Welcome to issue 28 of Gastroenterology Research Review.

The last issue for 2015 begins with an interesting paper looking at the prevalence of spondyloarthritides in patients receiving anti-TNF agents for IBD. Research out of China found that a Helicobacter pylori vaccine was safe and effective in children. Still on the topic of vaccines, patients with IBD, particularly those treated with infliximab or azathioprine, were found to have a low response rate to standard HBV vaccination. We finish the year with research showing that patients with IBD are at increased risk of invasive pneumococcal disease, both before and after IBD diagnosis.

I look forward to our next issue in 2016 – until then please keep comments and suggestions coming. I hope you all have an enjoyable and safe holiday season.

Kind Regards,
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Spondyloarthropathy in inflammatory bowel disease patients on TNF inhibitors

Authors: Subramaniam K et al.

Summary: Consecutive patients receiving TNF inhibitors for CD (n=96) or UC (n=44) completed a questionnaire to ascertain their self-reported prevalence of spondyloarthritides-associated musculoskeletal manifestations; 25% of respondents reported concurrent or historical inflammatory back pain. Based on imaging and clinical arms of the ASAS (Assessment of SpondyloArthritis International Society) criteria, 30% of respondents with CD and 14% with UC had axial spondyloarthritides. Arthritis was reported by 34% of respondents, enthesitis by 17%, dactylitis by 4%, uveitis by 6%, psoriasis by 6% and a family history of spondyloarthritides by 39%. According to the ASAS criteria, 41% of respondents had peripheral spondyloarthritides, with no significant differences between those with CD and UC. Positivity for antinuclear antibodies (1+80) was present in 19% of respondents pre-TNF inhibitor therapy, increasing to 78% on therapy. Four-percent of respondents had clinical drug-induced lupus erythematosus characterised by new clinical signs and symptoms, such as arthralgia, rash with elevated dsDNA titres and positive antinuclear antibodies.

Comment: The extraintestinal manifestations of IBD are well known with musculoskeletal problems chief among these. Spondyloarthritides includes IBD-related arthritis, anklyosing spondylitis, reactive arthritis, psoriatic arthritis and undifferentiated spondyloarthritides (Lipton S et al.). Despite this, spondyloarthritides remains under-reported in IBD, and the impact of anti-TNF therapy is not well understood. This study in a cohort of real-life IBD patients with a moderate-to-severe phenotype, i.e. requiring anti-TNF therapy, highlights how common spondyloarthritides is among patients with IBD, particularly those with a more severe phenotype, and that the employed questionnaire seems to warrant further consideration as a screening tool in this context. It would have been useful to know if any of these patients had been previously diagnosed with arthritis to better understand the degree of under-reporting, and confirmation of diagnosis in all cases by imaging would have been ideal. Nevertheless, the article is an excellent reminder to be vigilant of IBD-related spondyloarthritides.

Reference: Intern Med J 2015;45(11);1154–60

Abstract

Efficacy, safety, and immunogenicity of an oral recombinant Helicobacter pylori vaccine in children in China

Authors: Zeng M et al.

Summary: Children aged 6–15 years without past or present H. pylori infection were randomised to receive H. pylori vaccine (n=2222) or placebo (n=2223) in this phase 3 trial. 4403 children were included in the per-protocol efficacy analysis. Compared with placebo, H. pylori vaccine was associated with fewer H. pylori infection events during the first year (14 vs. 50), giving a vaccine efficacy of 71.8%. The respective adverse event and serious adverse event rates were 7% and <1% in each arm; no adverse events were deemed to be vaccine-related. See also the accompanying editorial.

Comment: Since being first described by Robin Warren and Barry Marshall, H. pylori has become a well-established major risk factor for gastric adenocarcinoma and lymphoma apart from peptic ulcer disease and chronic gastritis. Eradication of H. pylori is becoming progressively more difficult with emerging resistance and limited access to some second-line therapies in Australia. Thus, the current randomised, double-blind, placebo-controlled, phase 3 trial by Zeng et al. presents a major step forward after various failed vaccine approaches in the past. The trial consisted of 4403 children who completed the administration schedule. Notably, most H. pylori infections seemed to occur in childhood. Only 14 infections were noted within 12 months in the vaccine group as compared with 50 infections in the placebo group, translating into a vaccine efficacy of 71.8%. While there was gradual reduction in protection in a subgroup of patients followed for another 2 years, there were still 55% fewer infections in the vaccine group. While there remain some challenges in terms of making the vaccination protocol feasible in the global setting, particularly in poor resourced countries, this potential impact of such a vaccine may be substantial, not just in terms of gastric cancer, but also suffering and hospitalisations from chronic gastritis and peptic ulcer disease.

