Welcome to issue 23 of IBD Research Review.

I hope you have been enjoying receiving your copies of IBD Research Review, and I am delighted to provide the expert commentary for this issue. I have included research on a range of topics, beginning with a meta-analysis of studies reporting the prevalence and incidence of, and risk factors for, neoplasia in patients with IBD following colectomy. There are two papers focussing on pregnancy, one looking at anti-TNF drug exposure and clearance in neonates born to mothers receiving these agents, and the other reporting birth outcomes for women with IBD who have received assisted reproductive therapies. The last paper reports an association between higher adalimumab concentrations and mucosal healing in patients with CD.

I am keen to hear your thoughts on these papers and other research in IBD, so feel free to contact me at the email address below.

Kind Regards,

Dr Edward Shelton, MBBS (Hons.), FRACP
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Risk of neoplasia after colectomy in patients with inflammatory bowel disease

Authors: Derikx LAAP et al.

Summary: This systematic review and meta-analysis reported CRC (colorectal cancer) prevalences from patients who underwent rectal stump surgery (13 studies), IRA (ileorectal anastomosis; 35 studies) or IPAA (ileal pouch anal anastomosis; 33 studies). Compared with the IPAA group, significantly greater proportions of patients in the rectal stump and IRA groups developed CRC (2.1% and 2.4%, respectively, vs. 0.5%; OR for IRA plus rectal stump versus IPAA group, 6.4 [95% CI 4.3–9.5]). The most important risk factor for developing postcolectomy CRC was a history of CRC (respective ORs following IRA and IPAA, 12.8 [95% CI 3.31–49.2] and 15.0 [6.6–34.5]).

Comment: Colonic IBD patients may undergo colectomy with restorative procedures including IPAA, IRA or permanent end ileostomy with rectal stump. There is a risk for neoplasia in the ileoanal pouch or residual rectum, but data to guide our surveillance are limited. In this systematic review, a greater proportion of patients with residual rectums (2.1% and 2.4% for rectal stump and IRA) compared with patients with IPAA (0.5%) developed neoplasia (6.4× risk). Risk factors for neoplasia following IPAA and IRA included IBD duration and prior colorectal neoplasia, with insufficient data to assess primary sclerosing cholangitis and pouchitis as risk factors. This analysis helps to inform us on the risk of cancer following colectomy, with prevalence in the pouch after IPAA being very low and around 1/10 lifetime risk of CRC in the general population (~1 in 21). These estimates will be helpful when discussing surgical options with patients and guiding surveillance, particularly in patients with a residual rectum, long duration of IBD and prior colorectal neoplasia.


Abstract

Abbreviations used in this issue:
CD = Crohn’s disease; CRC = colorectal cancer; CTE = computed tomographic enterography; FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides and polyols; GI = gastrointestinal; IBD = inflammatory bowel disease; IPAA = ileal pouch anal anastomosis; IRA = ileorectal anastomosis; MRE = magnetic resonance enterography; OR = odds ratio; SCCAI = Simple Clinical Colitis Activity Index; TNF = tumour necrosis factor; UC = ulcerative colitis.

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Radiological response is associated with better long-term outcomes and is a potential treatment target in patients with small bowel Crohn's disease

Authors: Deepak P et al.
Summary: This paper reported on 150 patients with small-bowel CD of median 9 years duration who had undergone pretherapy CTE (CT enterography)/MRE and follow-up CTE or MRE after 6 months, or two CTE/MREs ≥6 months apart during maintenance therapy. The patients had 223 inflamed small bowel segments, including 76 with strictures and 62 with penetrating, nonperianal disease, and 49% had ileal distribution. The respective complete and partial radiological response rates were 37% and 26%, leaving 37% as nonresponders. Multivariable Cox models showed that complete and partial responses were associated with a lower likelihood of subsequent hospitalisation and surgery (0.28 [0.15–0.50] and 0.34 [0.18–0.63]), and that complete response was associated with lower likelihood of steroid usage (respective hazard ratios 0.37 [95% CI 0.21–0.64] and 0.45 [0.26–0.79]), and that complete response was associated with lower likelihoods of subsequent hospitalisation and surgery (0.28 [0.15–0.50) and 0.34 [0.18–0.63]).

