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In this issue:

Abbreviations used in this issue:

CD = Crohn's disease; **IBD** = inflammatory bowel disease; **IBS** = irritable bowel syndrome; **IRR** = incidence rate ratio; **OR** = odds ratio; **TNF** = tumour necrosis factor; **UC** = ulcerative colitis; **WBC** = white blood cell.

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Welcome to issue 29 of IBD Research Review.

This issue begins with a summary of consensus statements, developed by the Australian IBD Consensus Working Group, on the use of therapeutic drug monitoring of anti-TNF drugs to optimise their use in the management of IBD. Research published in Lancet reports on the use of telemedicine to reduce outpatient visits and hospital admissions in patients with IBD. Other highlights for this issue include the safety of herpes zoster vaccine in patients with IBD, and the apparent protective effects of being breastfed and also of living rurally on IBD risk. We end this issue and 2017 for IBD Research Review with a systematic review comparing chromoendoscopy with other endoscopic techniques for detecting dysplasia in IBD.

Thank you for your feedback and comments during the year. We look forward to bringing you more IBD-related research next year.

Kind Regards,

Professor Rupert Leong

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Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases

Authors: Mitrev N et al., IBD Sydney Organisation and the Australian Inflammatory Bowel Diseases Consensus Working Group

Summary: A committee of 25 Australian and international experts convened to develop the evidence-based consensus statements presented in this paper on therapeutic drug monitoring-guided anti-TNF therapy in patients with IBD. Consensus was met for 22 of the 24 accepted statements derived and modified using data from a systematic literature search. The committee also noted that more data are needed before therapeutic monitoring of drugs other than anti-TNF agents can be recommended.

Comment: These Australian consensus statements developed through the Australian IBD Consensus Working Group provide guidance on the optimisation of anti-TNF drugs through evidence-based use of therapeutic drug monitoring. Therapeutic drug monitoring should be performed when anti-TNF agents have demonstrated treatment failure with detectable active inflammation (such as by colonoscopy or magnetic resonance enterography). Reactive therapeutic drug monitoring identifies pharmacokinetic versus pharmacodynamic failure; the former may respond to dose increases and by adding/optimising immunomodulator cotherapy. Immunological failure with low anti-TNF trough concentrations and high antidrug antibody levels typically require switching. Low antibody levels, however, may be transient and non-neutralising, and repeat testing is recommended. For patients with confirmed therapeutic failure, a switch within class is preferred in those that have secondary loss of response and a switch out of class is preferred for those with primary nonresponse. Higher trough concentrations might be required for certain phenotypes such as fistulising CD. Proactive therapeutic drug monitoring is still controversial, but will play a greater role in the future. Overall, data are stronger for CD than UC. Limitations include that much of the current evidence relates to cross-sectional data rather than interventional studies. Also the current PBS system uses patient-reportable symptoms and disease activity indices rather than more objective therapeutic outcomes of disease recovery. More data are needed on the use of therapeutic drug monitoring in non-anti-TNF biological agents. Overall two out of 24 statements did not meet consensus – being that therapeutic drug monitoring data should be available at the time of registration of new therapies, and patients in clinical remission should be considered for a drug holiday when they are found to have subtherapeutic drug trough concentrations. The authors thank GESA and AIBDA for providing the project grant that funded this research output.

Reference: Aliment Pharmacol Ther 2017;46(11–12):1037–53

Abstract

Telemedicine for management of inflammatory bowel disease (myIBDcoach)

Authors: de Jong MJ et al.

Summary: Adult outpatients with IBD and without ileoanal or ileorectal pouch anastomoses were randomised to receive care via a telemedicine system (myIBDcoach) involving monitoring and registration of disease activity (n=465) or standard care (n=444) in this 12-month, pragmatic, multicentre trial. Compared with standard care, the telemedicine intervention was associated with significantly lower mean numbers of outpatient visits to a gastroenterologist or nurse (1.55 vs. 2.34 [p<0.0001]) and hospital admissions (0.05 vs. 0.10 [p=0.046]) with no significant between-group difference for mean patient-reported quality of life score or mean number of flares, corticosteroid courses, emergency visits or surgeries.

