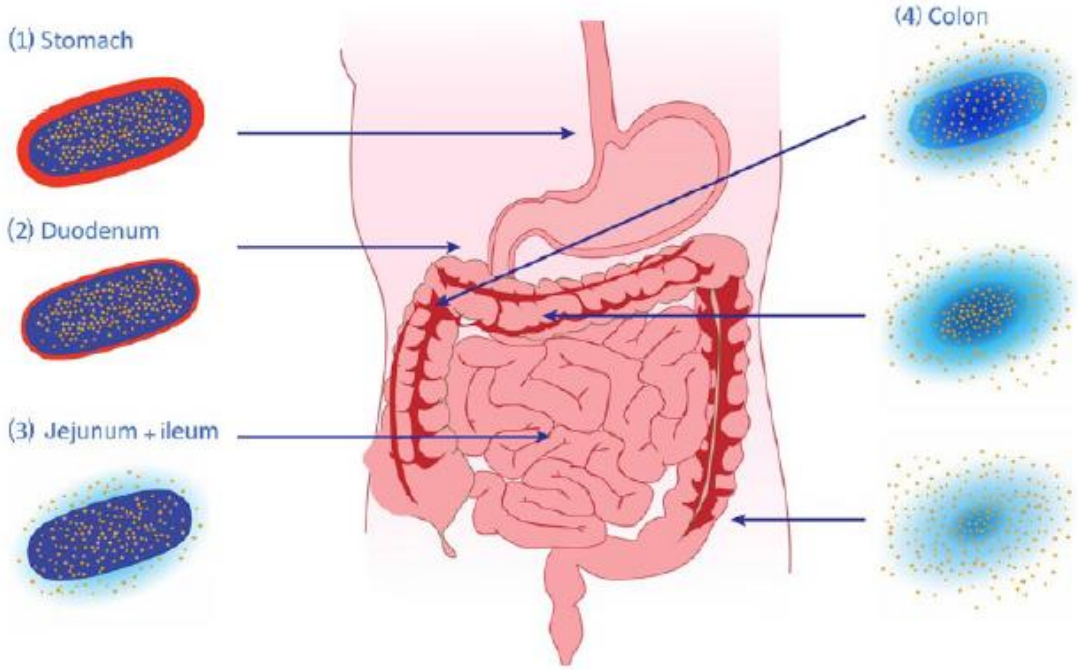
IBD Treatment : Old Drug – New Way

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



Nardeli S et al 2017. Ther Adv Gastroenterol 2017, Vol. 10(7) 545–552

Figure 1. MMX® technology release throughout the gastrointestinal tract. The gastro-resistant coating (1–2) avoids the release of the drug until the tablet is exposed to a pH ⩾ 7, normally reached in the terminal ileum (3). 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 (4).

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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

Product Name	**STELARA CONCENTRATE FOR SOLUTION FOR INFUSION 130MG/26ML** **STELARA SOLUTION FOR INJECTION 45MG/ 0.5ML, 90MG/1ML** **STELARA SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE 45 MG/0.5ML, 90 MG/1ML**
Active Ingredient	Ustekinumab
Product Registrant	JOHNSON & JOHNSON PTE. LTD.
Date of Approval	17/08/2020
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.	

