IBD Research Review™

Making Education Easy

Issue 64 - 2022

In this issue:

Abbreviations used in this issue:

AOI = appendiceal orifice inflammation; **CCI** = Charlson Comorbidity Index; **CD** = Crohn's disease; **CDAI** = Crohn's Disease Activity Index; **CRC** = colorectal cancer; **FMT** = faecal microbiota transplant; **HR** = hazard ratio; **IBD** = inflammatory bowel disease; **NSAID** = nonsteroidal anti-inflammatory drug; **TNF** = tumour necrosis factor; **UC** = ulcerative colitis.

Welcome to issue 64 of IBD Research Review.

We begin this issue with research suggesting that the frequently noted association between NSAID exposure and IBD exacerbation may be due to residual bias. This is followed by research reporting that AOI (appendiceal orifice inflammation) appears to facilitate UC diagnosis in patients with diffuse lesions in the distal colorectum, but does not influence treatment outcomes. Promising findings are reported for a phase 2 trial of obefazimod (ABX464), a small molecule that selectively upregulates miR-124 in immune cells, in the treatment of moderately or severely active UC. The final issue for this year concludes with a report of long-term effectiveness and safety outcomes for participants from the ADMIRE-CD trial of darvadstrocel for perianal fistulising CD.

Thank you for your comments and feedback during the year. We look forward to bringing you more interesting research in 2023.

Kind Regards,

Associate Professor Crispin Corte
crispin.corte@researchreview.com.au

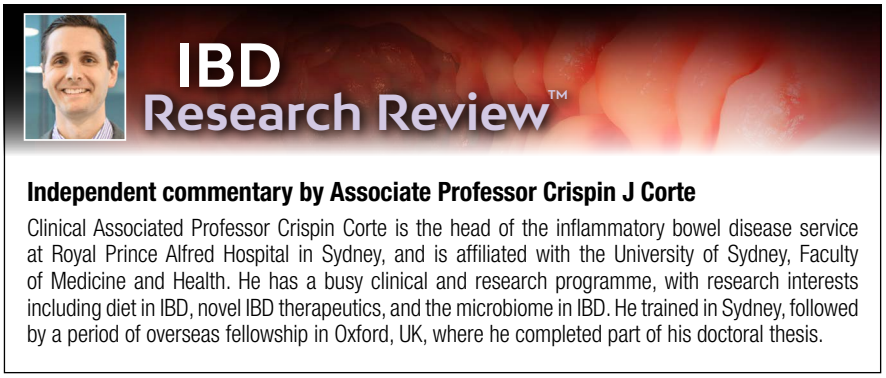
The association between nonsteroidal anti-inflammatory drug use and inflammatory bowel disease exacerbations: a true association or residual bias?

Authors: Cohen-Mekelburg S et al.

Summary: These researchers explored the role of NSAIDs on variations in the likelihood of IBD exacerbations in a cohort of patients with (n=15,705) or without (n=19,326) NSAID exposure. A Cox proportional hazards model suggested there was an association between NSAID exposure and IBD exacerbation (HR 1.24 [95% CI 1.16–1.33]), but there was a similar association in the NSAID-exposed arm prior to NSAID exposure (1.30 [1.21–1.39]). A self-controlled case series analysis (n=3968) revealed that patients both exposed to NSAIDs and exacerbation had similar exacerbation rates during the year prior to exposure, 2–6 weeks postexposure and 6 weeks to 6 months postexposure, but a higher rate during 0–2 weeks postexposure, suggestive of potential confounding by reverse causality.

Comment: This is a topic I discuss several times per week. There is a lot written about the association of NSAIDs and flares of IBD on the basis of ageing and scant literature. The changes in attitudes towards opioid analgesia, changes in prescribing regulations, and the association of poor outcomes in IBD in patients requiring opioid analgesia are clear. Furthermore, pain is a major symptom in patients with IBD, so we want to be very clear on the relationship of this important class of analgesics/anti-inflammatories to IBD flares before we 'rule them out'. This paper importantly establishes that whilst an increased flare rate is identified in those exposed to NSAIDs, the same can be seen in the time periods prior to exposure, and distantly after exposure, indicating confounding – possibly from reverse causality. Seventy-five percent of patients in this study (>35,000) who were prescribed an NSAID did not have a flare in the median 5.9 years of follow-up.

Reference: Am J Gastroenterol 2022;117:1851–7
Abstract



Independent commentary by Associate Professor Crispin J Corte

Clinical Associated Professor Crispin Corte is the head of the inflammatory bowel disease service at Royal Prince Alfred Hospital in Sydney, and is affiliated with the University of Sydney, Faculty of Medicine and Health. He has a busy clinical and research programme, with research interests including diet in IBD, novel IBD therapeutics, and the microbiome in IBD. He trained in Sydney, followed by a period of overseas fellowship in Oxford, UK, where he completed part of his doctoral thesis.

Significance of diagnosis and prognosis for appendiceal orifice inflammation in ulcerative colitis

Authors: Deng P et al.

Summary: The importance of AOI in UC diagnosis and prognosis was evaluated in this prospective, observational study of real-world patients who underwent AOI and controls who did not, followed for 1 year. The positive UC diagnosis rate was higher in patients with endoscopic diffuse inflammatory changes in the distal colorectum accompanied by AOI than in those without (96.5% vs. 78.0%). AOI was 95.2% specific and 28.3% sensitive for diagnosing UC. However, neither modified Mayo score nor Baron grading differed significantly between the AOI and control groups, suggesting that treatment outcomes are not affected by AOI.

Comment: This single-centre observational study from Western China looked at patients with colitis (who had not had appendicectomy) and compared outcomes in those with and without a discontinuous peri-appendiceal patch of inflammation (AOI). This marker proved unsurprisingly to be a very strong predictor for a diagnosis of UC, and of more mild disease. Superior response to treatment when comparing histological response using Baron score was seen in the AOI group. I was surprised to see that AOI was not strongly associated with E1 disease. In the absence of reliable tests to predict disease course, I am always keen to read about how better to make use of information we already have. Better characterising disease phenotype and subphenotype and following this, patients may yet lead to information to guide therapy.

Reference: BMJ Open 2022;12:e058973
Abstract

Comorbidity influences the comparative safety of biologic therapy in older adults with inflammatory bowel diseases

Authors: Cheng D et al.

Summary: Biologic agents were compared for safety according to CCI (Charlson Comorbidity Index) in a US health insurance cohort of patients with IBD aged ≥60 years (mean 67 years) who had newly initiated TNF-α antagonists (n=2369), vedolizumab (n=972) or ustekinumab (n=352). There was no significant difference between vedolizumab or ustekinumab initiators versus anti-TNF agent initiators for the risk of infection-related hospitalisation (respective HRs 0.94 [95% CI 0.84–1.04] and 0.92 [0.74–1.16]); however, the HRs were lower for patients with a CCI of >1 (0.66 [0.46–0.91] and 0.78 [0.65–0.94]), with no significant associations detected for those with a CCI of ≤1.

Comment: Older patients with IBD are becoming more common, and this is likely to increase. Comorbidity is closely correlated with age. Older and more comorbid patients are systematically excluded and under-represented in clinical trials. Given the outcome, it is relevant that the authors had no relevant conflicts of interests. 'High comorbidity' defined as a CCI >1 is not difficult to achieve, and will reflect a large number of older IBD patients. Acknowledging the retrospective nature of this study, it is still relevant to note that significantly lower rates of hospitalisation for infection were noted in the ustekinumab- and vedolizumab-treated groups with comorbidities. More research on the elderly with IBD is required.

Reference: Am J Gastroenterol 2022;117:1845–50
Abstract

Safety and efficacy of infliximab and corticosteroid therapy in checkpoint inhibitor-induced colitis

Authors: Dahl EK et al.

Summary: The efficacy and safety of infliximab and corticosteroids were assessed for a retrospective Danish cohort of 140 cancer patients who received such treatment for immune-mediated enterocolitis. A single infliximab dose provided a complete remission rate of 52%, which increased to 73% after ≥2 doses. Additional treatment with vedolizumab was received by 10% of the patients. The patients had heavy corticosteroid exposure (median accumulated dose 3978mg). There was an increased risk of death for patients who received prednisolone ≥75 mg/day at start of tapering (adjusted HR 1.67 [CI 1.04–2.69]). Infliximab responders had improved symptoms after 3 days and complete remission after 31 days. Twenty-four percent of the patients were hospitalised for a median 7 days due to infections that emerged during treatment. Sixteen percent of the patients developed secondary gastrointestinal infections, most frequently *Clostridioides difficile* (64%), and 10% experienced a thromboembolic event during the first 90 days following infliximab treatment.

Comment: Immune-mediated colitis is a frequent presentation in the hospital setting, and seems likely to remain so given the widening range of indications for immunotherapy. Whilst the efficacy of infliximab seems well established, there is not much guidance on strategy after the first dose (nor on other features of therapy that we would use for 'classic' IBD, like thromboprophylaxis). Diagnoses were made by endoscopy, CT scan showing colitis, faecal calprotectin level >250 or histology. Eighty-five percent of patients had a C-reactive protein level rise. This group of patients are obviously highly comorbid with high doses of steroids on board (median of around 4000mg prior to starting infliximab). Around two-thirds did have remission on steroids, and one-third were steroid dependent prior to infliximab. Eighty-two percent were hospitalised for infliximab, the remainder accessing it as an outpatient. The median response time to infliximab was 3 days, 86% of responders having responded by day 5. The median time to remission was 31 days. Ten percent had a venous thromboembolism within 3 months. Infectious complications were common.

Reference: Aliment Pharmacol Ther 2022;56:1370–82
Abstract

ABX464 (obefazimod) for moderate-to-severe, active ulcerative colitis

Authors: Vermeire S et al.

Summary: Patients aged 18–75 years with moderate-to-severe active UC (modified Mayo Score ≥5) who had not responded or were intolerant to previous treatment were randomised to receive oral obefazimod (ABX464) 100mg (n=64), 50mg (n=63) or 25mg (n=63) or placebo (n=64) once per day in this phase 2b trial. Compared with placebo, all three obefazimod doses were associated with a greater least squares mean change in modified Mayo Score from baseline to week 8 (–2.9, –3.2 and –3.6 for 100mg, 50mg and 25mg, respectively, vs. –1.9 [p values 0.0039, 0.0003 and 0.0010]). Headache, the most frequently reported adverse event, affected 42%, 30%, 21% and 8% of the obefazimod 100mg, 50mg and 25mg and placebo recipients, respectively, with grade ≥3 incidences of 5%, 3%, 2% and 0%. The only serious adverse event that affected ≥2 participants in any group was UC (one participant in each of the two higher obefazimod dose groups and three in the placebo group).

Comment: Initially developed as a therapy for HIV, obefazimod is an oral small molecule of the cap binding complex, at the 5 prime end of the pre-mRNA transcript. This is part of its interference with HIV retroviral replication. However, it also triggers splicing of a long non-coding RNA, housing miR-124 – which is anti-inflammatory. Therefore the drug specifically and selectively induces miR-124. This mRNA is a modulator of inflammation through promoting immune regulation and innate immunity. Obefazimod has also been shown to trigger IL-22 production in activated macrophages. The results are exciting, and phase 3 has already begun enrolment.

Reference: Lancet Gastroenterol Hepatol 2022;7:1024–35
Abstract

Inflammatory bowel disease-associated colorectal cancer epidemiology and outcomes

Authors: Birch RJ et al.

Summary: These researchers reported on the epidemiology and outcomes of IBD-associated CRC by analysing English National Health Service data for 390,614 patients with CRC; between 2005 and 2018, 5141 of the patients had a prior IBD diagnosis recorded. Compared with patients without IBD, those who also had IBD had a lower median age at CRC diagnosis (66 vs. 72 years [p<0.01]), were more likely to be diagnosed with CRC in an emergency setting (25.1% vs. 16.7% [p<0.01]), and were more likely to have a right-sided colonic tumour (37.4% vs. 31.5% [p<0.01]). Total colectomy was undertaken in 15.4% of the patients with CD, 44.1% of those with UC, 44.5% of those with IBD unclassified and 67.7% of those with IBD with cholangitis. The patients with IBD were significantly more likely to have synchronous and metachronous tumours than those without IBD (3.2% vs. 1.6% and 1.7% vs. 0.9%, respectively [both p<0.01]). Patients with IBD-associated cancers had significantly worse 2-year stage-specific survival.

Comment: This is the largest study to date of CRC cases in people with IBD (>5000), representing 1.3% of all CRCs in the UK – despite the rigorous screening recommended by the BSG and the plummeting estimates of colitis associated cancer risk over the decades. Strangely, despite significantly lower rates of late (stage III or IV) diagnoses, patients with IBD were more likely to die within 90 days and 2 years of cancer surgery than matched non-IBD controls. There were no specific data collected pertaining to primary sclerosing cholangitis, but within the limits of the database, some data were able to be obtained using ICD10 codes for cholangitis – and these patients had lower survival rates than noncholangitis patients. Whilst much of this information is what is expected, this large study is a good reminder that this feared outcome justifies appropriate screening.

Reference: Am J Gastroenterol 2022;117:1858–70
Abstract

Faecal microbiota transplantation with anti-inflammatory diet (FMT-AID) followed by anti-inflammatory diet alone is effective in inducing and maintaining remission over 1 year in mild to moderate ulcerative colitis

Authors: Kedia S et al.

Summary: Patients with mild-to-moderate, endoscopically active UC on stable medications were randomised to FMT each week for 7 weeks and an anti-inflammatory diet (evaluable n=35) or optimised standard medical therapy (evaluable n=31) in this open-label trial. Compared with standard medical therapy, greater proportions of the FMT with an anti-inflammatory diet arm achieved clinical response (65.7% vs. 35.5%; odds ratio 3.5 [95% CI 1.3–9.6]), remission (60% vs. 32.3%; 3.2 [1.1–8.7]) and deep remission (36.4% vs. 8.7%; 6.0 [1.2–30.2]) by week 8, and deep remission out to week 48 (25% vs. 0% [p=0.007]).

Comment: One of the main questions raised by successful trials of FMT is what to bridge to. This fascinating study from New Delhi engages with this question and more. There are many problems, and many questions – but nonetheless these are very interesting data. This was a single-centre open-label trial. The trial was interrupted by COVID, with a lot of phone follow-up used in place of clinic visits. Why rural donors? Where did the diet come from? What happens with FMT and these rural donors without the diet? Can we have some microbiome data? The supplemental tables on the diet make for very interesting reading – although the translatability of that diet to a western population may be variable.

Reference: Gut 2022;71:2401–13
Abstract

Adrenomedullin for biologic-resistant Crohn's disease

Authors: Kita T et al.

Summary: Twenty-four patients with biologic-resistant CD were randomised to receive 8-hour infusions of adrenomedullin 10 or 15 ng/kg/min or placebo each day for 7 days in this phase 2a trial. There were no significant differences between the adrenomedullin groups versus placebo group for change in CDAI at 8 weeks (primary endpoint). CDAI changes out to week 24 gradually decreased and disappeared in the placebo group, whereas in the adrenomedullin arms, they remained steady, with a significant difference between the adrenomedullin groups versus the placebo group in a mixed-effects model (p=0.043). Mild adverse events with adrenomedullin were due to the agent's vasodilatory effect.

Comment: Adrenomedullin is an endogenous peptide with vasodilatory and anti-inflammatory effects. A study showed recapture of response to infliximab in a patient with loss of response. The cohort of multibiologic-resistant/-refractory patients seems to grow as rapidly as the spectrum of therapies for IBD. Despite the expanding toolbox for IBD, the idea of a novel therapy is still very attractive, particularly an endogenous peptide. This paper hints at safety and tolerability in a very treatment-refractory group as well as some degree of efficacy. Tolerability may be an issue, and mode of administration sounds challenging.

Reference: J Gastroenterol Hepatol 2022;37:2051–9
Abstract

Earlier anti-TNF initiation leads to long-term lower health care utilization in Crohn's disease but not in ulcerative colitis

Authors: Targownik LE et al.

Summary: These researchers analysed health administrative records from Manitoba, Canada for new diagnoses of IBD treated with anti-TNF agents with ≥1 year of follow-up after initiation. For patients with CD (n=742), those who started anti-TNF therapy <2 (vs. >2) years after diagnosis had fewer IBD-specific and overall hospitalisations during the 5 years after starting such therapy, as well as a lower incidence of resective surgery if the first year following initiation was excluded from the analysis. Among patients with UC (n=318), the timing of anti-TNF therapy initiation had no significant impact on hospitalisation and surgery rates.

Comment: Efficacy, safety and cost, again – of the three of these, though, the one that remains to be best justified/established in IBD is the cost of using biologics early in IBD. REACT-CD and CALM have both shown advantages in early biologic therapy (both pharmaceutical funded). Late complications in CD relating to fibrosis and penetration suggest cumulative damage that could be averted with potent therapy. Conversely, the episodic inflammation of most patients in UC may explain why early intervention does not translate to reductions in long-term rates of surgery.

Reference: Clin Gastroenterol Hepatol 2022;20:2607–18
Abstract

INSPECT: a retrospective study to evaluate long-term effectiveness and safety of darvadstrocel in patients with perianal fistulizing Crohn's disease treated in the ADMIRE-CD trial

Authors: Panés J et al.

Summary: This chart review study assessed the long-term effectiveness and safety of darvadstrocel in 43 ADMIRE-CD trial participants with perianal fistulising CD who received the agents and 46 who did not. The respective 52-, 104- and 156-week post-treatment clinical remission rates were 67.4%, 53.5% and 53.5% in darvadstrocel recipients, compared with 52.2%, 43.5% and 45.7% of nonrecipients. Among participants who achieved 52-week clinical remission, the respective proportions in whom this was sustained at 104 and 156 weeks were 65.5% and 55.2% among darvadstrocel recipients, and 70.8% and 54.2% among controls. No significant between-group difference was apparent for time to or incidence of fistula relapse, or for new fistula occurrence. One control group participant developed malignant epidermoid carcinoma, and there were no cases of ectopic tissue formation recorded.

Comment: Unfortunately, we still do not have access to this therapy. However, one of the most remarkable features of the ADMIRE-CD trial was the terrifically high 'standard therapy' rate. Both the darvadstrocel arm and standard therapy arm continue to have high fistula remission rates at 3 years. Safety analysis of darvadstrocel shows no new signals.

Reference: Inflamm Bowel Dis 2022;28:1737–45
Abstract