Comment: We are increasingly adopting a treat-to-target strategy in CD to optimise patient outcomes. Mucosal healing with ileocolonoscopy is the most important target, but can be limited in assessing transmural involvement, more proximal disease and disease beyond strictures. Targets are also less clearly defined in isolated small-bowel CD. In addition, faecal calprotectin is less useful and assessment with capsule endoscopy is expensive. This study retrospectively evaluated disease progression using CTE and MRE in 150 small-bowel CD patients who had baseline imaging prior to treatment initiation with follow-up imaging on therapy (median time 451 days). Radiological response to medical therapy was associated with significant reductions in corticosteroid rescue, (median time 451 days). Radiological response to medical therapy was associated with significant reductions in corticosteroid rescue, (median time 451 days). Radiological response to medical therapy was associated with significant reductions in corticosteroid rescue, (median time 451 days). Radiological response to medical therapy was associated with significant reductions in corticosteroid rescue, (median time 451 days). Radiological response to medical therapy was associated with significant reductions in corticosteroid rescue, (median time 451 days).

Reference: Am J Gastroenterol; Published online May 10, 2016

Fermentable carbohydrate restriction (low FODMAP diet) in clinical practice improves functional gastrointestinal symptoms in patients with inflammatory bowel disease

Authors: Prince AC et al.
Summary: Eighty-eight consecutive patients with IBD and coexisting functional-like GI symptoms from routine clinical practice consumed a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet in this research. Compared with baseline, at follow-up of ≥6 weeks the proportion of participants reporting satisfactory relief of symptoms was significantly greater (76% vs. 16% [p<0.001]), and there were significant decreases in severity for most symptoms and in the mean Gastrointestinal Symptoms Rating Scale composite symptom score (0.7 vs. 1.2 [p<0.001]), and significant increases in ‘normal’ stool form and ‘normal’ stool frequency on the Bristol Stool Form Scale.

Comment: Functional GI symptoms occur in 35–57% of patients with quiescent IBD and patients commonly inquire about dietary therapy and seek nonmedical dietary recommendations via the Web. In this prospective study, patients were provided advice by a registered dietician rather than given a strict diet, which reflects real-world practice. Many of us have already extrapolated findings from non-IBD patients and utilised the low FODMAP diet in our IBD patients with functional GI symptoms. This study provides further evidence for its utility. We need to be judicious with implementation of dietary restriction in IBD to prevent unnecessary dietary restrictions. With the high proportion of IBD patients with functional GI symptoms, this study reinforces the need for objective measures of gut inflammation prior to therapy escalation.


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Reference: Am J Gastroenterol; Published online May 10, 2016

Abstract

Selection of research and expert commentary provided by Dr Edward Shelton, a gastroenterologist sub-specialising in IBD. He graduated from Monash University and completed a Luminal and Inflammatory Bowel Disease Fellowship at Monash Health. He undertook a further Advanced Inflammatory Bowel Disease Fellowship at Massachusetts General Hospital in Boston where he held a position as a Research Fellow in Medicine at Harvard University and published research on biological therapies in IBD. He works in the IBD service at Monash Health, Melbourne.


Abstract

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Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection

Authors: Julsgaard M et al.

Summary: In a prospective study of 80 pregnant women with IBD, researchers in this multinational trial examined adalimumab (n=36) and infliximab (n=44) concentrations in umbilical cord blood, the rate of clearance in newborns after birth and the occurrence of maternal drug concentrations and infection risk during the first year of life. Time from last exposure inversely correlated with cord blood adalimumab and infliximab concentrations (respective r values −0.64 [p=0.0003] and −0.77 [p<0.0001]) and mothers’ blood concentrations at the time of birth (β = −0.80 [p=0.0001]). The median infant-mother drug concentration ratio at birth for adalimumab was 1.21 while for infliximab it was 1.97. Mean infant drug clearance times were 4.0 months for adalimumab and 7.3 months for infliximab (<0.0001); drugs were undetectable in infants by 12 months. Five percent of infants developed bacterial infections and 20% developed viral infections. Where mothers had received the combination of an anti-TNF agent and thiopurine, the relative infection risk compared with anti-TNF monotherapy was 2.7 (95% CI 1.10–6.78).

Comment: There are limited data on anti-TNF clearance and development of infection in infants exposed to anti-TNFs in utero. This international multicentre prospective study included 80 pregnant women with IBD from Denmark, Australia and New Zealand. Time from last exposure was inversely correlated to umbilical cord drug concentration. The median time to drug clearance was slower for infliximab at 7.3 months versus adalimumab at 4.0 months. There was no significant difference in disease flares in women who stopped anti-TNF therapy before or after gestational week 30. These data add to our growing understanding of anti-TNF kinetics. The increased risk of infection in infants exposed to combination therapy is consistent with the PIANO study and we should exercise caution using combination therapy in pregnant patients. This important study will assist in counselling and managing pregnant patients exposed to these drugs.

Reference: Gastroenterology; Published online Apr 7, 2016

Live birth and adverse birth outcomes in women with ulcerative colitis and Crohn’s disease receiving assisted reproduction

Authors: Nærgård BM et al.

