Welcome to the seventeenth issue of IBD Research Review.

This issue includes research showing significant reductions in hospitalisation duration and in-hospital costs, but increases in total costs, since rescue infliximab replaced cyclosporin for severe UC. An analysis of CESAME trial data has shown that patients with IBD and prior cancer are at increased risk of developing any new or recurrent cancer, regardless of immunosuppressive treatment. Dutch researchers have reported improvements in lumbar spine bone mineral density after 2 years of risedronate and concomitant calcium plus vitamin D supplementation in patients with osteopenic CD. This issue concludes with a study reporting the effects of doubling the dose of mesalazine in patients with quiescent UC and increased faecal calprotectin levels.

I hope you find these and the other selected studies interesting, and I look forward to receiving any feedback you may have.

Kind Regards,

Dr Daniel van Langenberg
Gastroenterologist
daniel.vanlangenberg@researchreview.com.au

Adalimumab in Crohn's disease patients: pharmacokinetics in the first 6 months of treatment

Authors: Lie MRKL et al.

Summary: The pharmacokinetic properties of adalimumab were evaluated in a retrospective cohort of 76 patients with CD, naïve to anti-TNF-α therapy, who received six subcutaneous injections of the agent as loading doses of 160mg and 80mg at weeks 0 and 2, respectively, followed by 40mg every second week; the patients received 6–25 injections each (median 14). Although adalimumab concentrations were divergent among the patients, they were stable between weeks 12 and 28. No significant correlation was seen between adalimumab concentration and time since last administration. A multivariable regression analysis showed a weak but significant correlation between adalimumab concentration at week 28 and CRP level at week 28 and baseline body mass index (p=0.004), but not concomitant immunosuppressant use (p=0.304).

Comment: This retrospective study has demonstrated a remarkable lack of intra-individual variability of adalimumab drug concentrations in patients, regardless of the number of days postinjection the concentration is tested, between weeks 12 and 28. Furthermore in linear multivariate analysis, only CRP level and body mass index correlated with adalimumab concentrations at week 28 with any significant effect size. Concomitant immunomodulation or smoking had no significant effect on adalimumab concentrations. Pending further confirmation from other centres, these data provide important clues to optimal patient selection for adalimumab and timing of adalimumab concentration testing.


Abstract
Length of hospital stay and associated hospital costs with infliximab versus cyclosporine in severe ulcerative colitis

**Authors:** Löwenberg M et al.

**Summary:** These researchers analysed hospital records for 42 patients with corticosteroid-refractory UC who received rescue cyclosporin (n=26) or infliximab (n=16); cyclosporin recipients more often had a pancolitis (89% vs. 63% [p=0.046]). Compared with infliximab, cyclosporin users had a significantly longer median length of hospital stay (11.0 vs. 4.0 days [p<0.01]) and higher mean in-hospital costs (€6121 vs. €4853 [p<0.05]), but lower total costs up to 3 months after initiation of rescue therapy (€6787 vs. €9983 [p<0.01]) and no significant difference in colectomy rate at 6 months (23% vs. 31% [p=0.50]). Cyclosporin was associated with more side effects than infliximab.

**Comment:** As per other recent studies, this retrospective Dutch IBD centre audit demonstrates that compared with cyclosporin, infliximab is a cost-effective choice of medical salvage therapy for acute severe colitis. This is primarily due to the significant difference in length of inpatient stay (11 vs. 4 days). Consistent with prior data, there was no difference in efficacy between the two agents; however, more adverse effects were reported with cyclosporin. Once discharged however, outpatient costs for the first 3 months were significantly higher for infliximab due to drug costs. These findings are relevant to the Australian setting given the disparate funding models for inpatient and outpatient care (i.e. state versus federal government).

