IBD Practice Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

AE = adverse event;
AGITG ASM = Australasian Gastro-Intestinal Trials Group Annual Scientific Meeting;
CD = Crohn's disease; **CI** = confidence interval;
CPD = continuing professional development; **DCP** = digital care programme;
ECCO = European Crohn's and Colitis Organisation;
GESA = Gastroenterological Society of Australia;
HRQoL = health-related quality of life; **IBD** = inflammatory bowel disease;
IV = intravenous; **MaRIA** = magnetic resonance enterography index of activity;
MRE = magnetic resonance enterography;
NSAIDs = nonsteroidal anti-inflammatory drugs;
NZSG = New Zealand Society of Gastroenterology;
PRIQ = Patient-Reported Infections Questionnaire;
SES-CD = simple endoscopic score for CD; **TNF** = tumour necrosis factor;
UC = ulcerative colitis.

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Welcome to the 12th issue of Inflammatory Bowel Disease Practice Review.

Welcome to the 12th issue of Inflammatory Bowel Disease Practice Review. This Review covers news and issues relevant to clinical practice in inflammatory bowel disease. It will bring you the latest updates, both locally and from around the globe, in relation to topics such as new and updated treatment guidelines, changes to medicines reimbursement and licensing, educational, professional body news, and more. Finally, on the back cover, you will find our COVID-19 resources for Gastroenterologists, and a summary of upcoming local and international educational opportunities, including workshops, webinars, and conferences.

We hope you enjoy this Research Review publication and look forward to hearing your comments and feedback.

Kind Regards,

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Clinical Practice

ECCO guidelines on extraintestinal manifestations in IBD

Although the cause of extraintestinal IBD symptoms is still unknown, it may be related to the immune system, genetics, microbiota, and leukocyte movement. The European Crohn's and Colitis Organisation (ECCO) recently updated their guideline for managing extraintestinal manifestations in IBD, which aids healthcare professionals with providing evidence-based care for patients. Manifestations affecting various organs are covered, including fatigue and endocrine manifestations.

A panel of 20 gastroenterologists and experts from other disciplines collaborated to develop the guideline. Using the Oxford Centre for Evidence-Based Medicine methodology, they developed 32 consensus statements.

The key recommendations are:

- Patients with IBD have a higher risk of thrombotic events during active disease, hospitalisation, and surgery. During hospitalisation for acute medical illness or major surgery, prophylactic low-molecular-weight heparin or fondaparinux is recommended. Thromboprophylaxis may also be considered for patients with severe IBD flares.
- Iron supplementation is advised for patients with IBD and iron deficiency anaemia to normalise haemoglobin levels and iron stores. Intravenous (IV) iron is the first-line treatment for clinically active IBD or previous oral iron intolerance. Oral iron may be suitable for patients with mild iron deficiency anaemia and inactive disease.
- Patients with IBD and primary sclerosing cholangitis may benefit from ursodeoxycholic acid to improve liver biochemistry. However, it has no effect on disease progression.
- Patients with bone demineralisation can benefit from bisphosphonates for preventing bone loss and fractures, especially in corticosteroid-induced or postmenopausal osteoporosis.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) could cause flare-ups in Crohn's disease (CD). Thus, the use of NSAIDs in patients with IBD with joint disease should be approached with caution.
- Early dermatological involvement may help skin diseases associated with IBD.
- Ocular manifestations in IBD include anterior uveitis. The guideline recommends taking oral NSAIDs early on and considering corticosteroids or TNFα antagonists in refractory cases.
- Central nervous system manifestations may occur more frequently in patients with IBD, including venous sinus thrombosis, stroke, and central demyelination. TNFα antagonists are contraindicated for patients with IBD and central demyelination.
- Glucocorticoid-induced adrenal insufficiency may occur in patients with IBD using steroids. Thus, judicious use and alternative agents are recommended, especially for maintenance therapy.