Summary: This 20-year research explored the probabilities of live births and adverse birth outcomes in a cohort of 182 Danish women with CD and 432 women without an IBD who had undergone assisted reproductive technology treatments (respective totals of 554, 1360 and 148,540 treatments in each group). Women with UC, but not CD, had a significantly lower chance of a live birth for each embryo transfer (respective ORs 0.73 [95% CI 0.58–0.92] and 0.77 [0.52–1.14]); however, the likelihood was significantly reduced in women who had undergone CD surgery prior to assisted reproductive therapy (OR 0.51 [0.29–0.91]). Women with UC also had a significantly greater likelihood of preterm birth in analyses including singleton and multiple births (OR 5.29 [95% CI 2.41–11.63]) but not singleton births only (1.80 [0.49–6.62]).

Comment: Women with IBD are expected to have infertility rates at least as high as the general population (10–15%), particularly in the setting of pelvic surgery, and are therefore candidates for assisted reproductive therapy. This large nationwide cohort study allows us to do subgroup analyses on the outcomes of assisted reproductive therapy according to IBD type and prior surgery, but could not account for confounders including disease severity and/or medications. Both UC and CD patients have less success with assisted reproductive therapy. UC surgery does not affect fertility, possibly explained by removal of the colon and source of inflammation. This is reassuring, as patients with IPAA have higher infertility rates. The risk of higher preterm birth in women with UC, except those with singleton pregnancies, raises concern, and these patients need to be closely monitored during pregnancy. Women with CD can be reassured that they will have normal pregnancy outcomes with assisted reproductive therapy. This study did not address the effect of assisted reproductive therapy on the course of IBD.


Identifying predictors of low adherence in patients with inflammatory bowel disease

Authors: Coenen S et al.

Summary: These researchers surveyed 471 ambulatory patients with IBD and 99 controls without IBD during visits to a tertiary IBD-referral centre with the aim of identifying predictors of nonadherence to medical therapy. Compared with controls, the patients with IBD were less likely to report low adherence (MMAS-8 [Morisky 8-item Medication Adherence Scale] score <2; 36% vs. 49% [p=0.021]). A multivariable analysis revealed that low adherence among patients with IBD was independently predicted by age >40 years (OR 1.59 [95% CI 1.057–2.389]), higher educational level (1.961 [1.305–2.946]), being single (1.641 [1.020–2.639]) and mesalazine use (1.591 [1.018–2.467]), whereas self-employment protected against low adherence (0.397 [0.167–0.946]).

Comment: Nonadherence to therapy in IBD patients is an important consideration in assessment of our patients and in nonresponders. We can independently assess nonadherence with thiopurine metabolite testing and ensure patients receive their drug with infliximab infusions. The higher rate of nonadherence in patients taking mesalazine may be related to higher pill burden or milder disease activity. Higher education level is associated with decreased adherence similar to the trend seen with vaccination uptake. Paradoxically, taking time to educate our patients regarding disease and medication is likely to increase adherence.


Abstract

Association between breast cancer recurrence with immunosuppression in rheumatoid arthritis and inflammatory bowel disease

Authors: Mamtani R et al.

Summary: Recurrent breast cancer associated with methotrexate, thiopurines or anti-TNF therapy use was investigated in three retrospective cohort studies enrolling women with rheumatoid arthritis or IBD. Recurrent breast cancer was identified in 107 women during 5196 person-years of follow-up. There was no significant increase in breast cancer recurrence between medication users and nonusers for methotrexate (20.5 vs. 19.6 per 1000 person-years; adjusted hazard ratio 1.07 [95% CI 0.67–1.68]), thiopurines (22.3 vs. 17.6 per 1000 person-years; 2.10 [0.62–7.14]) or anti-TNF agents (22.3 vs. 19.5 per 1000 person-years; 1.13 [0.65–1.97]).

Comment: There are limited data to guide our management in the face of malignancy. Society guidelines generally recommend waiting 5 years prior to recommencement of immunosuppressive therapy, but this is expert opinion only. Due to the small number of agents, large population-based registries are needed to detect cancer recurrence. This study used Medicare data and combined IBD and rheumatoid arthritis populations to include 2684 women with a prior history of breast cancer to detect the risk of breast cancer recurrence. Reassuringly, there was no increased risk with immunosuppressive therapy compared with no therapy. There is no comment on combination therapy, and these data do not help us to select an individual therapy over another in a patient with prior breast cancer, although it doesn’t suggest that anti-TNF therapy is higher risk in this population as has been previously suggested. We are also not further informed regarding the optimal timing of therapy recommencement following a cancer diagnosis, and this needs to be a joint decision between the oncologist and IBD physician. These data are reassuring for clinicians and will help inform practice in the setting of malignancy.