**Reference:** Eur J Gastroenterol Hepatol 2014;26(11):1240–6

**Abstract**

The prevalence and predictors of opioid use in inflammatory bowel disease

**Authors:** Targownik LE et al.

**Summary:** This was a population-based analysis of all patients with IBD entered into a US IBD epidemiology database who had been prescribed opioids both pre- and postdiagnosis. Five percent of the patients with IBD became heavy users of opioids (>50 mg/day morphine equivalents for 30 days) within 10 years of diagnosis, and heavy opioid use was strongly predicted by moderate prediagnosis use. Compared with matched controls, the likelihood of becoming a heavy opioid user was significantly increased among patients with IBD (odds ratio 2.91 [95% CI 2.19–3.85]), and there was a strong relationship between heavy opioid use and death in this group remains uncertain.

**Comment:** Utilising the Manitoba IBD cohort and uniquely given the population-based methodology, this study has confirmed the link between ‘heavy’ opioid use (defined as equivalent of morphine >50mg daily) and mortality in IBD patients. This provides a stark reminder of the insidious danger of prescribing opioids to IBD patients, even though the actual mechanistic link between opioid use and death in this group remains uncertain.

**Reference:** Am J Gastroenterol 2014;109(10):1613–20

**Abstract**

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Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed

Authors: Sands BE et al.

Summary: Patients with moderately to severely active CD (CDAI score 220–400; n=416) were randomised to receive intravenous vedolizumab 300mg or placebo at weeks 0, 2, and 6 in this phase 3 trial. No difference was seen between vedolizumab and placebo recipients for the primary analysis of clinical remission (CDAI ≤150) at week 6 (15.2% vs. 12.1% [p=0.433]). In 315 participants who had failed previous anti-TNF therapy, vedolizumab was superior to placebo in this population for remission at 10 weeks (26.6% vs. 12.1% [p=0.01]) and 6-week and 14-week responses defined as a ≥100-point reduction in CDAI score (39.2% vs. 22.3% [p=0.001] and 46.8% vs. 24.8% [p=0.0001], respectively). In the overall study population, vedolizumab was significantly superior to placebo for response outcomes defined as CDAI score ≤150 and a ≥100-point reduction at 6 weeks (19.1% vs. 12.1% [p=0.046] and 39.2% vs. 22.7% [p=0.0002], respectively) and 10 weeks (25.7% vs. 13.0% [p<0.0001] and 47.8% vs. 24.2% [p<0.0001], respectively). Adverse events were similar between the groups.

Comment: This study emphasises the importance of rigorous study design in answering a clinical question. In retrospect, setting the primary endpoint at week 6 in this notoriously refractory population (i.e. CD patients refractory to anti-TNF therapy) was a huge error even if the drug (i.e. vedolizumab) has therapeutic potential. However, at week 10 there was a significant difference for the proportion in clinical remission between those on vedolizumab and placebo, so there is hope, and hopefully PBS listing (for UC at least for a start) may not be too far away.

Reference: Gastroenterology 2014;147(3):518–27

Risk of new or recurrent cancer under immunosuppressive therapy in patients with IBD and previous cancer

Authors: Beaugerie L et al., for the CESAME Study Group

Summary: The risks of new and recurrent cancers were investigated in 17,047 participants with IBD from the CESAME observational cohort, 405 of whom had a cancer diagnosis prior to study entry (May 2004 to June 2005). Patients with prior cancer had a significantly higher rate of incident cancer during follow-up (to the end of 2007) than those without prior cancer (21.1 vs. 6.1 per 1000 person-years; adjusted hazard ratio 1.9 [95% CI 1.2–3.0; p=0.003]). Among patients with prior cancer, no significant association was seen between immunosuppressant use at study entry and the risk of new or recurrent cancer.

Comment: This is the first prospective study evaluating the risk of new or recurrent cancer in patients with IBD and previous cancer. Clearly this is important given the uncertainty of how to treat increasing numbers of cancer patients needing treatment for IBD to maintain quality of life, yet at potentially increased risk of cancer recurrence with immunosuppression. This study suggested that this group were more likely to develop new cancers rather than cancer recurrence. There was no difference in those exposed and not exposed to immunosuppressants postcancer, which is somewhat reassuring; however ultimately, despite combing records of 17,000 patients in the CESAME cohort, the study was still underpowered to unequivocally answer this vexing question.

