IBD Research Review™

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Issue 54 - 2021

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Abbreviations used in this issue:

5-ASA = 5-aminosalicylate; **CD** = Crohn's disease; **CRP** = C-reactive protein; **GI** = gastrointestinal; **HBI** = Harvey-Bradshaw Index; **IBD** = inflammatory bowel disease; **TNF** = tumour necrosis factor; **UC** = ulcerative colitis.

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Welcome to issue 54 of IBD Research Review.

The first paper selected provides us with a comprehensive systematic review of diets in adult patients with IBD. Further to this, other included research confirms that typical Western diets, which are typically high in grains, oils, potatoes, processed meat, condiments/sauces and sugary foods, do increase the risk of IBD flare. A review of retrospective medical records has identified several predictors of ustekinumab failure in CD. This issue concludes with research reporting that the risk of CD progression can be reduced by achieving faecal calprotectin level normalisation within a year of diagnosis.

We hope you enjoy the research selected for this issue, and we look forward to receiving your comments and feedback.

Kind Regards,

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Systematic review with meta-analysis: dietary intake in adults with inflammatory bowel disease

Authors: Lambert K et al.

Summary: Of 40 cohort, case-control and cross-sectional studies reporting usual dietary intake in adults with IBD identified for this systematic review, 19 were included in a meta-analysis. It was found that energy intake was inadequate across subgroups of adults with IBD, with a mean daily intake of 1980 kcal overall, and mean daily fibre, folate and calcium intakes of 14g, 246mg and 521mg, respectively. Bread/cereal, legume, fruit, vegetable and dairy intakes were inadequate. Dietary fibre was significantly lower in adults with IBD compared with healthy individuals.

Comment: IBD is increasing in incidence and prevalence. This has often been attributed to increased urbanisation and the availability of processed foods. When patients are first diagnosed, the first question is often about whether their diet brought on the onset of disease and how they can modify their diet to manage it. Lambert et al. conducted a systematic review and meta-analysis of studies reporting the dietary habits of patients with IBD. IBD patients were found to be malnourished and have a poor intake of dietary fibre. More detailed controlled studies are required to assess the dietary factors that contribute to the development and flares of IBD.

Reference: Aliment Pharmacol Ther 2021;54:742–54

Abstract

Continued 5ASA use after initiation of anti-TNF or immunomodulator confers no benefit in IBD: a population-based study

Authors: Bernstein CN et al.

Summary: The frequency and outcomes of continuation of 5-ASA therapy after starting biologic or immunomodulator therapy were explored in this retrospective analysis of the University of Manitoba IBD Epidemiologic Database. Of database entries analysed, 85% of patients with UC and 68% of those with CD received ≥1 5-ASA dispensation, but these declined towards the end of the 1996–2018 period analysed, particularly for CD. The most common 5-ASA usage pattern was intermittent (65.1%), followed by persistent (17%), prior continuous (13.8%) and then one-time use (4.1%). The 5-ASA administration route (for UC and CD combined) was 59% for oral only, 3% for rectal only and 14% for both. Of all 5-ASA initiations, 25% were continued for >20 months. Neither patients with UC nor those with CD had significant differences between those who continued versus discontinued 5-ASA therapy on initiation of immunomodulator/anti-TNF therapy for hospitalisations, surgery, corticosteroid initiations, colorectal cancers or drug-related adverse events.

Comment: Patients with IBD, and particularly UC, are usually initiated on a 5-ASA as first-line therapy. When patients are escalated to anti-TNF agents, 5-ASAs are often continued due to perceived additive benefit or for chemoprotection against the development of dysplastic lesions. The study by Bernstein and colleagues performed a retrospective assessment of the persistence of 5-ASA therapy after initiation of anti-TNF therapy, and assessed for differences in outcomes in those who continued on 5-ASAs versus those who didn't. They concluded that continuation of 5-ASAs added no benefit. These findings should be interpreted with caution due to the retrospective observational nature of the study. The study also did not account for scenarios, such as flares of proctitis, where topical 5-ASA administration is of significant benefit.

Reference: Aliment Pharmacol Ther 2021;54:814–32

Abstract

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Effect of point-of-care gastrointestinal ultrasound on decision-making and management in inflammatory bowel disease

Authors: Friedman AB et al.

