Welcome to the sixteenth issue of IBD Research Review.

One of the papers included in this issue, albeit a retrospective assessment, has reported good efficacy and tolerability when thioguanine doses for IBD were split to avoid exceeding 3 mg/kg. Canadian researchers have compared effectiveness and costs of different CRC screening intervals for patients with IBD-PSC. Other Canadian research has reported that IBD increases the risk of death, but only during the first year postdiagnosis in the case of UC. This issue concludes with an interesting paper reporting that patients with CD who have a concurrent functional GI disorder are more likely to misuse narcotics.

I hope you enjoy the selection, and I encourage you to send us your comments, feedback and suggestions.

Kind Regards,

Professor Jane Andrews

jane.andrews@researchreview.com.au

Influence of combination therapy with immune modulators on anti-TNF trough levels and antibodies in patients with IBD

Authors: van Schaik T et al.

Summary: These researchers retrospectively analysed records of patients treated with adalimumab (n=109) or infliximab (n=108) for IBD over a 2-year period to assess the effect of cotreatment on trough concentrations of the immunomodulators and antidrug antibodies. Compared with monotherapy, combination therapy was associated with a significantly higher trough concentration (7.5 vs. 4.6 µg/mL [p=0.04]) and a significantly higher incidence of antibody formation (29.8% vs. 5.7% [p=0.001]) in the infliximab group. Trough concentrations were significantly higher in recipients of infliximab at a suboptimal dose compared with an optimal dose (p=0.02). Infliximab recipients who immediately started with immunomodulators had a significantly lower incidence of antibody formation compared with those who did not (33.3% vs. 66.7% [p=0.04]). The difference in trough concentration between monotherapy and combination therapy recipients was not significant in the adalimumab group.

Comment: This study continues to add data to an area of practical interest when using biologicals in IBD – whether and when to use concomitant immunosuppressant therapy? Although it was not able to report on actual clinical outcome data – which are the key thing missing from most of the literature on drug concentrations and antibody formation – the study does provide further convincing data that using concomitant immunosuppression is important in maintaining higher drug concentrations when using infliximab (which in turn, appears to be associated with clinical response). Moreover, it adds weight to the existing observational data, that if you want to get the best benefit from combination therapy, it should be used when starting infliximab. For adalimumab, the signal is less convincing, but may be consistent. Of course, what is missing from this field is a well-designed prospective study reporting on clinical outcomes – however such strategy studies are hard to fund, so retrospective clinical cohort reports such as this are valuable to refine our knowledge.

Reference: Inflamm Bowel Dis; Published online Sep 16, 2014
http://tinyurl.com/qg9cfft

Abbreviations used in this review:
CD = Crohn’s disease; CRC = colorectal cancer; FMT = faecal microbiota transplantation; GI = gastrointestinal; IBD = inflammatory bowel disease; OR = odds ratio; PSC = primary sclerosing cholangitis; QALY = quality-adjusted life-year; UC = ulcerative colitis

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2. Ferring Pharmaceuticals Pty Ltd Pymble, NSW, 2073 PA/1492/2014/AU Date prepared: September 2014.

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### Natural history of perianal Crohn’s disease after fecal diversion

**Authors:** Sauk J et al.

**Summary:** These researchers reported on the natural history of 49 patients with CD and perianal involvement who had undergone faecal diversion during the period 1991–2011. Intestinal continuity was re-established in 15 patients during follow-up, ten of who required an additional procedure to divert the faecal stream. Three of the five patients who remained reconnected needed further procedures to control sepsis. A decrease was seen between 2000 and 2011 in the proportion of patients with CD needing perianal surgical interventions.

**Comment:** This sobering report reminds us of the morbidity and treatment resistance of established severe perianal disease. Once faecal diversion was judged necessary, only 5/49 patients regained long-term continuity. This is despite much of the cohort being treated in the biological era. The take-home message appears to be that prevention of severe disease by early intervention is better than playing ‘catch up’ with diversion later. Fortunately in this centre at least, future cases at risk of anal failure appear to be declining, as the proportion of people with CD requiring perianal surgical interventions declined during 2000–2011. This suggests that prompt therapy, including with biologicals, is reducing the need to intervene.