Up to 50% of patients with IBD may develop at least one extraintestinal manifestation, leading to significant morbidity and even mortality in certain cases. Identifying and managing these conditions are crucial to improving patient outcomes.

https://tinyurl.com/57kaf9at

Biological treatment cycles in Crohn's disease

An increasing number of licensed biological therapies are now available to treat CD. However, the long-term use of these therapies for maintenance may pose significant financial burden and raise concerns about potential adverse events (AEs). As a result, there is a growing interest in exploring elective discontinuation of biological treatment in specific patients who have achieved sustained remission. There is evidence that re-treatment with the same biological agent often restores remission. This observation has given rise to the concept of utilising cycles of biological therapy, particularly in a subgroup of low-risk patients. This strategy can lessen the burden of treatment for many patients without sacrificing disease control. By adopting this strategy, a substantial number of patients can experience a reduced overall therapeutic burden, limiting their exposure to biological therapy while still maintaining adequate disease control.

ECCO formed a panel of experts to review literature and establish consensus practice points for cycles of biological treatment in patients with CD because of uncertainties about the balance of benefits and risks. The panel aimed to offer evidence-based guidance on various aspects of biological treatment discontinuation and cycling. This included evaluating the risk of relapse after elective treatment discontinuation, identifying predictors of probable relapse or remission, assessing safety considerations, accounting for patient preferences, and considering pharmacoeconomic aspects. It must be noted that most of the data on biological treatment discontinuation and cycling in CD are from anti-TNF medication. Interventional randomised controlled trials are needed to compare biological treatment cycling to current maintenance therapy strategies. Nonetheless, it is crucial to recognise that discussions revolving around biological treatment discontinuation and cycling should be individualised, enabling shared decision-making between patients and their healthcare providers. This patient-centred approach ensures that the most suitable treatment plan is tailored to the individual's specific needs and circumstances.

https://tinyurl.com/bdh2skft

Magnetic resonance enterography scores correlate with the degree of mucosal healing in paediatric Crohn's disease

A recent pilot study assessed the feasibility of using magnetic resonance enterography (MRE) index of activity (MaRIA) and Clermont scores as surrogates for ileocolonoscopy in assessing mucosal healing post-induction treatment in paediatric patients with CD. Sixteen children with known or newly diagnosed ileocolonic CD underwent ileocolonoscopy and MRE at two time points (Week 0 and 12) to evaluate the correlation between the global MaRIA and Clermont indices with the simple endoscopic score for CD (SES-CD).

Both global MaRIA and Clermont scores were effective in detecting mucosal inflammation after treatment and correlated with SES-CD ($p<0.005$). There was a moderate correlation between SES-CD and global MaRIA/Clermont scores for pooled time-point assessments ($p<0.001$). The inter-rater reliability for both global MaRIA and Clermont scores was good ($p<0.001$).

This study highlights the potential of MRE-based global scores, such as MaRIA and Clermont, as reliable tools to monitor disease changes in paediatric patients with CD undergoing induction treatment. More research with bigger groups of patients is needed to confirm these results and establish the usefulness of MRE-based scores in regular clinical practice.

https://tinyurl.com/4texr8mr

Mirikizumab as induction and maintenance therapy for ulcerative colitis

Mirikizumab is a p19-directed antibody targeting interleukin-23. Two randomised, double-blind, placebo-controlled, phase 3 clinical trials tested this treatment for moderate-to-severe ulcerative colitis (UC).

A total of 1,281 patients underwent randomisation in the induction trial. Patients received either IV mirikizumab (300 mg) or a placebo every 4 weeks for 12 weeks during the induction trial. In the maintenance trial, 544 patients who responded well to mirikizumab in the first trial got either a placebo or subcutaneous mirikizumab (200 mg) every 4 weeks for 40 weeks.

Significantly more patients in the mirikizumab group achieved clinical remission (primary endpoint) compared with the placebo group at week 12 of the induction trial (24.2% vs. 13.3%; $p<0.001$) and at week 40 of the maintenance trial (49.9% vs. 25.1%; $p<0.001$). Major secondary endpoints included a clinical response, endoscopic remission, and improvement in bowel-movement urgency. Both trials met the criteria for major secondary endpoints.

Although some AEs, such as nasopharyngitis and arthralgia, were reported more frequently with mirikizumab than with placebo, it was well-tolerated by the patients. Although a few patients treated with mirikizumab experienced opportunistic infections (including herpes zoster infection) and cancer, these occurrences were infrequent.