Reference: Arthritis Rheumatol; Published online May 9, 2016

Abstract

Diagnostic performance of the Simple Clinical Colitis Activity Index self-administered online at home by patients with ulcerative colitis

Authors: Marin-Jiménez I et al., and on behalf of the CRONICA-UC study investigators

Summary: The CRONICA-UC study followed 199 patients with UC for 6 months, during which time they completed the SCCAI (Simple Clinical Colitis Activity Index) assessment online at home at 3 months and 6 months. For reference, gastroenterologists completed the in-clinic SCCAI within 48 hours. There was good correlation between the patients’ and physicians’ SCCAI scores (Spearman’s r=0.79), with 85% agreement for remission or activity (κ=0.66). Agreement between the patients and physicians was greater at 6 months than at 3 months (89.3% vs. 80.8% [p=0.027]). The respective negative and positive predictive values for active disease were 94.5% and 68.0%.

Comment: New communication technologies including telemedicine and smartphone applications are well accepted by patients, but not commonly implemented by clinicians. The SCCAI is a simple disease assessment tool and is entirely composed of clinical items, making it useful in the clinic and also feasible for patients to remotely self-assess UC activity. The high negative predictive value for active disease means that this tool could be implemented to remotely assess patients. This could limit requirement for stable patients to attend clinic, allowing physicians in busy clinics to focus on the sicker patients and decrease the burden on patients. This assessment tool could also allow patients to be more involved in self-management.


Abstract
Switching between infliximab originator and biosimilar in paediatric patients with inflammatory bowel disease: preliminary observations

Authors: Sieczkowska J et al.

Summary: This paper reported on 32 paediatric patients with CD and seven with UC who were switched from the infliximab originator to a biosimilar, Remsima. The mean numbers of infliximab originator infusions prior to switching to the biosimilars in the CD and UC patients were 9.9 and 5.1, respectively. The clinical remission rates after biosimilar use were 86% and 57% in the CD and UC patients, respectively, and at latest follow-up 80% of patients with CD and four of those with UC were in remission. One of the patients with CD had an infusion reaction to the biosimilar, leading to discontinuation. Switching to the biosimilar did not significantly alter the incidence of sporadic mild adverse events, with the safety profile of the biosimilar consistent with that of infliximab.

Comment: Inflectra, a biosimilar for infliximab, is now available on the PBS and there are other biosimilars on the horizon. There is limited information on the long-term efficacy and safety of switching from one biological drug to a biosimilar, and there is concern that this may occur at a pharmacy level. Due to subtle differences in structure between the biosimilar and the originator, there is a risk of immunogenicity. This is a very small study showing that a switch appears to be safe, but certainly not sufficient to allay concerns. We require larger registry studies, and in the interim, pharmacovigilance is required.

Reference: J Crohns Colitis 2016;10(2):127–32

Abstract

Higher adalimumab drug levels are associated with mucosal healing in patients with Crohn's disease

Authors: Zittan E et al.

Summary: These authors reviewed data from 60 patients who had received adalimumab for CD. Compared with patients without mucosal healing, those with mucosal healing had a significantly lower median C-reactive protein level (1.2 vs. 14.4 mg/dL) and a significantly higher median adalimumab trough concentration (14.7 vs. 3.4 µg/mL). Median adalimumab trough concentration was also significantly higher in patients with clinical and endoscopic remission (13.0 vs. 4.8 µg/mL). A cutoff adalimumab trough concentration of 8.14 µg/mL was identified as best for discriminating between patients with versus without mucosal healing, with respective sensitivity and specificity values of 91.4% and 76.0% and respective positive and negative predictive values of 84.2% and 86.4%.

Comment: Most prior studies assessing anti-TNF drug concentrations have looked at infliximab. Those assessing adalimumab trough concentrations have mostly used clinical indices as the primary outcome measure. In this retrospective study, patients in the maintenance phase of adalimumab therapy with mucosal healing had higher adalimumab trough concentrations compared with those without. The optimum adalimumab trough concentration in this study, using the Prometheus assay, of 8.14 µg/mL is higher than previously reported. This threshold may vary depending on the assay used, timing of sampling and the study population (UC versus CD). In this study, serum was taken at various times, not truly trough, although it is thought that subcutaneously administered drugs have a more flat drug-concentration curve. This study further suggests that higher anti-TNF levels are associated with mucosal healing and may assist in a step towards personalised medicine. We need to await large, prospective trials.


Abstract