Summary: The utility of point-of-care GI ultrasonography as an assessment tool was explored from the perspectives of clinicians and patients in this prospective, observational cohort study. For 259 patients, ultrasonography was performed in 73, and this occurred 9.2 years after diagnosis; the patients who did not undergo ultrasonography were assessed 11.3 years after diagnosis. Compared with the patients who did not undergo ultrasonography, those who did were better able to self-report disease activity immediately afterwards, showed better understanding of all disease aspects and symptoms, were more confident in their ability to make informed disease management decisions and had improved knowledge domain scores ($p<0.05$ for all). The patients' abilities to manage their own healthcare were not impacted by undergoing ultrasonography, although there was a tendency for transient improvements in medication adherence. Following the ultrasound, clinicians' assessments of patients' disease activity was changed in 22% and management altered in 56%, including anti-inflammatory therapy escalation in 33 patients. Compared with the non-ultrasound group, greater proportions of patients who underwent ultrasonography had a medication change (47% vs. 22% for CD [p=0.002], and 68% vs. 26% for UC [p=0.005]).

Comment: Patient assessment in the clinic is inherently difficult, with the clinician often relying on subjective information such as symptoms and the patient's overall sense of wellbeing. Investigations are often delayed due to availability or poor patient compliance. In the pandemic era, face-to-face visits are infrequent, so clinicians must work to optimise their efficacy in this setting. Friedman and colleagues performed a prospective study of the effect of point-of-care intestinal ultrasound on clinician decision making among other factors. They found that point-of-care ultrasound resulted in significantly more alterations to patient management. As more gastroenterologists are becoming trained in this modality, it is likely that in time, intestinal ultrasound will become an integral part of the IBD clinic.

Reference: Aliment Pharmacol Ther 2021;54:652–66
Abstract

An observational study of switching infliximab biosimilar: no adverse impact on inflammatory bowel disease control or drug levels with first or second switch

Authors: Luber RP et al.

Summary: These researchers reported on patients with IBD who had switched from the infliximab biosimilar CT-P13 to another biosimilar, SB2, with a comparison of outcomes for those switching for the first versus second time; of 186 patients on stable infliximab dosing who were switched, 99 were switched for a second time. No significant change from baseline was seen for CRP level, clinical disease activity score or median trough infliximab concentration at the early timepoint (infusion 3 or 4; from 5.7 to 6.6 µg/mL [p=0.05] and from 4.3 to 4.9 µg/mL [p=0.07] for the first- and second-switch groups, respectively) or at 1 year (to 5.7 µg/mL [p=0.37] and to 4.7 µg/mL [p=0.06], respectively). There was also no significant change in the proportion of patients in clinical remission in the early timepoint (from 91% to 92% [p=0.75]) or at 1 year (from 95% to 91% [p=0.16]). Time to loss of response also did not differ significantly between first- versus second-switch patients (p=0.69).

Comment: Anti-TNF agents have been in clinical practice for close to two decades, offering prolonged remission for a significant number of patients. With the advent of biosimilars, anti-TNF agents are becoming more affordable and accessible to the healthcare system and the consumer. However, concerns still remain regarding whether patients will remain in remission after switching to a biosimilar. Luber et al. collected information on drug concentrations and rates of clinical remission early after switching to a first or second biosimilar and at 1 year. Rates of clinical remission remained unchanged as did trough drug concentrations. However, reporting of biochemical markers of remission such as faecal calprotectin levels or endoscopic findings at the relevant timepoints would have strengthened the message of this study.

Reference: Aliment Pharmacol Ther 2021;54:678–88
Abstract

Dietary intake pattern is associated with occurrence of flares in IBD patients

Authors: Peters V et al.

Summary: Associations between dietary patterns and IBD flares were explored over 2 years in Dutch cohorts from two geographically distinct areas (northern [n=486] and southern [n=238]). The exacerbation rate during follow-up was 24.8%. Compared with the southern cohort, northern cohort patients were younger at diagnosis, more were females, and they had lower overall energy intakes ($p<0.05$ for all). A principal component analysis revealed three dietary patterns that explained 28.8% of total variance: a pattern characterised by intake of grain products, oils, potatoes, processed meat, red meat, condiments/sauces, and sugar, cakes and confectionery was the most pronounced, explaining 11.6% of the variance, and was associated with IBD flare (hazard ratio 1.51 [95% CI 1.04–2.18]); female sex was also associated with IBD flare (1.63 [1.04–2.55]).