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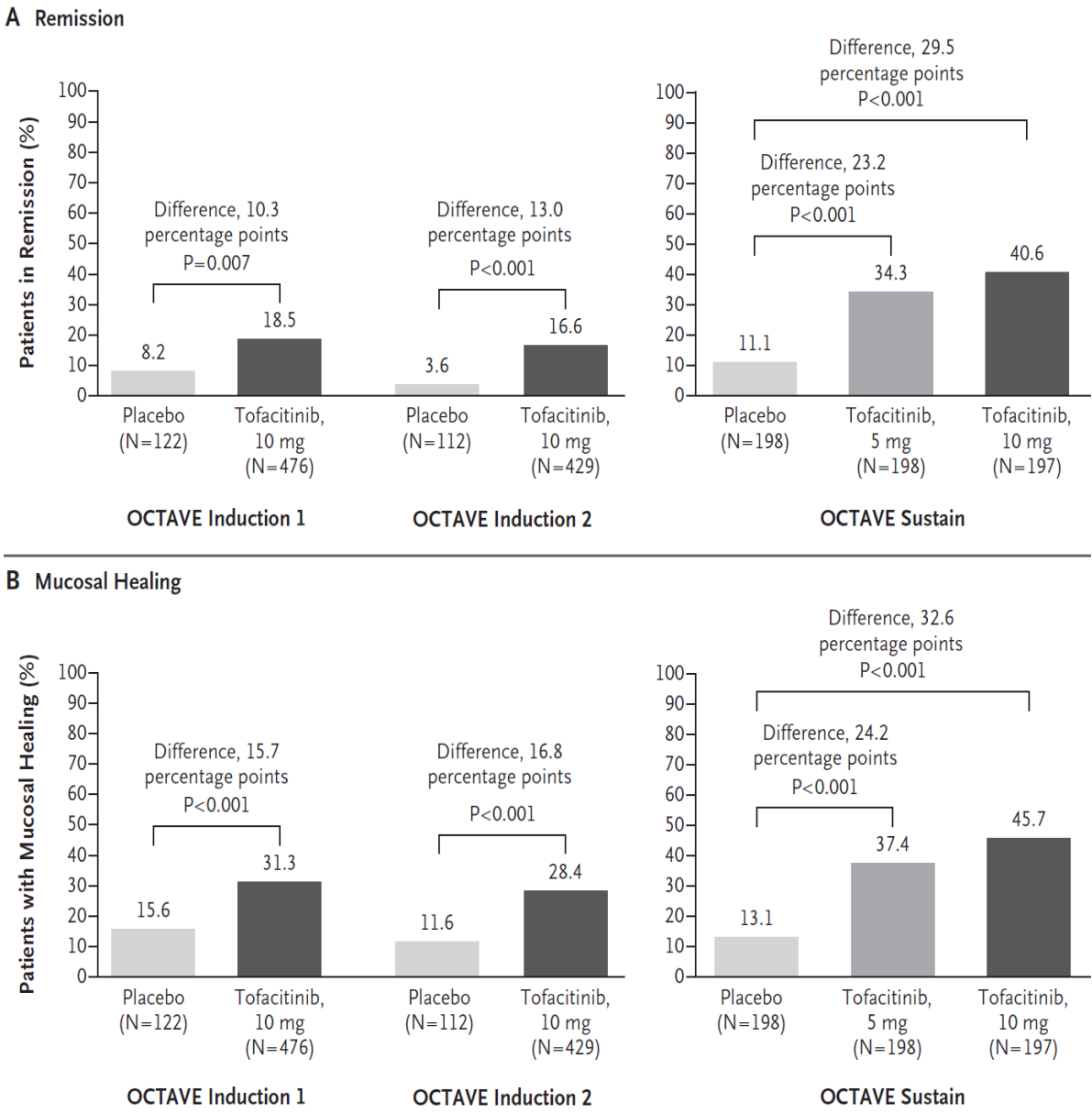
Oral Tofacitinib – HSA approved this year

- 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

Biologics	Small Molecules
Large Complex Structure	Small Simple Structure
Immunogenic	Non Immunogenic
Produced in living cell culture	Chemical Synthesis
Injection (Intravenous or Subcutaneous)	Oral