In conclusion, patients with moderate-to-severe UC experienced better results with mirikizumab than with placebo. The safety profile was favourable, although isolated cases of infections and cancer were observed. More research and monitoring are needed to know if mirikizumab is safe and effective in the long-term. Further, it is currently unclear why patients in the mirikizumab group had a higher rate of cancers. This warrants further investigation and remains to be clarified.

https://tinyurl.com/bdevzv3e

Delayed ustekinumab response has a similar prognosis to early response in ulcerative colitis, despite severity

A recent post-hoc analysis of patient-level data from a phase 3 clinical trial investigated the 1-year outcomes of patients with UC treated with ustekinumab. The study aimed to determine if there were any differences in outcomes between early and delayed responders to ustekinumab and to identify factors that distinguished delayed responders from non-responders.

The study included 642 patients treated with ustekinumab, of which 321 (50%) were early responders, 115 (17.9%) were delayed responders, and 205 (32.1%) were non-responders. Early responders were defined as patients who showed a clinical response to ustekinumab at Week 8. This was indicated by a reduction in total Mayo score of ≥30%, and a reduction in rectal bleeding sub score of ≥1 or a rectal bleeding sub score of ≤1. Delayed responders were Week 8 non-responders who subsequently responded to the treatment at Week 16.

The primary outcome assessed was 1-year clinical remission, defined as a total Mayo score of ≤2 and no sub score >1. There were no significant differences in 1-year clinical remission rates between early and delayed responders ($p=0.233$). Both groups had similar outcomes regardless of the induction dose used.

However, there were some important factors that differentiated delayed responders from early responders. Delayed responders showed a greater inflammatory burden at baseline, with more severe Mayo endoscopic disease ($p=0.015$) and higher levels of C-reactive protein ($p=0.004$). Delayed responders showed a significant decrease in C-reactive protein level and faecal calprotectin level through Week 16, distinguishing them from non-responders ($p<0.0001$).

These findings highlight that early and delayed responders to ustekinumab have similar 1-year outcomes. The key differentiating factor between these groups is the baseline inflammatory burden, which is higher in delayed responders. Monitoring decline of biomarkers, such as C-reactive protein and faecal calprotectin levels, in delayed responders, can be valuable in distinguishing them from non-responders.

https://tinyurl.com/mwsf5eud

Effect of biologics on the risk of advanced-stage IBD-associated intestinal cancer

A recent study evaluated the effect of biologics on the risk of advanced-stage IBD-associated intestinal cancer using data from a nationwide multicentre database. Medical records of patients with CD and UC diagnosed with IBD-associated intestinal neoplasia (dysplasia or cancer) from 1983–2020 were included. Therapeutic agents were classified into three types: biologics, 5-aminosalicylic acid, and immunomodulators. The study compared the pathological cancer stage based on the drug used in patients with both CD and UC.

The study included 1,042 patients, comprising 214 (20.5%) with CD and 828 (79.5%) with UC. Among patients with CD, none of the drugs showed a significant association with cancer stage. Patients with UC who used fewer biologics, 5-aminosalicylic acid, and immunomodulators, however, had a higher chance of developing advanced cancer ($p<0.001$). Biologic therapy decreased the occurrence of advanced-stage cancer in patients diagnosed through regular surveillance ($p=0.043$). Further, multivariate analysis showed that biologic use was significantly associated with a lower risk of advanced-stage disease ($p<0.001$).

Overall, biologic therapy was associated with a lower risk of advanced IBD-associated cancer in patients with UC, but not in those with CD. The findings suggest that the mechanisms of cancer progression may differ between UC and CD, warranting further investigation.

https://tinyurl.com/mu7tmtvs

Remote monitoring tool for assessing infections in IBD

IBD management relies significantly on immunomodulators and biologics, which is associated with an increased risk of infections. Since existing post-marketing surveillance registries tend to focus mainly on severe infections, there is a gap in our understanding of the prevalence of mild and moderate infections. To address this, a remote monitoring tool was developed to assess infections in real-world scenarios among patient with IBD patients. It was validated in a recent study.

A 7-item Patient-Reported Infections Questionnaire (PRIQ) covering 15 different infection categories was created. The questionnaire required patients to recall events over a 3-month period. Infection severity was categorised as mild (self-limiting or treated topically), moderate (requiring oral antibiotics, antivirals, or antifungals), or severe (necessitating hospitalisation or IV treatment). The questionnaire's effectiveness, including comprehensiveness and ease of understanding, were evaluated during cognitive interviews with 36 outpatients with IBD.