Comment: IBD patients frequently want to know what diet they should adhere to in order to get their IBD into remission and to prevent flares. Diets high in additives, preservatives and processed foods have been implicated in the development of IBD. Peters and colleagues looked at dietary patters of patients from the north and the south of the Netherlands. It emerged that a diet high in grain products, oils, potatoes, processed meat, condiments and sauces as well as sugar, cakes and confectionary was associated with flare occurrence. This dietary pattern is consistent with high levels of processed food intake, which has been suggested to be problematic for IBD in other studies. Prospective studies using dietary interventions are needed to validate these findings.

Reference: J Crohns Colitis 2021;15:1305–15
Abstract

Dual biologic and small molecule therapy for the treatment of refractory pediatric inflammatory bowel disease

Authors: Dolinger MT et al.

Summary: This study assessed the efficacy and safety of two biologics used concomitantly or a biologic plus tofacitinib combination for refractory UC/IBD unspecified (n=9) or CD (n=7) in an observational cohort of patients aged <18 years. After failing ≥2 biologic therapies, nine of the patients received vedolizumab/tofacitinib, four received ustekinumab/vedolizumab and three received ustekinumab/tofacitinib. The 6-month steroid-free remission rate (primary outcome) was 75% (seven patients with UC/IBD unspecified, five with CD). By 6 months, significant reductions were seen for erythrocyte sedimentation rate and CRP level (respective p values 0.021 and 0.015) and albumin levels had increased (p=0.003). Septic arthritis and deep vein thrombosis developed in one patient receiving vedolizumab/tofacitinib and prednisone daily.

Comment: As new biologics and small molecules target different parts of the aberrant immune response, clinicians often wonder whether combining complimentary agents would have a cumulatively beneficial response. There is always a concern about cumulative toxicities as well. Dolinger et al. examined the combinations of vedolizumab/tofacitinib, ustekinumab/vedolizumab and ustekinumab/tofacitinib in 16 paediatric patients with a mean age of 15.9 years who had failed two previous biologics. Twelve of the sixteen patients studied achieved steroid-free remission at 6 months. A significant adverse event of septic arthritis and deep vein thrombosis was seen in a patient on prednisolone/vedolizumab/tofacitinib. The study was not powered to assess the safety and efficacy of individual combinations, and large prospective studies are required to evaluate this in detail. This does, however, provide a promising signal about the future use of combination therapies.

Reference: Inflamm Bowel Dis 2021;27:1210–4
Abstract

Predictors of ustekinumab failure in Crohn's disease after dose intensification

Authors: Dalal RS et al.

Summary: Predictors of ustekinumab failure were reported for a retrospective cohort of adults with CD after they underwent dose intensification to every 4, 5, 6 or 7 weeks (respective n values 64, 1, 55 and 3). A multivariable logistic regression analysis revealed that factors associated with failure to achieve corticosteroid-free remission (primary outcome) were presence of perianal disease, HBI score and opioid use at time of intensification, and a Cox regression analysis revealed that perianal disease and corticosteroid use at time of intensification were associated with a shorter time to starting a new biologic.

Comment: Ustekinumab is a relative newcomer to the biologic armamentarium for the treatment of IBD. Whilst it is effective for luminal CD, its role in patients with perianal disease is still not entirely clear. Often patients who do not respond to standard-dose ustekinumab are dose escalated to 6- or 4-weekly dosing. Dalal and colleagues performed a retrospective study evaluating the factors that are associated with ustekinumab failure after dose intensification. They found that perianal disease, as well as opioid and corticosteroid use, were predictors of failure after dose intensification. This may indicate that particularly in patients with perianal disease, rather than going through ustekinumab dose intensification, it may be more useful to switch to another agent.

Reference: Inflamm Bowel Dis 2021;27:1294–301
Abstract

References: 1. Sandborn WJ, et al. Clin Gastroenterol Hepatol. 2021 Feb 19: S1542-3565(21)00203-2. doi: 10.1016/j.cgh.2021.02.025. Epub ahead of print.

Subclinical pulmonary involvement in active IBD responds to biologic therapy

Authors: Ellrichmann M et al.

Summary: This prospective longitudinal study of 49 consecutive patients with CD, 43 with UC and 20 healthy controls investigated pulmonary manifestations of IBD and the impact of anti-TNF-α therapy on pulmonary function tests. Compared with patients with remission and controls, patients with active IBD had significant reductions in pulmonary function, including FEV_1 (forced expiratory volume in 1 second) percent predicted (78.8% vs. 86.1% and 87.3%, respectively [p values 0.0002 and 0.001]). Anti-TNF agent use was associated with significant relief of pulmonary obstruction compared with baseline. Degree of pulmonary obstruction was significantly correlated with clinical inflammation scores (HBI or Mayo).