Comment: This prospective, randomised, controlled study demonstrated that use of telemedicine can significantly reduce outpatient visits and hospitalisations in comparison with standard ambulatory clinic visits. The benefit of telemedicine might be also to prioritise resource utilisation in managing sicker patients and to maintain well subjects in the community. Telemedicine did not reduce mean flares, corticosteroid courses, emergency visits or surgeries, some of the important clinical endpoints. There is selection bias in that subjects with better health literacy, greater acceptance of teleconferencing or are more motivated are those who have the greatest likelihood of benefit. Patients who are less engaged with healthcare would still be at risk of loss to follow-up and poorer outcomes, and would have been excluded from the study.

Reference: Lancet 2017;390(10,098):959–68
Abstract

Risk factors for thiopurine-induced myelosuppression and infections in inflammatory bowel disease patients with a normal *TPMT* genotype

Authors: Broekman MMTJ et al.

Summary: This *post hoc* analysis of data from the TOPIC trial, which investigated responses to thiopurines in patients with IBD, explored risks of thiopurine-induced leucopenia and infections in the 695 participants who did not carry a *TPMT* variant. Leucopenia was recorded for 45 of these participants, developing in a median of 56 days. Mercaptopurine recipients had a higher risk of developing leucopenia than azathioprine recipients (adjusted hazard ratio 2.61 [95% CI 1.39–4.88]), and participants with a higher WBC count at baseline had a lower risk (0.80 [0.71–0.89]). The risk of infection was increased with each 10-year increase in age (hazard ratio 2.07 [1.18–3.63]) and concomitant biological agent use (2.15 [1.14–4.07]).

Comment: This study aimed to identify leucopenia, defined as WBC count $<3.0\times10^9$/L, and infections in *TPMT* wildtype subjects commencing thiopurines. Risk of leucopenia was increased in subjects who had a lower baseline WBC count and use of mercaptopurine. Patients at risk of infections were older subjects, and concomitant biological agent users. The study simply reminds us of the need to monitor WBC counts in subjects commencing and continuing on thiopurines, and that *TPMT* variant assessment only accounts for a minority of those who develop leucopenia. Mild leucopenia might not necessarily result in clinical sequelae. In Australia, frequent use of thioguanine metabolite monitoring also serves to risk manage patients. Elderly patients and those who are on biological agents require more intensive monitoring and counselling for avoidance, prevention, earlier presentation and better management of sepsis.

Reference: Aliment Pharmacol Ther 2017;46(10):953–63
Abstract

A multi-centre audit of excess steroid use in 1176 patients with inflammatory bowel disease

Authors: Selinger CP et al.

Summary: Steroid use was evaluated in 1176 unselected outpatients, and factors associated with excess exposure assessed, in this British research; 30% of the patients had received steroids in the prior 12 months. Steroid dependency/excess was identified in 14.9%, and was more common among patients with moderate/severe UC than those with CD (42.6% vs. 28.1% [p=0.027]). The researchers judged steroid dependency/excess to be avoidable in 49.1% of cases. Inappropriate steroid excess occurred at an annual incidence of 7.1%. Independent predictors of inappropriate steroid excess included moderate-to-severe versus mild/quiescent disease activity for both UC and CD (respective ORs 4.59 [95% CI 1.53–20.64] and 4.60 [2.21–12.00]). Inappropriate steroid excess was less likely in patients with CD from centres with an IBD multidisciplinary team (OR 0.62 [95% CI 0.46–0.91]) and patients with UC attending dedicated IBD clinics (0.64 [0.21–0.94]). There was also an association between the total number of gastroenterology trainees and inappropriate steroid excess.

Comment: This large audit of steroid usage involved 1176 IBD patients using a British database. These population-based data revealed key quality indicators of steroid use in the previous 12 months to be 30%, steroid-dependency or excess in 15% and avoidable steroid use in 7%. Steroid use was higher in UC (43%) than CD (28% [p=0.027]) and in those with greater disease severity. Predictors of inappropriate use in CD included management outside of IBD multidisciplinary teams, and in UC, treatment outside of dedicated IBD clinics. These data can be used for personal or departmental audits. Shared care of steroid-dependent IBD subjects through comanagement with IBD clinics is also a reasonable recommendation.

Reference: Aliment Pharmacol Ther 2017;46(10):964–73
Abstract

Systematic review with meta-analysis: breastfeeding and the risk of Crohn's disease and ulcerative colitis

Authors: Xu L et al.

