Highlights from the literature: inflammatory bowel disease

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CALM trial showed tight control resulted in better outcomes for patients with Crohn's disease

CALM trial compared endoscopic and clinical outcomes in patients with moderate to severe Crohn's disease who were managed with a tight control algorithm, using clinical symptoms and biomarkers, versus patients managed with a clinical management algorithm.¹ This was an open-label, randomised, controlled phase 3 study, done in 22 countries which evaluated adult patients with active endoscopic Crohn's disease, and no previous use of immunomodulators or biologics. Patients were randomly assigned at a 1:1 ratio to tight control or clinical management groups, stratified by smoking, weight and disease duration after 8 weeks of prednisone induction therapy, or earlier if they had active disease. Treatment was escalated in both groups in a stepwise manner, from no treatment, to adalimumab induction followed by adalimumab every other week, adalimumab every week and, lastly, to both weekly adalimumab and daily azathioprine. In the tight control group the therapy escalation was initiated if a patient's Crohn's Disease Activity Index (CDAI) score was at least 150, or if they had elevated C-reactive protein or calprotectin. In the clinical management group treatment escalation was based on CDAI score being above 200 and the need for use of prednisolone in the previous week. A significantly higher proportion of patients in the tight control group achieved the primary endpoint of mucosal healing (Crohn's Disease Endoscopic Index of Severity <4) with absence of deep ulcers at week 48 (56/122 patients (46%)) than in the clinical management group (37/122 (30%)), with a risk difference of 16.1% (95% CI 3.9 to 28.3; $p=0.010$). More patients in the tight control group had their therapy escalated than in the clinical management group, and 36 weeks after randomisation, 59% of patients in the clinical management group were still on adalimumab every other week compared with only 26% in the tight control group. The rates of treatment-emergent adverse events were similar in both the

tight control and the clinical management group (86% vs 82%). This study had shown the benefit of tight control of Crohn's disease and it is also reassuring to see that patients in the tight control group did not have excessive adverse events.

Levels of biologic medications in inflammatory bowel disease are low in breast milk

Patients and healthcare professionals are very apprehensive of stopping biologic therapies without valid reasons because of the concerns of disease flares and the potential of suboptimal response on restarting the previous treatment. However, there are only limited safety data available about exposure to biologic and immunosuppressant agents during breast feeding. Dr Mahadevan and colleagues² performed a multicentre prospective study of women with inflammatory bowel disease (IBD) and their infants, collecting breast milk samples ($n=72$) from patients receiving biologic therapy from October 2013 to November 2015. Drug concentrations were measured in all breast milk samples at several time points within 48 hours of collection and within 168 hours for some samples. Breast milk concentrations of these drugs were very low—infliximab in 19 of 29 treated women (max 0.74 µg/mL), adalimumab in 2 of 21 treated women (max 0.71 µg/mL), certolizumab in 3 of 13 treated women (max 0.29 µg/mL), natalizumab in 1 of 2 treated women (max 0.46 µg/mL), ustekinumab in 4 of 6 treated women (max 1.57 µg/mL) and golimumab no trace (1 woman). Rates of infection and developmental milestones did not differ among infants whose mothers received treatment with biologics, immunomodulators or combination therapy compared with unexposed infants (whose mothers received treatment with mesalamines or steroids or no medication). Sample sizes were smaller for golimumab, natalizumab and ustekinumab. This study results of low levels of biologic medications in breast milk will reassure

many women with IBD who wish to breast feed their infants.

Anti-tumour necrosis factor treatment for IBD does not affect serious infections after arthroplasty

Patients with IBD needing arthroplasty are often asked to stop their anti-tumour necrosis factor (TNF) treatment prior to joint surgeries because of the fear of serious infections. Using the Market-Scan Database in the USA, a retrospective case-control study of patients with IBD 18–64 years of age undergoing hip, knee or shoulder replacement surgery was conducted.³ After controlling for comorbidities, patients with IBD were not at increased risk of serious infection following joint replacement. Among patients with IBD, corticosteroids were associated with increased risk of serious infection (composite of joint infection, surgical site infection, pneumonia, sepsis) within 90 days of operation (HR 4.6; 95% CI 2.2 to 9.8; $p<0.01$) while anti-TNF was not. Opioids were also associated with increased risk of infection (HR 1.5; 95% CI 1.2 to 1.8; $p<0.01$). These results should reassure patients and healthcare professionals in continuing anti-TNF treatment prior to arthroplasty.

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