Comment: IBD is known to be associated with a number of extraintestinal manifestations. The typical extraintestinal manifestations are arthralgias, uveitis and pyoderma gangrenosum. Patients often report fatigue and some reduced functional capacity. However, until recently pulmonary involvement was not readily recognised as an extraintestinal manifestation of IBD. A study by Ellrichmann and colleagues found that patients with active IBD showed a significant reduction in their pulmonary function test parameters. Treatment with anti-TNF agents led to a significant reduction in the obstruction seen at baseline. These findings are important, particularly in the era of COVID-19 where patients with active IBD may be particularly vulnerable to this pathogen due to previously unrecognised pulmonary involvement. Studies of the effects of other biologic agents and small molecules on the pulmonary manifestations of IBD are needed.

Reference: J Crohns Colitis 2021;15:1339–45
Abstract

Depression in individuals who subsequently develop inflammatory bowel disease

Authors: Blackwell J et al., POP-IBD study group

Summary: The association of depression with subsequent IBD after adjustment for pre-existing GI symptoms was explored in 10,829 patients with UC and 4531 with CD from the Clinical Practice Research Datalink, each matched to a non-IBD control. Compared with controls, an excess of prevalent depression 5 years prior to IBD diagnosis was seen for the UC and CD cases (3.7% vs. 2.7% and 3.7% vs. 2.9%, respectively). Compared with individuals without depression, those who had GI symptoms before being diagnosed with depression had significantly increased likelihoods of developing UC and CD (respective adjusted odds ratios 1.47 [95% CI 1.21–1.79] and 1.41 [1.04–1.92]), whereas those who did not have GI symptoms prior to their depression diagnosis did not (1.13 [0.99–1.29] and 1.12 [0.91–1.38]).

Comment: Patients with IBD often develop symptoms of depression; however, when this was studied in more detail, patients with IBD often suffered from symptoms of depression prior to the diagnosis being made. Depression has subsequently been identified as a risk factor for IBD. Blackwell and colleagues investigated this question by looking into whether depression adjusted for pre-existing GI symptoms is associated with subsequent IBD. They found that individuals with GI symptoms prior to the diagnosis of depression had an increased risk of subsequently developing CD and UC. This may indicate that individuals presenting for investigation of GI symptoms with a concomitant diagnosis of depression should be treated with a higher index of suspicion for IBD than those without depression.

Reference: Gut 2021;70:1642–8
Abstract

Normalization of fecal calprotectin within 12 months of diagnosis is associated with reduced risk of disease progression in patients with Crohn's disease

Authors: Plevris N et al.

Summary: These researchers sought to determine if faecal calprotectin level normalisation within 12 months of CD diagnosis was associated with reduced disease progression in a retrospective UK cohort; 375 patients who had a faecal calprotectin level ≥250 µg/g at diagnosis, ≥1 follow-up faecal calprotectin level measured within the first 12 months of diagnosis, and >12 months of follow-up (median 5.3 years) were included in the analyses. Faecal calprotectin level normalisation within 12 months of diagnosis was recorded for 43.5% of the patients, and these patients had a significantly lower risk of a composite disease progression primary endpoint (Montreal disease behaviour B1 to B2/3, B2 to B3 or new perianal disease, or CD-related surgery or hospitalisation; hazard ratio 0.36 [95% CI 0.24–0.53]), with lower risks of each component (0.22 [0.11–0.45] for progression of Montreal behaviour or new perianal disease, 0.33 [0.21–0.53] for CD-related hospitalisation, and 0.39 [0.19–0.78] for CD-related surgery).

Comment: It is now widely accepted that a treat-to-target approach and early aggressive therapy for CD results in better outcomes. Plevris et al. looked at faecal calprotectin levels and rates of progression of newly diagnosed CD in a retrospective single-centre study over a 12 year period. They defined an elevated calprotectin level as >250 µg/g and normalisation of calprotectin as a level <250 µg/g. They found that patients whose calprotectin level normalised within 12 months of diagnosis had a lower risk of progressive CD (this included a progressive luminal phenotype, CD-related surgery and the development of perianal disease). These findings could suggest that regular monitoring of the patients biochemical response to therapy in the first year should be employed to ensure normalisation of the calprotectin level as well as improvement in clinical symptoms in order to reduce the patient's risk of progressive disease.

Reference: Clin Gastroenterol Hepatol 2021;19:1835–44
Abstract

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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 IBD. 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.