4-year Safety Data

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

	Maintenance cohort			Overall cohort (induction + maintenance + OLE)
	Placebo (n = 198)	Tofacitinib 5 mg BID (n = 198)	Tofacitinib 10 mg BID (n = 196)	Tofacitinib all (n = 1157)
	n (%) IR (95% CI)	n (%) IR (95% CI)	n (%) IR (95% CI)	n (%) IR (95% CI)
Serious infections	2 (1.0) 1.9 (0.2–7.0)	2 (1.0) 1.4 (0.2–4.9)	1 (0.5) 0.6 (0.0–3.5)	33 (2.9) 2.0 (1.4–2.8)
HZ	1 (0.5) 1.0 (0.0–5.4)	3 (1.5) 2.1 (0.4–6.0)	10 (5.1) 6.6 (3.2–12.2)	65 (5.6) 4.1 (3.1–5.2)
OIs[a]	1 (0.5) 1.0 (0.0–5.4)	2 (1.0) 1.4 (0.2–4.9)	4 (2.0) 2.6 (0.7–6.7)	21 (1.9) 1.3 (0.8–2.0)
OIs (excluding HZ)[a]	0 (0.0) 0.0 (0.0–3.6)	0 (0.0) 0.0 (0.0–2.5)	0 (0.0) 0.0 (0.0–2.4)	4 (0.4) 0.2 (0.1–0.6)
Malignancy (excluding NMSC)[a]	1 (0.5) 1.0 (0.0–5.4)	0 (0.0) 0.0 (0.0–2.5)	0 (0.0) 0.0 (0.0–2.4)	11 (1.0) 0.7 (0.3–1.2)
NMSC[a]	1 (0.5) 1.0 (0.0–5.4)	0 (0.0) 0.0 (0.0–2.5)	3 (1.5) 1.9 (0.4–5.6)	11 (1.0) 0.7 (0.3–1.2)
MACE[a]	0 (0.0) 0.0 (0.0–3.6)	1 (0.5) 0.7 (0.0–3.8)	1 (0.5) 0.6 (0.0–3.5)	4 (0.4) 0.2 (0.1–0.6)
GI perforations[a]	1 (0.5) 1.0 (0.0–5.4)	0 (0.0) 0.0 (0.0–2.5)	0 (0.0) 0.0 (0.0–2.4)	3 (0.3) 0.2 (0.0–0.5)