**Reference:** Inflamm Bowel Dis; Published online Sep 16, 2014

http://tinyurl.com/k47h244

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### Splitting a therapeutic dose of thioguanine may avoid liver toxicity and be an efficacious treatment for severe inflammatory bowel disease

**Authors:** Pavlidis P et al.

**Summary:** This two-centre observational cohort study enrolled 62 patients with severe IBD unresponsive to prednisolone, conventional thiopurines, biologics or calcineurin inhibitors to receive oral thioguanine split daily to avoid individual doses >0.3 mg/kg (median dosage 0.6 mg/kg/day for a median of 8 months); 29 participants were lost to follow-up, medical adverse events or surgery. Improved clinical activity was seen at 6 months in 19/21 participants with CD and 27/38 with UC, and 53% of participants maintained improved clinical activity of steroids at study end. No previous thiopurine-related adverse events were encountered. Liver biopsy revealed that one participant who was heterozygote deficient for thiopurine methyltransferase had possible early nodular regenerative hyperplasia on liver biopsy, and the thioguanine dose was reduced. One participant with nodular regenerative hyperplasia and concomitant antiphospholipid syndrome discontinued thioguanine. One successful full-term pregnancy was reported, during which low cord blood and breastmilk thioguanine concentrations were recorded.

**Comment:** This collaborative study from the UK and Brisbane provides one of the larger datasets describing the clinical experience with using thioguanine in IBD patients. It is clearly a refractory group of patients having failed multiple agents and the risks of therapy appear to be balanced by benefit in some subjects; however, caution should be exercised as 29 subjects withdrew and at least one developed nodular regenerative hyperplasia. In an appropriately informed patient with refractory disease, this provides another therapeutic option where surgery is either declined, not likely to help (widespread small bowel disease with risk of short gut) or fraught with difficulty. It should only be used under close supervision and probably in expert centres until we have further information in larger groups of subjects.

**Reference:** Inflamm Bowel Dis; Published online Sep 16, 2014

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Fecal microbiota transplantation as therapy for inflammatory bowel disease

Authors: Colman RJ & Rubin DT

Summary: This systematic review and meta-analysis of nine cohort studies, eight case studies and one randomised controlled trial evaluating FMT for the treatment of IBD in a total of 122 patients reported an overall clinical remission rate of 45%, which was broken down in subgroup analyses to 60.5% and 22% for CD (n=39) and UC (n=79), respectively. The clinical remission rate in participants from the cohort studies (moderate heterogeneity risk; Cochran’s Q [p=0.011; I²=36.2%]) was 36.2%.

Comment: It seems as soon as there are a few reports on a ‘hot’ new therapy, we get a meta-analysis! Although it may be helpful to have data on FMT summarised in one paper, given that most of it comes from uncontrolled reports, the validity of performing a meta-analysis and giving summary statistics for efficacy is questionable. We do not know the denominator of people with IBD who have undergone FMT to yield the ones who are reported in the literature in these various cohort and case studies, and this makes interpretation of the data uncertain. It is refreshing to see more controlled science coming into this field, with two Australian studies underway – amongst other international projects evaluating FMT. If it is effective, one of the biggest hurdles may be the regulation of the ‘therapeutic product’, and hence many groups are watching closely and trying to develop a more marketable, targeted ‘poo pill’, assuming the desirable microbiome can be described and quantified.

Reference: J Crohns Colitis; Published online Sep 14, 2014 http://tinyurl.com/jwz6zhc

Environmental risk factors in inflammatory bowel disease

Authors: Ng SC et al., on behalf of the Asia-Pacific Crohn’s and Colitis Epidemiology Study (ACCESS) Group

Summary: Risk factors present prior to the development of IBD were investigated in 186 and 256 incident cases of CD and UC, respectively, diagnosed during 2011–2013 in Australia and eight Asian countries, and 940 matched controls; 374 cases and 789 controls were of Asian ethnicity. Multivariate modelling showed that the risk of developing CD was lower in Asians who: i) had been breastfed for >12 months (adjusted OR 0.10 [95% CI 0.04–0.30]); ii) had received antibiotics (0.19 [0.07–0.52]); iii) owned dogs (0.54 [0.35–0.83]); iv) consumed tea on a daily basis (0.62 [0.43–0.91]); and v) undertook daily physical activity (0.58 [0.35–0.96]). The risk of developing UC was decreased in Asians who: i) had been breastfed for >12 months (adjusted OR 0.16 [95% CI 0.08–0.31]); ii) had received antibiotics (0.48 [0.27–0.87]); iii) consumed tea (0.63 [0.46–0.86]); or coffee (0.51 [0.36–0.72]) on a daily basis; and iv) had a hot water tap (0.65 [0.46–0.91]) and flush toilet in childhood (0.71 [0.51–0.98]). Asian former smokers had an increased risk of developing UC (adjusted OR 2.02 [95% CI 1.22–3.35]).