Reference: Gut 2014;63(9):1416–23

Altered intestinal microbiota and blood T cell phenotype are shared by patients with Crohn's disease and their unaffected siblings

Authors: Hedlin CR et al.

Summary: These researchers analysed faecal microbiology, faecal calprotectin levels, blood T-cell phenotype and intestinal permeability in 22 patients with inactive CD, 21 of their healthy siblings and 25 control subjects. Aspects of intestinal dysbiosis in patients with CD versus controls were shared by their siblings, including lower levels of Faecalibacterium prausnitzii (p=0.048), Clostridia cluster IV (p=0.003) and Roseburia spp. (p=0.02). Patients with CD and their siblings also had a predominance of memory T-cells (p=0.002) and elevated naïve CD4 T-cell β7 integrin expression (p=0.01) compared with controls. Faecal calprotectin levels of >50 μg/g occurred in a significantly greater proportion of CD patients’ siblings than controls (38% vs. 8% [p=0.028]), while intestinal permeability did not differ. A discriminant function analysis showed that combinations of these factors significantly discriminated between groups (χ²=80.4 [p<0.001]). Immunological and microbiological variables separated the CD patients’ siblings from control subjects.

Comment: Although it is already known that first-degree relatives of patients with CD have higher rates of increased intestinal permeability and faecal calprotectin, this study takes our pathogenic understanding one step further in showing that siblings of CD patients also tend to have similar traits of dysbiosis, including reduced numbers of F. prausnitzii, which may influence disease course. Furthermore, siblings are more likely to display abnormal T-cell phenotypes similar to their affected relatives. The unique strengths of this study include the additional healthy unrelated control group as a comparator and the multiple measurements of phenotype, microbiology and inflammatory markers in a genotypically well-characterised cohort.

Reference: Gut 2014;63(10):1578–86

Treatment of bone loss in osteopenic patients with Crohn's disease

Authors: van Bodegraven AA et al., on behalf of the Dutch Initiative on Crohn and Colitis (ICC)

Summary: Patients with osteopenic CD were randomised to receive oral risedronate 35mg (n=64) or placebo (n=67) once weekly with concomitant calcium and vitamin D supplementation for 2 years. Compared with placebo, risedronate was associated with a significantly greater average lumbar spine bone mineral density increase (0.04 vs. 0.01 g/cm² [p=0.007]), a nonsignificantly greater average total hip bone mineral density increase (0.03 vs. 0.01 g/cm² [p=0.07]) and consistent improvements in T-scores and bone turnover marker levels, but similar fracture prevalence and incidence. The benefits of risedronate were seen mainly during the first 12 months of treatment.

Comment: This double-blind randomised controlled trial showed a beneficial effect of risedronate in osteopenic CD patients as assessed by dual x-ray absorptiometry. This oral bisphosphonate appeared to be tolerated well with few adverse effects and no impact on disease activity. It should be noted that these patients were osteopenic only and that statistical significance was achieved at the lumbar spine but not quite at the hip. Therefore, there may be a benefit in treating CD patients with osteopenia earlier and more aggressively in order to halt/reverse progression of bone loss given these findings.

Reference: Gut 2014;63(9):1424–30

Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab

Authors: Cornillie F et al.

Summary: This retrospective post hoc analysis of data from the ACCENT I placebo-controlled trial of infliximab explored the relationship between serum infliximab trough concentrations and CRP levels. The participants received induction infliximab 5 mg/kg, followed by maintenance infliximab 5 mg/kg (n=147) or 10 mg/kg (n=144) every 8 weeks through to week 54; sustained responses were seen in 25% and 33% of participants, respectively. Compared with participants without a durable sustained response, those with a durable sustained response (CDAI decrease of ≥70 and reduction of ≥25% from baseline) had a significantly higher median trough concentration with infliximab 5 mg/kg at week 14 (4.0 vs. 1.9 μg/mL [p=0.033]). Predictors of a durable sustained response with maintenance infliximab 5 mg/kg included a trough concentration of ≥3.5 μg/mL at week 14 and a ≥60% decrease in CRP level in participants with a baseline CRP level of >9.0 mg/L (respective odds ratios 3.5 [95% CI 1.1–11.4] and 7.3 [1.4–36.7]). A serum infliximab concentration of ≥3.5 μg/mL at week 14 did not predict durable sustained response to maintenance infliximab 10 mg/kg.