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

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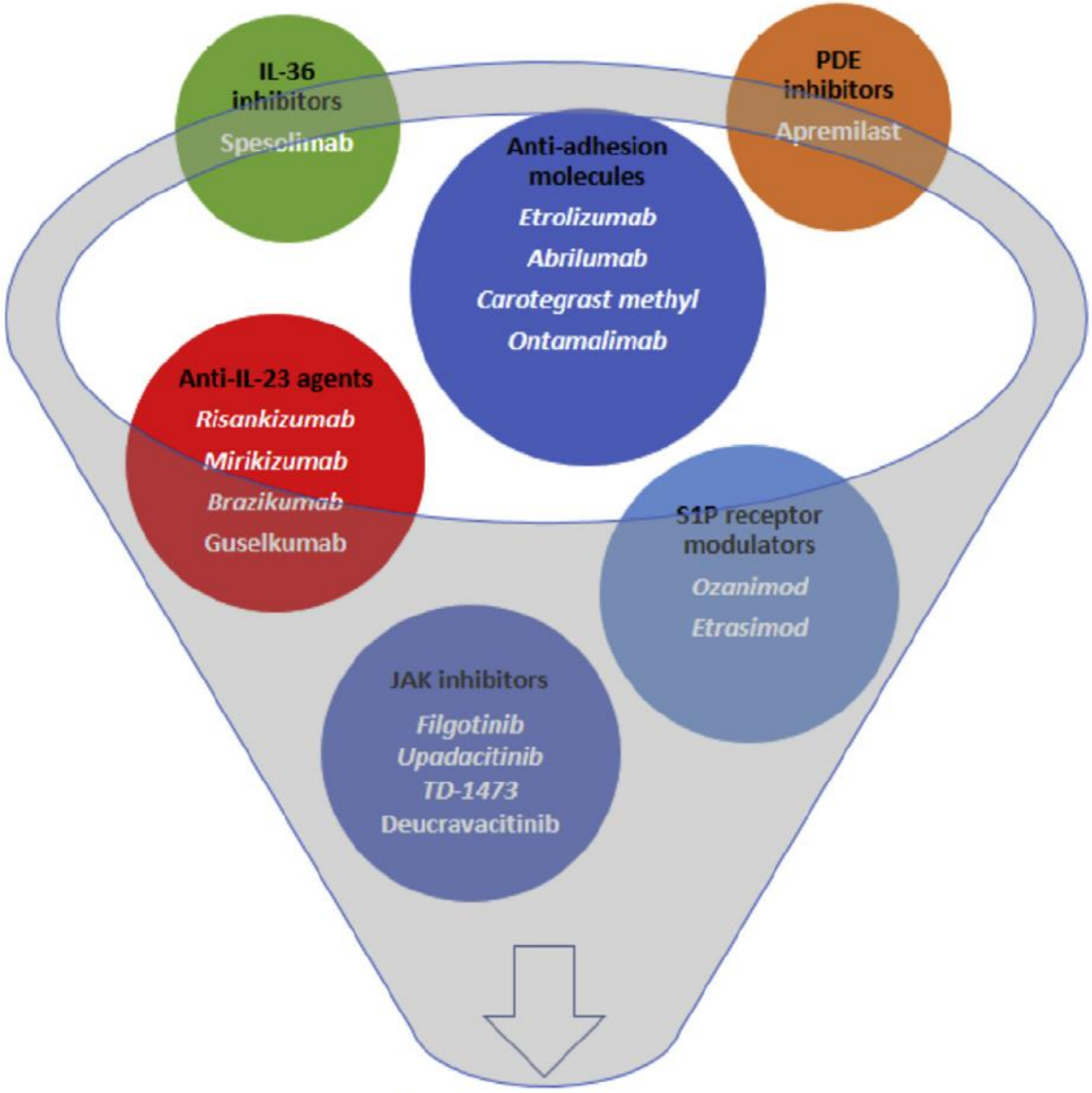
Sandborn W. Clinical Gastroenterology and Hepatology 2019;17:1541–1550

IBD Treatment Pipeline



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 (**α4β7 and αEβ7 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%)