Comment: This report from Asia Pacific is interesting as whilst it confirms some previously described protective factors against IBD development, such as being breastfed, it also identified protective factors that run counter to the previously well-accepted ‘hygiene hypothesis’. In particular for UC, having hot water and a flush toilet in the house were protective. These factors are yet to be explained, and run counter to helping us account for why the incidence in developing parts of the world has been rising – as if they are truly protective, the incidence should be falling. As stated by the authors, many or all the factors can be linked to the gut microbiome either directly or indirectly, and studies examining how these individual factors influence the microbiome deserve further study.

Reference: Gut; Published online Sep 12, 2014 http://qut.biomedicine.qut.edu.au/content/early/2014/09/12/gutjnl-2014-307410

Predictors and risks for death in a population-based study of persons with IBD in Manitoba

Authors: Bernstein CN et al.

Summary: Predictors of risk for death were identified in 10,788 cases with CD or UC versus 101,860 matched controls from the general population in this research. Patients with prevalent CD were at significantly increased risk of death from any cause compared with controls (adjusted hazard ratio 1.26 [95% CI 1.16–1.38]), while the risk in cases with prevalent UC was marginally increased (1.04 [0.96–1.12]). Compared with controls, case patients with CD were more likely to die of CRC, non-Hodgkin’s lymphoma, digestive diseases, pulmonary embolism and sepsis, while case patients with UC were more likely to die from CRC, digestive diseases and respiratory diseases. Significant effects on mortality by socioeconomic status, comorbidity score and surgery were seen among incident cases. The greatest mortality risk for patients with CD or UC was within the first 30 days following GI surgery. The risk of death was increased during the first postdiagnosis year in patients with CD and those with UC, but persisted beyond the first year in only patients with CD.

Comment: This large case-control study from Canada continues to build the knowledge base around relative mortality risk for people with IBD. Whilst we do worry about disease-related risks, we can be reassured that UC, in particular, does not increase one’s relative mortality risk beyond the first year of diagnosis, and whilst there is a significantly elevated mortality risk in CD, the effect size is small. It also provides a reminder that whilst modern IBD surgery is usually safe, it does pose an additional risk. However, one might propose that it is the phenotype of the disease requiring surgery, rather than the surgery itself, that drives a significant proportion of this risk. However, we also know that surgical delay (especially in the acute severe UC setting) adds risk, and so the take-home message here might be to optimise patient care before and after surgery – and to make collaborative decisions to operate in a controlled setting rather than positioning resection as an admission of failure or therapy of last resort – which might be the other explanation for surgery enhancing one’s risk of mortality up to 1 year postoperatively.

Reference: Inflamm Bowel Dis; Published online Sep 16, 2014 http://tinyurl.com/pg7qju
Narcotic use and misuse in Crohn’s disease

Authors: Crocker JA et al.

Summary: This was a retrospective chart review of 931 patients with CD, including 87 with concurrent functional GI disorder and 192 chronic narcotic recipients, followed at a US gastroenterology clinic over 6 years. The proportion of chronic narcotic users was significantly greater among patients with versus without functional GI disorder (44% vs. 18% [p<0.001]), as was the narcotic misuse rate (37% vs. 9.6% [p<0.0001]). Multivariate logistic regression revealed that patients with CD who had a concurrent functional GI disorder were significantly more likely to misuse narcotics (OR 3.33 [95% CI 1.87–5.93]).

Comment: This is a lovely practical paper alerting us to a problem that gets insufficient attention – especially when one remembers that opioids were one of the classes associated with the worst outcomes in the TREAT registry (the other offender being steroids). They used a prescription monitoring programme to good effect, and it has enabled them to track narcotic use and identify those most at risk of use and misuse. It serves to remind us that symptoms are the driver of narcotic use – and that GI symptoms are common in this patient group and not always due to ongoing inflammatory problems. We have previously published that a high proportion of people with IBD have functional symptoms (Aliment Pharmacol Ther 2008;28[4]:475–83), and that the higher the symptom burden, the higher the rates and degrees of comorbid anxiety and depression (J Gastroenterol Hepatol 2011;26[5]:916–23). I would propose that it is this psychological distress – left under-treated – that drives narcotic use. This hypothesis is consistent with other data where we previously documented that just the introduction of an IBD service with a helpline and easy access to an IBD nurse significantly reduced opioid use (Frontline Gastroenterol 2012;3[3]:137–42). It is thus disappointing that most Australian IBD centres are still struggling to have IBD nursing support funded.

Reference: Inflamm Bowel Dis; Published online Sep 9, 2014
http://tinyurl.com/llnaaq7

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