Summary: There were 35 studies reporting data on breastfeeding during infancy in patients with CD (n=7536) or UC (n=7353) versus healthy controls (n=330,222) included in this systematic review and meta-analysis. The risks of developing CD and UC were lower among participants who had ever been breastfed (respective ORs 0.71 [95% CI 0.59–0.85] and 0.78 [0.67–0.91]); the magnitude of this inverse association was significantly greater among Asian versus Caucasian participants with CD (ORs 0.31 vs. 0.78 [p=0.0001]). The protective effect of breastfeeding was greater as duration of breastfeeding increased, with breastfeeding for ≥12 months associated with lower risks of developing CD and UC (respective ORs 0.20 [95% CI 0.08–0.50] and 0.21 [0.10–0.43]) compared with 3 or 6 months.

Comment: Data from our Sydney IBD cohort were included in this meta-analysis on the benefit of breastfeeding on the risk of developing IBD in newborns. Breastfeeding modifies babies' intestinal microbiomes, such as decreased colonisation of harmful strains of *Clostridium difficile*. Breastmilk also contains immunomodulatory compounds that influence the development of the innate mucosal immunity. The development of immunological memory to pathogens may prevent inappropriate hyperimmune responses seen in IBD. Modifying early life events have a stronger effect in comparison to modifying exposures during adult life, and may offer the greatest potential for primary prevention of IBD. What was most surprising was the magnitude of benefit, with a 29% reduction in CD and a 22% reduction in UC with any breastfeeding. When breastfed for >12 months, the risk of CD was further decreased with an OR of 0.20 (95% CI 0.08–0.50), as was the risk of UC with an OR of 0.21 (0.10–0.43); this duration response suggests that for every 3 months of breastfeeding, the risk of developing IBD decreased by 10–20% cumulatively. New knowledge provided by this meta-analysis of 14,889 IBD subjects and 330,222 controls includes that the benefit was independent of maternal ethnicity, but carried an even greater magnitude of benefit in developing regions of the world compared with Caucasians. These data need to be translated to our consultations, and breastfeeding should be strongly promoted to our IBD patients contemplating pregnancy.

Reference: Aliment Pharmacol Ther 2017;46(9):780–9
Abstract

Systematic review with meta-analysis: enteral nutrition therapy for the induction of remission in paediatric Crohn's disease

Authors: Swaminath A et al

Summary: This was a systematic review of nine eligible studies comparing exclusive enteral nutrition with exclusive corticosteroid treatment for paediatric patients with CD; eight of these studies (n=451) were able to be meta-analysed. There was no significant difference between exclusive enteral nutrition versus corticosteroids for inducing remission (OR 1.26 [95% CI 0.77–2.05]), a finding that was consistent in patients with newly diagnosed CD (1.61 [0.87–2.98]) and in those with relapsed CD (0.76 [0.29-1.98]). Exclusive enteral nutrition was associated with a greater likelihood of intestinal healing compared with corticosteroids (OR 4.5 [95% CI 1.64–12.32]), but there was no significant difference for the frequency of C-reactive protein level or faecal calprotectin level normalisation (0.85 [0.44–1.67] and 2.79 [0.79–10.90], respectively).

Comment: Exclusive enteral nutrition induces remission in paediatric CD. This meta-analysis was performed to promote the benefit of exclusive enteral nutrition to units that have yet to adopt this strategy. There was no significant difference between the efficacy of exclusive enteral nutrition and corticosteroids. Mucosal healing, however, was significantly higher with exclusive enteral nutrition compared with corticosteroids (OR 4.5 [95% CI 1.64–12.32]). These data confirm exclusive enteral nutrition to be similar to steroids for the induction of remission in paediatric CD, but with avoidance of steroid-induced side effects and the additional benefit of mucosal healing.

Reference: Aliment Pharmacol Ther 2017;46(7):645–56
Abstract

Safety of herpes zoster vaccination among inflammatory bowel disease patients being treated with anti-TNF medications

Authors: Khan N et al.

Summary: The safety of herpes zoster vaccine during anti-TNF therapy was evaluated in a retrospective cohort of 56,417 US patients with IBD. There were 59 patients who received herpes zoster vaccine, at a median age of 64.9 years, while receiving an anti-TNF agent; 12 were also receiving a thiopurine and 95% had a Charlson Comorbidity Index score of ≥2. There was a median of two encounters within 42 days after receiving herpes zoster vaccine, during which time no cases of herpes zoster developed.