Subsequently, the PRIQ was integrated into the myIBDcoach telemedicine platform for a prospective, multicentre cohort study involving 584 patients between June 2020 and June 2021. The aim was to assess the tool's diagnostic accuracy in detecting infections. The researchers cross-referenced reported events with data from general practitioners and pharmacies, which is considered the gold standard for evaluation. To account for within-patient level correlation, agreement was evaluated using linear-weighted kappa with cluster-bootstrapping.

Patients understood the questionnaire well, and no changes were needed. During the validation phase, 584 IBD patients (57.8% female; mean age, 48.6 ± 14.8 years; disease duration, 12.6 ± 10.9 years) completed 1,386 periodic assessments, reporting 1,626 events. The agreement between the PRIQ and the gold standard was high, with a linear-weighted kappa of 0.92 (95% confidence interval [CI], 0.89–0.94). The sensitivity and specificity of the PRIQ for detecting infections (yes/no) were 93.9% (95% CI, 91.8–96.0) and 98.5% (95% CI, 97.5–99.4), respectively.

Thus, the PRIQ has proven to be a valid remote monitoring tool for assessing infections in patients with IBD. Implementing it successfully will help healthcare professionals personalise treatment decisions and improve patient care and safety for IBD management.

https://tinyurl.com/y2fymxjw

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News in Brief

SARS-CoV-2 infection in patients with IBD

An observational longitudinal study compared 937 Italian patients with IBD patients with SARS-CoV-2 infection between the first and second pandemic waves. Compared with the second-wave patients, first-wave patients were older and had more comorbidities. They also had more negative outcomes, like pneumonia, hospitalisation, ventilator use, and death. These differences were attributed to distinct epidemiological situations and diagnostic possibilities between the waves.

https://tinyurl.com/mr3szu49

Self-evidence-based digital care programme improves health-related quality of life

The impact of a digital care program on the quality of life of adults with long COVID and autoimmune diseases, including IBD, was evaluated in a retrospective study. The DCP utilised patient data to guide personalised diet and integrative interventions. Results showed statistically significant improvements in all ten HRQoL domains that were assessed. Participants with more severe symptoms at baseline experienced greater improvements. The evidence based DCP demonstrated high engagement, adherence, and meaningful HRQoL enhancements for participants.

https://tinyurl.com/mr3mpnsf

Patients with Crohn's disease and permanent ileostomy are universally excluded from clinical trials

A systematic review of 81 induction and maintenance clinical trials evaluating biologics and small molecules showed that none of the trials allowed the enrolment of patients with CD and permanent ileostomy. There is a pressing need to identify barriers and establish eligibility and outcome measures to enable the inclusion of CD patients with permanent ileostomy in future clinical trials.

https://tinyurl.com/ykkcrmjc

Declining enrolment and other challenges in IBD clinical trials

Fewer people are signing up for clinical trials on IBD, causing delays and higher costs in developing new treatments. A group of experts from academia and pharmaceutical companies recently examined issues in IBD clinical trials. They focused on study design, investigative centres, physicians, and patients. Higher trial demands in CD made it tough to correlate clinical and endoscopic activity, leading to a drop in enrolment. Complex trial protocols, restrictive eligibility criteria, and increased administrative burdens also contributed to the issue. Enrolment was further hampered by the lack of dedicated time and training for physicians. Patients cited long washout periods and unrealistic protocol requirements as being obstacles to participating in trials. This collaborative effort aims to pave the way for transformative changes in clinical trials, involving investigative centres, research organisations, sponsors, and regulatory agencies.

https://tinyurl.com/2ek3kv4r

COVID-19 Resources for Gastroenterologists

British Society of Gastroenterology

American Gastroenterological Association

American College of Gastroenterology

European Crohn's and Colitis Organisation

Conferences, Workshops, and CPD

Please click on the links below for upcoming local and international Gastroenterology meetings, workshops, and CPD.

NZSG

GESA

AGITG ASM, Christchurch, NZ, 13-16 Nov 2023

World Gastroenterology Organisation – meetings and events

COMS – conferences and meetings on gastroenterology

Research Review Publications

Gastroenterology Research Review with Dr Andrew Buckle and Associate Professor Jonathan Segal.

IBD Research Review with Associate Professors Britt Christensen, Crispin Corte, Jonathan Segal and Dr Emily Wright.

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