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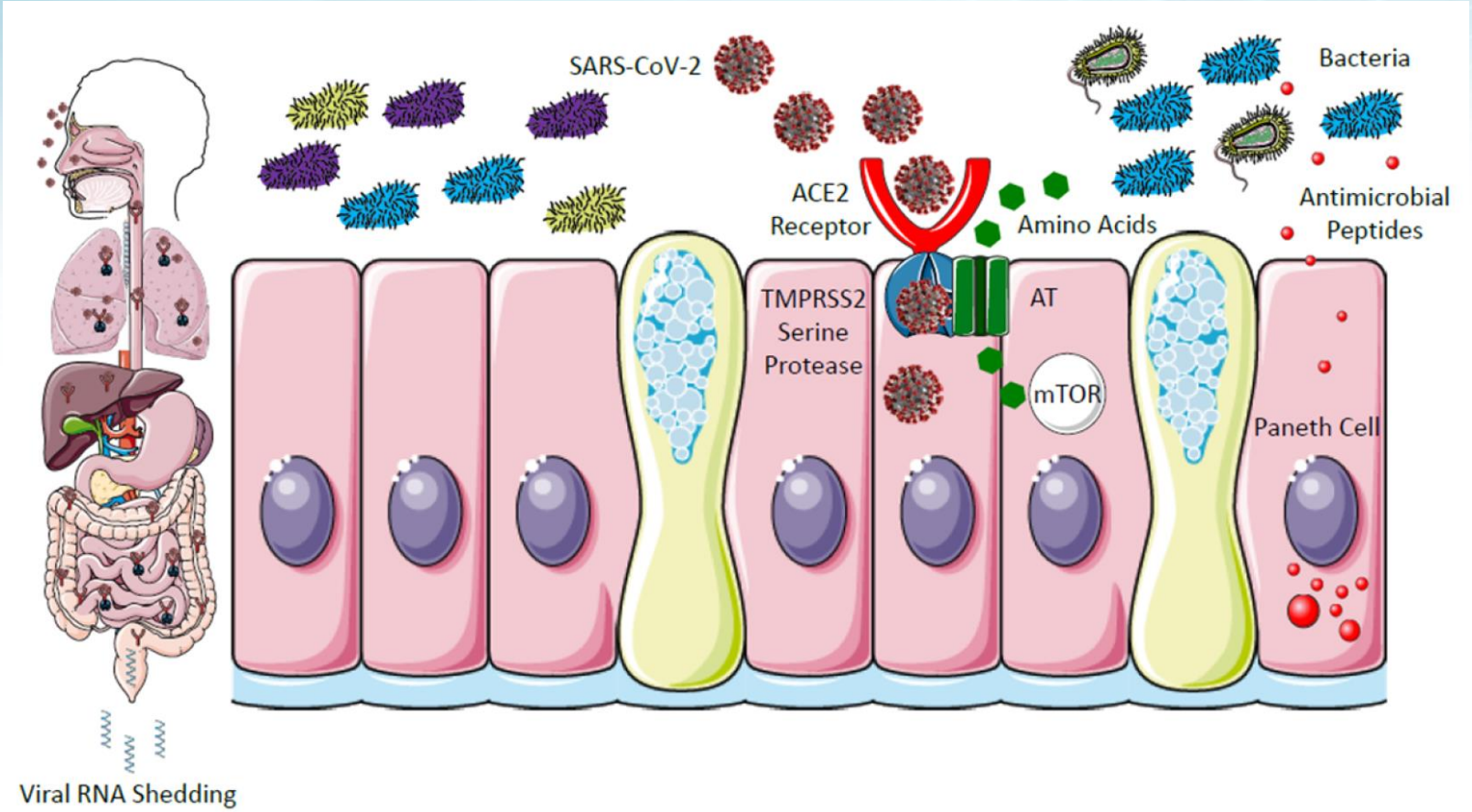
Tariq R, et al. Mayo Clin Proc. 2020;95(8):1632-1648

Covid and GI Tract Involvement



- ACE2 and TMPRSS2 is also expressed in GI tract.
- However, ACE2 is not increased in patients with IBD and with immunosuppressants/ biologics

D'Amico F et al. *Clinical Gastroenterology and Hepatology* (2020)
Burgueno JF. Inflamm Bowel Dis • Volume 26, Number 6, June 2020

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)

TABLE 2 Risk of COVID-19 in patients with IBD and matched general population comparators from 1 February to 31 July 2020 (*n* IBD/*n* comparators = 67,292/297,910)

	N events (%)		Time at risk (years)		Incidence rate (95% CI) per 1000 PY			
Outcome	IBD	Comparators	IBD	Comparators	IBD	Comparators	HR[a] (95% CI)	HR[b] (95% CI)
Secondary outcomes								
Main outcomes combined	202 (0.30%)	558 (0.19%)	33,206	147,297	6.1 (5.2–6.9)	3.8 (3.5–4.1)	1.42 (1.21–1.68)	1.38 (1.16-1.64)
All-cause mortality	486 (0.72%)	1265 (0.42%)	33,242	147,405	14.6 (13.3–15.9)	8.6 (8.1–9.1)	1.31 (1.17–1.45)	1.19 (1.07–1.33)
Any COVID-19	811 (1.21%)	2890 (0.97%)	33,093	146,880	24.5 (22.8–26.2)	19.7 (19.0–20.4)	1.23 (1.13–1.33)	1.21 (1.12–1.31)

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Ludvigsson JF. United European Gastroenterol J. 2021;1–16
Aziz M. et al. Inflamm Bowel Dis. 2020