Comment: There is a need to avoid live vaccines in IBD patients on anti-TNF therapy. The magnitude of risk on exposure to live vaccines, however, is not known. Herpes zoster vaccine is currently a live vaccine. This retrospective study using the US Veterans Affairs healthcare database identified 59 subjects on anti-TNF therapy who received herpes zoster vaccine, and found no cases of herpes zoster within 42 days of vaccination. Subjects had a median age of 65 years and a high proportion had comorbidities, in whom the vaccination has the greatest benefit. These data are reassuring of the relative safety of herpes zoster vaccination, but best practice remains vaccination of IBD subjects prior to the commencement of immunosuppression whenever possible.

Reference: Aliment Pharmacol Ther 2017;46(7):668–72
Abstract

Responsiveness of endoscopic indices of disease activity for Crohn's disease

Authors: Khanna R et al.

Summary: Responsiveness to SES-CD (Simple Endoscopic Score for Crohn's Disease) and CDEIS (Crohn's Disease Endoscopic Index of Severity) score changes were investigated using 56 pairs of colonoscopy video recordings performed at baseline and at week 8–12 in participants in a trial of adalimumab for CD. High correlations were seen between changes in both endoscopic instruments and Global Endoscopic Evaluation Of Severity; effect sizes for SES-CD were numerically higher for change defined according to treatment assignment and absolute change in total PRO2 (a patient-reported outcome) score of 50. SES-CD had standardised effect size and Guyatt's responsiveness statistic estimates based on treatment assignment of 0.84 (95% CI 0.53–1.15) and 0.79 (0.48–1.09), respectively, and the respective estimates for CDEIS were 0.72 (0.42–1.02) and 0.75 (0.45–1.06). When based on an absolute change in total PRO2 score of ≥50 points, the respective estimates for standardised effect size and Guyatt's responsiveness statistic for SES-CD were 0.76 (95% CI 0.49–1.02) and 0.93 (0.64–1.21), and the respective estimates for CDEIS were 0.70 (0.44–0.97) and 0.83 (0.55–1.10). There was no improvement in the responsiveness estimates when stenosis was omitted as an index item and adjustments were made for observed segments.

Comment: This study is of interest to those designing clinical trials but of little relevance to most clinicians. The use of endoscopic scoring systems in CD is currently limited to clinical drug trials. Neither CDEIS nor SES-CD has been fully validated, and this study of adalimumab tested the responsiveness of both scoring systems. SES-CD demonstrated greater responsiveness to treatment, and as such will likely be the preferred scoring system used in trials in the assessment for mucosal healing.

Reference: Am J Gastroenterol 2017;112(10):1584–92
Abstract

Rural and urban residence during early life is associated with risk of inflammatory bowel disease

Authors: Benchimol EI et al., on behalf of the Canadian Gastro-Intestinal Epidemiology Consortium

Summary: The relationship between IBD and residence in a rural versus urban household at diagnosis or within the first 5 years of life was explored in this population-based covering four Canadian provinces. Compared with residents from rural areas (n=6662), those from urban areas (n=38,905) had a higher incidence of IBD (33.16 vs. 30.72 per 100,000; IRR 0.90 [95% CI 0.81–0.99]), with the association particularly strong in children aged <10 and 10–17.9 years (respective IRRs 0.58 [0.43–0.73] and 0.72 [0.64–0.81]). In a birth cohort of 331 rural and 2302 urban residents, living in a rural area during the first 1–5 years of life significantly decreased the risk of developing IBD (IRRs 0.75–0.78).

Comment: This Canadian study showed growing up in a rural environment was associated with a decreased risk of developing IBD. The younger the age, the stronger was the protection. One can speculate the role of the hygiene hypothesis in this association. Growing up in an urban environment might be associated with greater hygiene standards and higher socioeconomic standards that result in decreased diversity of the microbiome. Microbiome diversity might protect against dysbiosis that results in immune-related diseases. There are many confounding factors, but there seems to be consistency where urban density is frequently associated with the increased risk of developing IBD.

Reference: Am J Gastroenterol 2017;112(9):1412–22
Abstract

Exposure to oral contraceptives increases the risk for development of inflammatory bowel disease

Authors: Ortizo R et al.

Summary: This was a meta-analysis of 20 case-control and cohort studies comparing IBD development in individuals with or without prior oral contraceptive pill exposure. Compared with oral contraceptive pill nonexposure, exposure was associated with a significant increase in the likelihood of developing IBD (OR 1.32 [95% CI 1.17–1.49]), an association that was seen both for CD and UC (1.24 [1.09–1.40] and 1.30 [1.13–1.49], respectively).