Reference: Lancet 2015;386(10002);1457–64

Abstract
Early combined immunosuppression for the management of Crohn’s disease (REACT)

Authors: Khanna R et al., for the REACT Study Investigators

Summary: Community gastroenterology practices from Belgium and Canada, each providing data on <60 patients with CD, were assigned to early combined immunosuppression (evaluable n=921) or conventional management (evaluable n=806) in this cluster randomised trial. No significant difference was seen between early combined immunosuppression versus conventional management for practice-level corticosteroid-free remission rates at 12 months (primary outcome; 66.0% vs. 61.9% [p=0.0169]), but practices assigned to early combined immunosuppression reported a significantly lower 24-month patient-level composite major adverse event rate (occurrence of surgery, hospital admission or serious disease-related complications; 27.7% vs. 35.1% [p=0.0003]); serious drug-related adverse events did not differ between the groups. See also the accompanying editorial.

Comment: The incidence of CD is increasing worldwide and its fistulogram and fistulising complications remain challenging to manage, despite the introduction of immunosuppressive drugs such as anti-TNF agents. While there are some data from well-characterised tertiary hospital cohorts that early aggressive combination therapy may be better than a stepped approach, real-life data are missing. Khanna et al. present data on early combined immunosuppression in the community setting, with 1084 patients randomised to early combined immunosuppression and 898 randomised to conventional therapy based on a cluster randomisation strategy. While there was no difference in 12-month remission rates or serious drug-induced adverse events, occurrence of surgery and serious disease-related complications were less common with early combined immunosuppression than conventional management therapy at 24 months. While the study has some weaknesses, the importance is that it is based on community gastroenterologists managing real-world patients. With respect to early combined immunosuppression versus non-early combined immunosuppression as initial therapy, the potentially serious adverse events associated with some immunosuppressive drugs and early aggressive combination therapy often present in disease phenotype and stage of progression need to be considered in this context, and further work is required to better risk stratify patients.

Reference: Lancet 2015;386(10006):1825–34

Abstract

Treatment with infliximab or azathioprine negatively impact the efficacy of hepatitis B vaccine in inflammatory bowel disease patients

Authors: Andrade P et al.

Summary: Response to HBV vaccination was evaluated in 172 patients with CD and 45 with UC treated with infliximab and/or azathioprine. The HBV vaccine response rate was 76%. Among patients vaccinated after infliximab was initiated (n=14), only two had antibody levels <10 IU/L. Among patients vaccinated before starting infliximab, 88% of those vaccinated before starting azathioprine developed antibodies, compared with 55% already receiving azathioprine. A multivariable analysis showed that response to HBV vaccination was weakened by infliximab and azathioprine therapies (respective adjusted ORs 17.642 [95% CI 8.514–33.937] and 3.344 [1.653–6.945]).

Comment: Vaccination against HBV is recommended for all patients with IBD. Reactivation of HBV infection in the context of significant immunosuppressive therapy such as anti-TNF therapy can cause fulminant hepatitis with high morbidity and mortality. The current study analysed retrospectively the efficacy of HBV vaccination in IBD patients treated at a tertiary centre. The first interesting observation is that the vaccination rate was only 71.4%. While this is relatively high as compared with other studies, the vaccination rate still falls substantially short of 100%, and thus highlights the need to actively consider this in IBD patients. The overall response rate to vaccination was 76% in this IBD cohort, as compared with an expected response rate of 95% in healthy adults. Response rates were 68% in the absence of azathioprine or infliximab, 55% with azathioprine and 14% with infliximab. While the numbers were small for the anti-TNF cohort, this study clearly highlights that IBD patients should be vaccinated as early as possible and preferably before initiation of long-term immunosuppression.


Abstract

Incidence and mortality of colorectal cancer in individuals with a family history of colorectal cancer

Authors: Schoen RE et al.

Summary: Data from the 144,768 participants enrolled in the US Prostate, Lung, Colorectal and Ovarian cancer screening randomised controlled trial (comparing flexible sigmoidoscopy with usual care) were analysed to explore the impact of family history on CRC incidence and mortality and after age 55 years; 10% of the participants reported a family history of CRC. Among 2000 incident CRC cases, 13.1% had a family history of CRC, and among 538 CRC fatalities, 13.2% were participants with a family history of CRC. The risk of CRC incidence was significantly increased by a family history of CRC (HR 1.30 [95% CI 1.10–1.50]), as was mortality risk (1.31 [1.02–1.69]). While the risk of CRC was increased by having one first-degree relative with CRC (HR 1.23 [95% CI 1.07–1.42]), having ≥2 first-degree relatives with CRC increased the risk further (2.04 [1.44–2.86]). Among participants with one first-degree relative with CRC, the risks of incident CRC were not significantly different for participants with relatives diagnosed at ages ≤60, 60–70 and >70 years (respective HRs 1.27 [95% CI 0.97–1.63], 1.33 [1.06–1.62] and 1.14 [0.93–1.45]; p=0.59 for trend). See also the accompanying editorial.