Comment: There is growing interest into whether anti-TNF drug concentrations and/or other biomarkers may be accurately utilised postinduction to predict future response, thus enabling earlier interventions such as anti-TNF dose optimisation and/or concomitant immunomodulation to be selectively utilised if needed. This post hoc analysis of the ACCENT I trial showed that in those with an elevated CRP level (>8 mg/L) prior to induction, a week 14 infliximab trough concentration of ≥3.5 mg/mL and a ≥60% CRP level decrease from baseline accurately predicted a durable clinical response to infliximab maintenance up to week 54. This may become another potential clinical use for anti-TNF drug concentration monitoring.

Capsule endoscopic findings correlate with fecal calprotectin and C-reactive protein in patients with suspected small-bowel Crohn's disease

Authors: Höög CM et al.

Summary: Possible correlations between capsule endoscopy findings, biochemical parameters (CRP and faecal calprotectin levels) and symptoms were explored in 30 patients with inflammatory small bowel lesions. Endoscopic inflammation significantly, persistently correlated with faecal calprotectin level at baseline and follow-up assessment at 9 months (respective p values 0.003 and <0.001), while CRP level significantly correlated with endoscopic inflammation at baseline (p=0.006) but not at follow-up. No correlations were seen between symptoms and endoscopic inflammation.

Comment: Patients with suspected small-bowel CD pose a major diagnostic challenge. This study further examined this area, and suggested that in those with a clinical picture suggestive of small bowel CD, testing for CRP, calprotectin and small bowel endoscopy (in this case, capsule endoscopy) is worthwhile. This is a three-pronged approach, which may then render a histological diagnosis unnecessary (which is often not possible anyway). In particular, the authors showed that the severity of inflammatory lesions depicted by capsule endoscopy (graded by the Lewis score) correlated well with faecal calprotectin level, more so than CRP level, and recommended that serial measurement of calprotectin in particular is useful in confirming the diagnosis of small bowel CD, given the diagnosis may not be clear at a single point in time.

Reference: Scand J Gastroenterol 2014;49(9):1084–90
Abstract

Mesalamine dose escalation reduces fecal calprotectin in patients with quiescent ulcerative colitis

Authors: Osterman MT et al., on behalf of the DEAR Investigators

Summary: Patients with UC in remission, a faecal calprotectin level of >50 µg/g and receiving mesalazine ≤3 g/day were randomised 1:1 to continue mesalazine at the same dose (controls) or increased to 4 g/day for another 6 weeks. Compared with the control group, the dose escalation group had significantly higher rates of continued remission with faecal calprotectin levels <50 µg/g (primary outcome; 26.9% vs. 3.8% [p=0.0496]), and levels <100 µg/g (p=0.04) and <200 µg/g (p=0.005) among participants with prerandomisation levels greater than the respective cutoff levels. Among the participants in remission postrandomisation, those with a faecal calprotectin level >200 µg/g clinically relapsed significantly sooner than those with lower levels (p=0.01).

Comment: This study aimed to address a relatively simple but clinically relevant question – are patients with UC in clinical remission, yet at increased risk of relapse with ongoing disease activity as determined by elevated calprotectin, better off on a higher mesalazine dose? The answer appears to be yes. In patients with an elevated calprotectin level despite mesalazine 2.4 g, dose escalation to 4.8 g/day resulted in a higher proportion achieving a normal calprotectin level (<50 µg/g) and a reduced risk of relapse. This has immediate application in clinical practice, given that many IBD clinicians already escalate mesalazine doses in this context.

Abstract