Outcome IBD patients with Covid

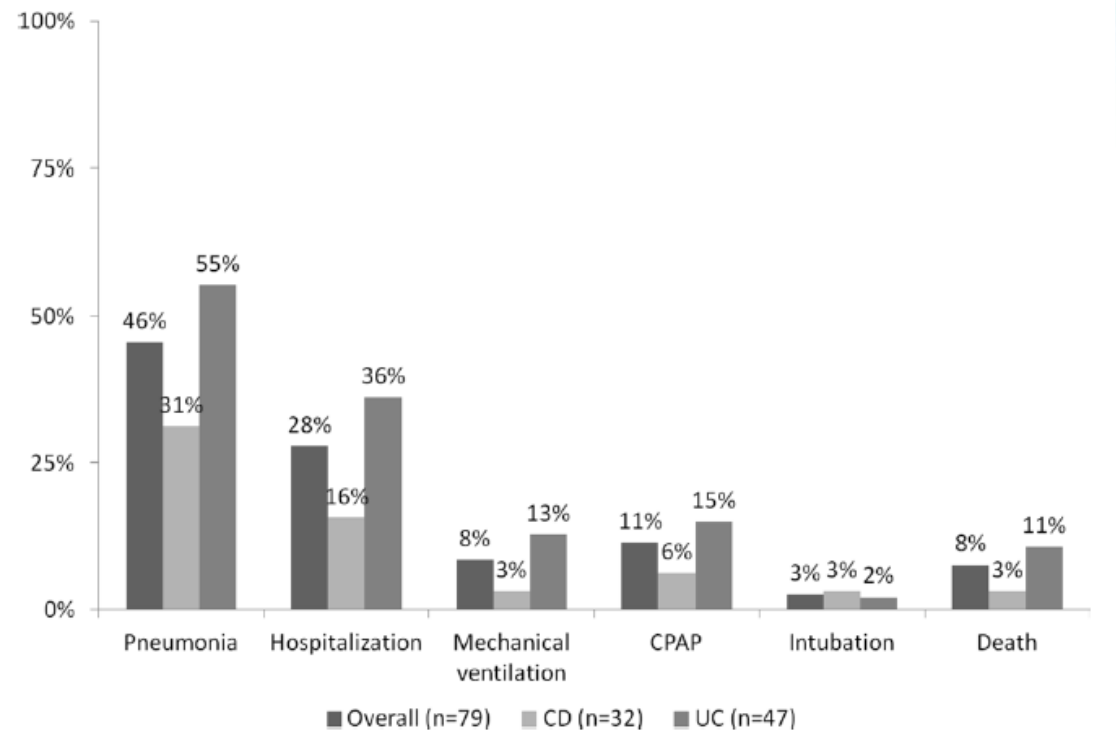

Figure 1 Negative outcomes of COVID-19 in the overall IBD cohort, and for patients with Crohn's disease (CD) and UC. CPAP, continuous positive airway pressure.

Italian Group Study : Covid infection in IBD patients

Outcomes comparable with general population

Bezzio C, et al. Gut 2020;**0**:1–5. doi:10.1136/gutjnl-2020-321411

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	N events (%)		Time at risk (years)		Incidence rate (95% CI) per 1000 PY			
Outcome	IBD	Comparators	IBD	Comparators	IBD	Comparators	HR[a] (95% CI)	HR[b] (95% CI)
Main outcomes								
Hospital admission	179 (0.27%)	500 (0.17%)	33,207	147,299	5.4 (4.6–6.2)	3.4 (3.1–3.7)	1.45 (1.22–1.72)	1.43 (1.19–1.72)
Severe COVID-19[c]	65 (0.10%)	183 (0.06%)	33,239	147,389	2.0 (1.5–2.4)	1.2 (1.1–1.4)	1.24 (0.92–1.66)	1.11 (0.81–1.52)
Intensive care admission	18 (0.03%)	80 (0.03%)	33,239	147,389	0.5 (0.3–0.8)	0.5 (0.4–0.7)	0.96 (0.57–1.60)	0.98 (0.54–1.75)
Death due to COVID-19	53 (0.08%)	122 (0.04%)	33,242	147,405	1.6 (1.2–2.0)	0.8 (0.7–1.0)	1.40 (1.00–1.96)	1.20 (0.83–1.72)