Comment: Screening for CRC is usually recommended from age 50 years in individuals with an average risk. In the context of a family history with a first-degree relative with CRC before age 60 years or ≥2 relatives with CRC at any age, screening is usually recommended from age 40 years or 10 years earlier than the youngest relative. However, outside well-established inheritable genetic syndromes, the risk from family history seems to increase with increasing age. Schoen et al. pooled patients from various studies that included 144,768 subjects aged 55–74 years with up to 13 years follow-up. They found a family history of CRC translated into an increased risk for CRC of 1.3-fold. This difference seemed to wane with age, but remained significantly higher with ≥2 affected first-degree relatives (2-fold) as compared with only one (1.23-fold). These results are in line with previous studies and suggest that screening approaches for individuals beyond age 55 years, but particularly above age 65 years with only a single affected relative, could be considered to be adjusted to that of average-risk patients.

Reference: Gastroenterology 2015;149(6):1438–45

Abstract

Statin use reduces risk of esophageal adenocarcinoma in US veterans with Barrett’s esophagus

Authors: Nguyen T et al.

Summary: This nested case-control study included US veterans with Barrett’s oesophagus; 311 who developed new oesophageal adenocarcinoma during follow-up were compared with 856 matched controls. Compared with controls, patients who developed oesophageal adenocarcinoma were less likely to use statins (40.2% vs. 54.0% [p<0.01]), including use for 6–18 and ≥18 months (10.0% vs. 17.1% and 19.5% vs. 24.0%, respectively [p<0.01]), and the proportions using simvastatin (which accounted for 86.9% of statin use) at 21–40 and >40 mg/day were lower (9.3% vs. 14.5% and 8.4% vs. 12.6%, respectively [p<0.01]). An inverse association was found between statin use and oesophageal adenocarcinoma adjusted OR 0.65 (95% CI 0.47–0.91); the adjusted ORs were 0.62 (0.54–1.33) and 0.44 (0.25–0.79) for patients developing stages 0–1 and 2–4 oesophageal adenocarcinoma, respectively. No associations were evident between oesophageal adenocarcinoma and other lipid-lowering medications.

Comment: The incidence of oesophageal adenocarcinoma is increasing with a high mortality and an average 5-year survival of <20%. Known risk factors are gastroesophageal reflux, smoking, high fat intake and obesity. Statins have been proposed to be chemopreventive in oesophageal adenocarcinoma and while current meta-analyses are in favour, clinical data from patients are limited. Barrett’s oesophagus is the well-established precursor to oesophageal adenocarcinoma, and thus patients with Barrett’s oesophagus would likely be the group with the most benefit from statin therapy, but clinical data are controversial. The current observational study is the largest study of its kind so far, and showed that statin use reduced the odds for oesophageal adenocarcinoma by 35% in Barrett’s oesophagus patients. The effect seemed to be dose dependent and was most apparent in advanced oesophageal adenocarcinoma and specifically to statins among lipid-lowering drugs. This suggests that statins may be useful in high-risk patients, such as those with Barrett’s oesophagus, as a chemopreventative. However, it is unclear whether statins influence the actual progression to oesophageal adenocarcinoma or merely the speed of its progression, given that the association was strongest in patients with advanced oesophageal adenocarcinoma.


Abstract

Inflammatory Bowel Disease (IBD) Research Review

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Introducing VIEKIRA PAK (ombitasvir/paritaprevir/ritonavir + dasabuvir) and VIEKIRA PAK-RBV (ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin) for the treatment of patients with GT1 chronic HCV.

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HCV=Hepatitis C Virus. RNA=Ribonucleic Acid. SVR=Sustained Virologic Response. GT1=Genotype 1. RBV=Ribavirin.
Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice

Authors: Böhm L et al.

Summary: Patients with IBS were randomised to consume a low-FODMAP diet (n=39) or an IBS-recommended diet emphasising how and when, rather than what, to eat (n=57). No significant between-group difference was seen for reduction in IBS Symptom Severity Scale (p=0.62) or the proportion of participants achieving a reduction of ