IBD Research Review™

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Issue 57 - 2022

In this issue:

Abbreviations used in this issue:

CD = Crohn's disease; **GI** = gastrointestinal; **IBD** = inflammatory bowel disease; **TNF** = tumour necrosis factor; **UC** = ulcerative colitis.

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Welcome to issue 57 of IBD Research Review.

We begin this issue with the phase 3 GARDENIA trial of etrolizumab versus infliximab in patients with moderately to severely active UC, and we also present the final analysis of the OCTAVE Open long-term, extension trial of 7 years of treatment with tofacitinib for UC. COVID-19 features in several papers, including the impact that IBDs themselves and their treatments have on the incidence, disease severity and outcomes of COVID-19. An assessment of cellular and humoral immune responses to vaccination against COVID-19 in patients with IBD is also reported. While not a paper on COVID-19 *per se*, its associated lockdowns have impacted how we care for our patients, including therapeutic drug monitoring of biologic therapy, and a paper from the UK has evaluated this, with particular attention on comparing finger-prick testing, which facilitates remote monitoring, with conventional venepuncture to obtain blood samples for analysis. Therapeutic drug monitoring is also the subject of our final paper, this time evaluating the use of an ultra-proactive algorithm.

Please don't hesitate to send us any comments or feedback you have regarding this issue.

Kind Regards,

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Etrolizumab versus infliximab for the treatment of moderately to severely active ulcerative colitis (GARDENIA)

Authors: Danese S et al., on behalf of the GARDENIA Study Group

Summary: The double-blind, double-dummy phase 3 GARDENIA trial randomised anti-TNF agent-naïve adults with moderately to severely active UC to receive subcutaneous etrolizumab 105mg once every 4 weeks (n=199) or intravenous infliximab 5 mg/kg at weeks 0, 2 and 6 and every 8 weeks thereafter (n=198) for 52 weeks; study completion rates were 48% and 52% for the respective study arms. There was no significant difference between the etrolizumab versus infliximab group for the proportions of participants meeting the primary endpoint of clinical response at week 10 and clinical remission at week 54 (18.6% vs. 19.7% [p=0.81]) or for experiencing ≥1 adverse event (77% vs. 76%), but there were more serious adverse events (including serious infections) in the etrolizumab group (16% vs. 10%).

Comment: UC remains a significant cause of morbidity to a multitude of patients worldwide. Therapies targeted at novel pathways are being investigated in the hopes that patients will achieve improved outcomes, either as first-line or subsequent therapy. The subject of this study is etrolizumab, which prevents targeting to the intestinal mucosa and retention within the intestinal epithelial barrier. Etrolizumab demonstrated superiority over placebo in phase 2 studies when evaluated based on clinical activity scores. In this study, response rates to etrolizumab were compared with infliximab. The study failed to demonstrate superiority of etrolizumab over infliximab, but showed similar response rates and adverse events. The rate of serious adverse events was slightly higher in the etrolizumab group. Further evaluation of the safety profile of etrolizumab will be required in order to determine whether this agent will find a place in the therapeutic armamentarium for UC.

Reference: Lancet Gastroenterol Hepatol 2022;7:118–27
Abstract

Independent commentary by Dr Rimma Goldberg

Dr Rimma Goldberg is a clinical Gastroenterologist and a senior lecturer at Monash University. Dr Goldberg completed her PhD in Mucosal Immunology and Biology at King's College in London focusing on cell-based therapies for inflammatory bowel disease. Dr Goldberg has published her research in top tier Gastroenterology journals, including Gut, Gastroenterology and Nature Reviews Gastroenterology. She leads a research group focused on immune phenotyping patients with IBD and developing novel cell-based therapies. She was the recipient of the British Society of Gastroenterology Best Scientific Abstract Award as well as the Society of Mucosal Immunology – Rising Stars in Mucosal Immunology award.

Antibodies-to-infliximab accelerate clearance while dose intensification reverses immunogenicity and recaptures clinical response in paediatric Crohn's disease

Authors: Colman RJ et al.

Summary: The impact of antibodies to infliximab on infliximab clearance and loss of response was evaluated in a cohort of 78 paediatric patients with CD prospectively followed for 1 year. Peak and trough serum concentrations of infliximab and antibodies to infliximab were assessed after 660 infliximab infusions during the first year of therapy. Fifty three of the patients (68%) were positive for anti-infliximab antibodies; the median concentration was 76 ng/mL and 73.6% had a maximum concentration of <200 ng/mL. Significant independent predictors of antibodies to infliximab were neutrophil-CD64 ratio >6 and infliximab starting dose <7.5 mg/kg, but presence of HLA-DQA1*05 was not. Compared with patients negative for anti-infliximab antibodies, those who were positive had significantly greater median infliximab clearance. Anti-infliximab antibodies resolved in 37.5% of patients on dose adjustment, accompanied by infliximab concentration and clearance recovery. A maximum anti-infliximab antibody concentration of ≤99 ng/mL was a significant predictor of resolution of anti-infliximab antibodies.

Comment: Anti-TNF agents such as infliximab remain a mainstay of therapy for paediatric and adult CD. Loss of response due to antibody formation and subsequent increased drug clearance remains a major impediment to the longevity of this therapy. Traditionally, once antibodies are detected, patients are switched to a different drug type, either within the anti-TNF class or out of class. This study tracked patients who developed anti-infliximab antibodies and subsequently increased drug clearance, and found that in 37.5% of cases, this issue could be overcome with dose adjustment. Additionally, it found that starting doses <7.5 mg/kg were predictive of developing anti-infliximab antibodies. These findings have important implications for how we may prescribe infliximab in the future. Patients in whom it is important to maintain infliximab therapy may undergo careful dose optimisation to overcome the presence of anti-infliximab antibodies, prior to switching therapy.

Reference: Aliment Pharmacol Ther 2022;55:593–603
Abstract

Safety and efficacy of tofacitinib for treatment of ulcerative colitis

Authors: Sandborn WJ et al.

Summary: The final analysis of the open-label OCTAVE Open extension trial was presented. OCTAVE Open included nonresponders from OCTAVE Induction 1 and 2 and completers/treatment failures from OCTAVE Sustain who received tofacitinib 5mg twice daily if in remission or else 10mg twice daily; of 944 participants in OCTAVE Open, 81.5% initially received tofacitinib 10mg twice daily. Over 2440.8 patient-years of exposure, the incidence rate for death was 0.25 (95% CI 0.09–0.54) and for adverse events of interest they were 1.61 (1.14–2.20) for serious infection, 3.16 (2.47–3.97) for herpes zoster (nonserious and serious), 0.87 (0.54–1.33) for opportunistic infections, 0.16 (0.04–0.42) for major adverse cardiovascular events, 1.03 (0.67–1.52) for malignancies other than nonmelanoma skin cancer, 0.75 (0.45–1.19) for nonmelanoma skin cancer, 0.04 (0.00–0.23) for deep vein thrombosis, and 0.21 (0.07–0.48) for pulmonary embolism. At 36 months, the respective clinical response rates in the respective tofacitinib 5mg twice daily and 10mg twice daily groups were 66.9% and 40.3%, the endoscopic improvement rates were 64.6% and 37.1%, and the remission rates were 58.9% and 33.7%.

Comment: Tofacitinib is an oral Janus kinase inhibitor used for the treatment of UC. It blocks the signalling of several proinflammatory cytokines, and as a result, is a potent agent for treating autoimmune disease. It's potent anti-inflammatory action also leads to a potential for increased propensity for infection in patients who are treated with this agent. Tofacitinib is also associated with an increased risk of thromboembolic events, particularly in older patients. As it is a newer agent, it is also important for clinicians to know whether these adverse events increase over time or remain steady over the years that the patient receives treatment. This final long-term open-label follow-up of OCTAVE describes up to 7-year follow-up of patients treated with 5mg twice daily or 10mg twice daily of tofacitinib. It demonstrated safety up to 7 years of follow-up; of particular interest, incidence rates for serious infections, malignancies and thromboembolic events remained low. The rates of clinical response, endoscopic improvement and maintenance of remission remained steady up to 36 months. These data support the longer-term efficacy and safety of treatment with tofacitinib for UC.

Reference: Aliment Pharmacol Ther 2022;55:464–78
Abstract

Effect of inflammatory bowel disease and related medications on COVID-19 incidence, disease severity, and outcome

Authors: Richter V et al.

Summary: These researchers sent an anonymised questionnaire to members of the Israel Crohn's Disease and Ulcerative Colitis Foundation asking respondents about their IBD disease course and COVID-19 infection over the prior year. Responses to the questionnaire were obtained from 2152 patients with IBD (mean age 39 years, 60.5% female, 75.6% with no comorbidities), 4.8% of whom reported having been infected with COVID-19, a proportion that was significantly lower than 'expected' for the Israeli population (p=0.033). There was no correlation detected between IBD type or severity and COVID-19 infection, and most infected respondents reported mild COVID-19 irrespective of the IBD medication type. Independent risk factors for COVID-19 infection were younger age, elevated BMI and diabetes, whereas receipt of 5-aminosalicylic acid, smoking and hypertension were protective. IBD treatment discontinuation was reported by 25.2% of respondents who acquired COVID-19 infection, compared with 8.5% of those who remained uninfected, and patients who did discontinue their treatment were significantly more likely to experience flare of their IBD.

Comment: Patients with autoimmune diseases and particularly those treated with immune modulating medications have felt increased anxiety about their susceptibility to severe COVID-19 disease. Patients and clinicians may discontinue IBD medications because of concerns about immune suppression. This study performed through a self-reporting questionnaire administered to members of a Crohn's and colitis support organisation demonstrated that patients with IBD were not more susceptible to COVID infection. Importantly, IBD medications were not associated with increased rates of COVID-19 infections. This study may be confounded by reporting bias, as patients who were highly motivated and health literate may have been more likely to respond to the questionnaire, and similarly may have been more likely to have taken more precautions against contracting COVID-19 infection. However, this and other studies have demonstrated that it is safe for patients to continue with their IBD medications during the COVID-19 pandemic.

Reference: Eur J Gastroenterol Hepatol 2022;34:267–73
Abstract

Flexible sigmoidoscopy may be sufficient for initial evaluation of suspected immunotherapy-mediated colitis

Authors: De Silva S et al.

Summary: The optimal strategy for endoscopic evaluation of immunotherapy-mediated colitis was assessed in this retrospective cross-sectional review of 51 patients receiving immune checkpoint inhibitors who had been referred for evaluation; 47 were evaluated with colonoscopy, and four with flexible sigmoidoscopy. Histological evidence of immunotherapy-mediated colitis was seen in the distal rectosigmoid biopsies obtained from all the flexible sigmoidoscopy procedures. The colonoscopies revealed the presence of immunotherapy-mediated colitis in all segments of colon simultaneously for 35 patients, or absence from all segments in 12. Immunotherapy-mediated colitis was not seen on any proximal colonic biopsy. Histological evidence of immunotherapy-mediated colitis was seen in up to 68.6% of the time in endoscopically normal mucosa. The sensitivity values for endoscopically abnormal right, transverse and left colon for histological presence of immunotherapy-mediated colitis were low at 35.3%, 34.3% and 41.7%, respectively, but their respective specificity values were high at 100.0%, 100.0% and 91.7%.

Comment: Patients on immune checkpoint inhibitors who develop diarrhoea are often referred to gastroenterology services for evaluation. Guidelines about the optimal approach to investigation and management of immune checkpoint inhibitor-associated colitis are evolving. Patients may often be quite unwell, with questionable fitness to undergo a full colonoscopy. This study by De Silva et al. demonstrates that it is sufficient to perform a flexible sigmoidoscopy to diagnose immunotherapy-mediated colitis. This will allow for more efficient evaluation of these patients in the future, expediting the path to diagnosis and management. The authors also found that frequently when normal tissue was sampled, changes of immunotherapy-mediated colitis were found. This highlights the importance of sampling normal and abnormal looking tissue when performing endoscopic evaluation for this indication.

Reference: J Gastroenterol Hepatol 2022;37:284–90
Abstract

Dietary gluten intake is not associated with risk of inflammatory bowel disease in US adults without celiac disease

Authors: Lopes EW et al.

Summary: The relationship between gluten intake and incident IBD risk was explored in 208,280 participants from the US Nurses' Health Study, Nurses' Health Study II and the Health Professionals Follow-up Study without IBD at baseline or coeliac disease. Over 5,115,265 person-years of follow-up, there were 337 cases of CD and 447 cases of UC identified. Semiquantitative food frequency questionnaires completed by the participants revealed that gluten consumption in the highest versus lowest quintile did not significantly increase the risk of developing CD or UC (respective adjusted hazard ratios 1.16 [95% CI 0.82–1.64] and 1.04 [0.75–1.44]), with no notable change after additional adjustment for primary sources of gluten intake.

Comment: Patients with IBD are frequently interested in modifying their diet to help manage disease activity. Gluten exclusion is often recommended in a number of diets as a proposed means of reducing inflammation in the GI tract. There has been little evidence to date that gluten causes GI inflammation in individuals without coeliac disease. This study of three large prospective, well-characterised patient cohorts shows that gluten consumption is not associated with risk of IBD. These data can be used to support dietary recommendations for patients, particularly those who are concerned about mitigating the risks of developing IBD in their offspring. Additional data are required on the role of gluten exclusion and IBD severity in patients who currently have a diagnosis of IBD.

Reference: Clin Gastroenterol Hepatol 2022;20:303–13
Abstract

Risk of serious infections with vedolizumab versus tumor necrosis factor antagonists in patients with inflammatory bowel disease

Authors: Kirchgesner J et al.

Summary: The serious infection risk associated with vedolizumab versus anti-TNF use for IBD was explored using data from two US nationwide commercial insurance databases and the French nationwide health insurance database; 8768 adult vedolizumab initiators were propensity score matched to 26,656 anti-TNF initiators for analysis. Over 37,725 person-years of follow-up, 893 serious infections were recorded. The risk of serious infection was not significantly increased for vedolizumab versus anti-TNF agent initiators in the overall IBD cohort (hazard ratio 0.95 [95% CI 0.79–1.13]) or those with CD (1.10 [95 0.87–1.38]), but was reduced for those with UC (0.68 [0.50–0.93]) even after GI infections were excluded (0.59 [0.39–0.90]).

Comment: Vedolizumab is often prescribed to patients in whom infectious complications of immunomodulator use are a significant consideration, because vedolizumab is perceived to be associated with a lower risk of infection. This large study from US and French nationwide insurance databases examined the risk of serious infections in patients prescribed vedolizumab compared with those treated with infliximab. Interestingly, it did not find that vedolizumab was associated with a reduced infection risk when looking at the IBD population as a whole. However, it was associated with a reduced risk of serious infections in the UC cohort. It may be that the occurrence of perianal and luminal fistulising disease in CD affects the proportions of patients reported to have serious infections in this cohort.

Reference: Clin Gastroenterol Hepatol 2022;20:314–24
Abstract

Patient-led Remote IntraCapillary pharmacoKinetic Sampling (fingerPRICKS) for therapeutic drug monitoring in patients with inflammatory bowel disease

Authors: Chee D et al.

Summary: This research examined the impact of the COVID-19 pandemic on requests for therapeutic drug monitoring, and low volume patient-led remote intracapillary pharmacokinetic sampling versus conventional venepuncture, using cross-sectional blood sampling methods. Compared with the 6-month period prior to the UK's stay-at-home lockdown, therapeutic drug monitoring requests for adalimumab fell from 96.5 to 52 per week ($p<0.001$) during the first lockdown period, but those for infliximab did not fall significantly (from 184.5 to 161 per week [$p=0.34$]). Equivalence was reported between finger-prick sampling and conventional venepuncture for adalimumab, infliximab, vedolizumab and ustekinumab drug concentrations, as well as anti-adalimumab and anti-infliximab antibody levels. Intracapillary sampling median serum volume was 195µL. Responses to a purpose-designed questionnaire revealed that >87% of respondents rated intracapillary testing as easy, with 69% preferring it to conventional venepuncture. Data from routine care showed that 75.3% of patients returned two blood samples within 14 days to enable remote assessment of biologic therapeutic drug monitoring.

Comment: Therapeutic drug monitoring has evolved to be an important keystone in the management of IBD. Drug monitoring has been limited by cost in some scenarios, as well as patient acceptability around the necessity to obtain additional blood tests. In Australia, therapeutic drug monitoring is no longer limited by cost, as pathology providers and major health services recognise its importance in the patient management armamentarium. In the era of the COVID-19 pandemic, access to therapeutic drug monitoring is further limited by reduced movement in the community and the delivery of healthcare remotely. This single-centre study assessed the acceptability of remote therapeutic drug monitoring, and found that the majority of patients found it easy and preferable to routine venepuncture. Remote therapeutic drug monitoring may find a role in ambulatory IBD care if the cost and reliability can be shown to be comparable with current methods involving venepuncture.

Reference: J Crohns Colitis 2022;16:190–8
Abstract

T cell response after SARS-CoV-2 vaccination in immunocompromised patients with inflammatory bowel disease

Authors: Reuken PA et al.

Summary: These researchers reported cellular and humoral immune responses after SARS-COV-2 vaccination in 28 patients with IBD, with 27 age- and sex-matched healthy controls used for comparisons. Anti-SARS-COV-2 antibody levels exceeding the cutoff (33.8 binding antibody units per mL) did not differ significantly between patients with IBD and controls after the first vaccine dose (71.4% vs. 85.2% [p=0.329]). Moreover, the patients with IBD had significant T-cell responses after their first vaccine dose compared with healthy controls even when SARS-COV-2 antibodies were absent, and this was not affected by immunosuppressant regimen. A slight postvaccination increase of TNF production was also detected in SARS-COV-2-reactive helper T-cells both in patients with IBD and healthy donors. After their second vaccine dose, humoral immune response increased further in all but one of the patients with IBD.

Comment: Vaccination against COVID-19 is widely regarded as the exit route from the crippling pandemic. It has previously been suggested that patients who are treated with immune modulating medications do not mount robust enough responses to vaccination as their counterparts who do not use such medications. This study looked at antibody production following vaccination as well as helper T-cell responses in patients with IBD. They did not find a significant difference in antibody production in the IBD population. They also observed similar helper T-cell responses between IBD patients and healthy controls. The antibody production or helper T-cell responses did not appear to be affected by immune modulating medications in the IBD cohort. This is a small single-centre study, so observation of a larger number of patients on a broad range of IBD medications needs to take place in order to make definitive comments about responses to vaccination.

Reference: J Crohns Colitis 2022;16:251–8
Abstract

Ultra-proactive therapeutic drug monitoring of infliximab based on point of care testing in inflammatory bowel disease

Authors: Bossuyt P et al.

Summary: Patients with IBD receiving maintenance infliximab from two centres comprised the subjects for this pragmatic trial. In one of these centres (n=155), an ultra-proactive therapeutic drug monitoring algorithm that incorporated point-of-care testing was applied, while at the second centre (n=72), reactive therapeutic drug monitoring was used. Compared with reactive therapeutic drug monitoring, use of the ultra-proactive therapeutic drug monitoring algorithm was associated with more trough drug concentration measurements being undertaken (8.8 vs. 1 per patient per year [p<0.0001]), with significantly more resultant dose optimisations. The first round of ultra-proactive therapeutic drug monitoring was associated with point-of-care testing being required in 27%, but over subsequent rounds, the mean was 6.3%. *Ad hoc* extra dosing was required for 13% of the point-of-care tests. There was no significant difference between the ultra-proactive versus reactive therapeutic drug monitoring algorithm for the 1-year infliximab failure rate (primary endpoint; 19% vs. 10% [p=0.08]) or the 1-year sustained clinical remission rate (75% vs. 83% [p=0.17]). Mucosal remission, evaluated in 71 patients, was more frequent in the reactive therapeutic drug monitoring cohort (p=0.02).

Comment: Therapeutic drug monitoring whilst on infliximab treatment allows us to optimise the drug dose and subsequently patient outcomes. A common point of debate is whether we need to proactively measure infliximab concentrations and optimise before the patients become symptomatic. In this study, the authors assessed ultra-proactive therapeutic drug monitoring of infliximab at the point of care with *ad hoc* dose adjustment, compared with standard reactive drug monitoring. The study was performed at two separate centres, each adopting a different approach. The data collection was partially retrospective in the reactive drug monitoring cohort. Overall, the study demonstrates that the patients who underwent the ultra-proactive therapeutic drug monitoring did not have improved disease outcomes at 1 year. This was a small study with a mixed IBD phenotype cohort. A larger study that is able to report on outcomes of CD and UC patients over a longer period may shed more light on the utility of point of care drug monitoring and *ad hoc* dose adjustment in different patient groups. Patients with complex perianal and extensive luminal CD who routinely require higher anti-TNF drug concentrations may benefit more from this approach.

Reference: J Crohns Colitis 2022;16:199–206
Abstract

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