- 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

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

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 2 Association between potential risk factors and COVID-19-related pneumonia

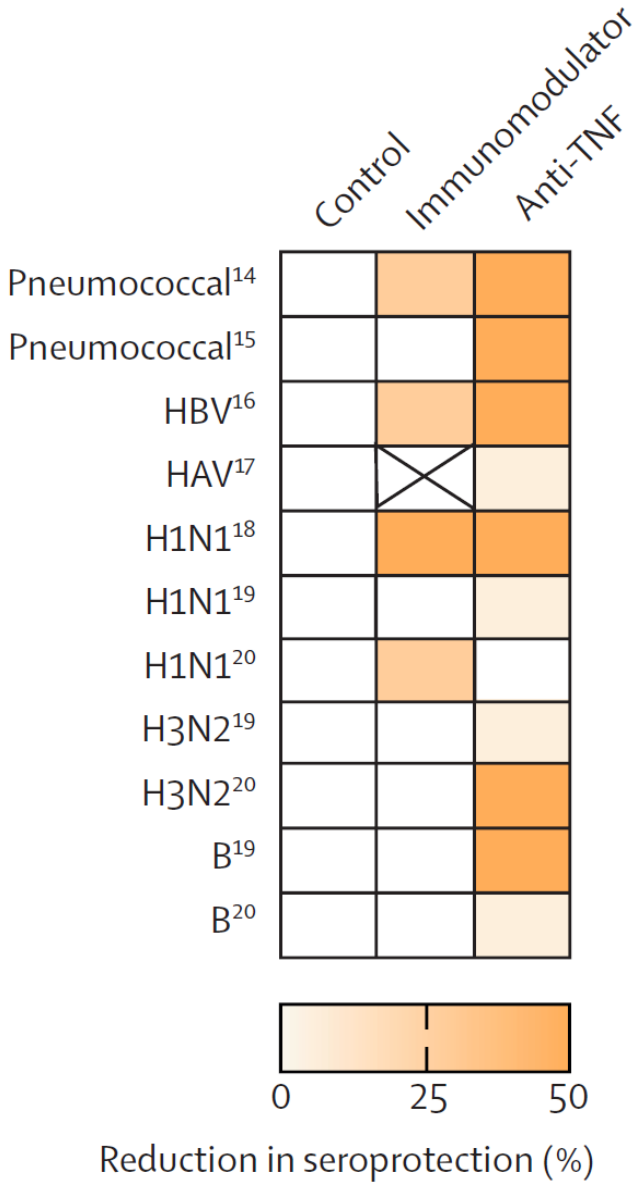
Risk factor	OR	95% CI	P value
Age >65 years	5.87	1.15 to 29.66	**0.03**
CCI score >1	2.91	1.06 to 9.21	**0.04**
UC diagnosis	2.72	1.06 to 6.99	**0.03**
Active IBD	10.25	2.11 to 49.73	**0.003**
Corticosteroids	4.94	0.95 to 25.55	0.05
Thiopurines	1.21	0.22 to 6.40	0.82
Anti-TNF	1.18	0.47 to 2.97	0.71
Vedolizumab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

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

Bezzio C, et al. Gut 2020;**0**:1–5. doi:10.1136/gutjnl-2020-321411

Effect of IBD Meds on Vaccination

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



Alexander JL. *Lancet Gastroenterol Hepatol* 2021; 6: 218–24

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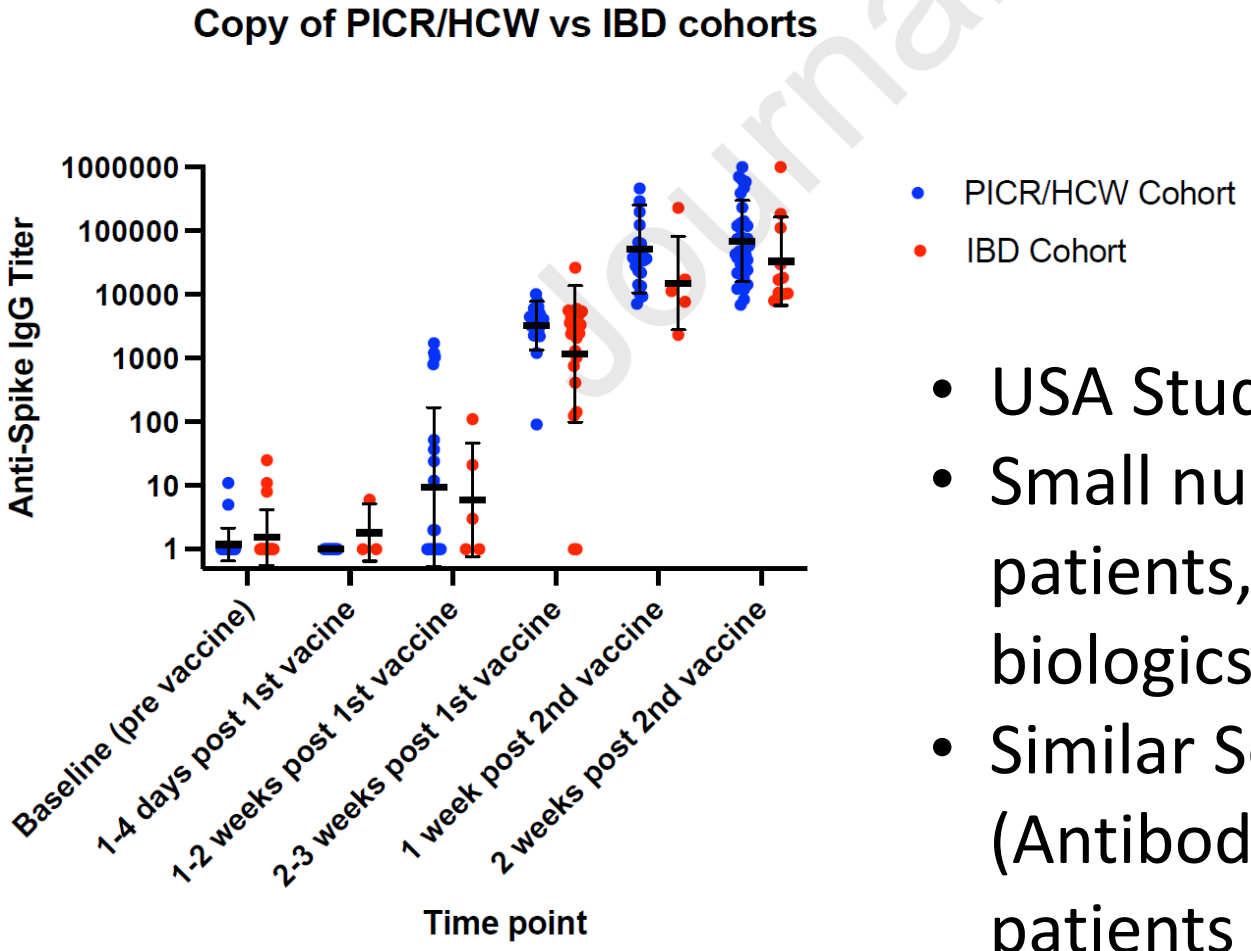
ICARUS-IBD Study



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

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Wong SY. Gastroenterology. 2021 Apr 19;S0016-5085(21)00648-X

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

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Thank You