Comment: This meta-analysis found an association between use of oral contraceptive pills and subsequent development of IBD. Oral contraceptive pill use was linked to an OR of 1.32 (95% CI 1.17–1.49), which is not very strong. The risk was for both CD and UC. However, the case-control studies included might be criticised for recall bias. Data stemming from older generations of oral contraceptive pills containing higher oestrogen strengths might not be translatable to current formulations.

Reference: Eur J Gastroenterol Hepatol 2017;29(9):1064–70
Abstract

The prevalence of irritable bowel syndrome-type symptoms in inflammatory bowel disease patients in remission

Authors: Hoekman D et al.

Summary: The prevalence of IBS-type symptoms in IBD patients with low faecal calprotectin levels (biochemical remission) and the relationship of these symptoms with faecal calprotectin levels were explored in this observational, cross-sectional study of 74 adults with a history of IBD who had calprotectin levels <200 µg/g during routine follow-up at a single institution. Rome III questionnaire IBS criteria were met by 33 of the patients (45%). Compared with patients without IBS-type symptoms, a greater proportion of those with such symptoms had ileal disease (55% vs. 24% [p=0.03]); the two groups were similar for other characteristics, and there was no significant difference for calprotectin levels (p=0.91). Among the patients with IBS-type symptoms, 64% were diarrhoea-predominant and 27% were mixed-type IBS.

Comment: This study used faecal calprotectin to determine whether ongoing bowel symptoms might be related to IBS. However, the cutoff used of 200 µg/g faeces might be too high and a large proportion of the 45% with symptoms may have ongoing intestinal inflammation. The reliability of these data is therefore questionable. This is supported by the fact that ileal CD, the phenotype where calprotectin underestimates disease, was most likely to exhibit symptoms. Dietary causes of gut symptoms also need to be excluded. Patients with IBD, even in mucosal healing, are likely to have impaired intestinal permeability responsible for ongoing bowel symptoms. One should not simply attribute ongoing bowel symptoms with 'true IBS' in IBD subjects, as concluded in this study, as this potentially results in under-treatment.

Reference: Eur J Gastroenterol Hepatol 2017;29(9):1086–90
Abstract

Chromoendoscopy for surveillance in ulcerative colitis and Crohn's disease

Authors: Iannone A et al.

Summary: This systematic review of ten randomised trials (n=1500) found that compared with other endoscopic techniques, chromoendoscopy was associated with a higher likelihood of detecting dysplasia in patients with IBD (risk ratio 1.37 [95% CI 1.04–1.79]); however, subgroup analyses confirmed this was the case only when compared against standard-definition white-light endoscopy (2.12 [1.15–3.91]). Chromoendoscopy also took significantly longer to perform than other techniques (mean difference 8.91 min [95% CI 1.37–6.45]), and did not differ significantly in terms of detecting dysplastic subtypes, dysplasia by targeted biopsies, sensitivity or specificity.

Comment: This study confirms the role of chromoendoscopy in identifying more patients with dysplasia when compared against standard-definition white-light endoscopy. Chromoendoscopy doubled the number of patients identified with dysplasia (risk ratio 2.12 [95% CI 1.15–3.91]), which is clinically significant as this would then modify follow-up intervals as well as permit resection of the lesion prior to development of invasive cancer. However, chromoendoscopy was associated with longer procedural times, which was not surprising. Few studies to date have compared high-definition white-light colonoscopy with chromoendoscopy. The recently published FUSION study using FUSE (full-spectrum endoscopy) with high-definition white-light colonoscopy (IBD Research Review, issue 28) showed that even panoramic visualisation in conjunction with high-definition white-light colonoscopy cannot replace chromoendoscopy.

Reference: Clin Gastroenterol Hepatol 2017;15(11):1684–97
Abstract

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Independent commentary by Professor Rupert Leong MBBS, FRACP, MD, AGAF is a Senior Staff Specialist gastroenterologist, Director of Endoscopy and leads the Inflammatory Bowel Disease Services at Concord Hospital, Sydney. He has made a substantial contribution to research with over 170 publications. He holds executive positions on the Research Committee of GESA, is section editor of the Journal of Gastroenterology and Hepatology, and international editorial board member of the American Journal of Gastroenterology, Gastrointestinal Endoscopy and Intestinal Research. Rupert is a principal supervisor to PhD, MPhil and Masters Research students through UNSW, University of Sydney and Macquarie University.

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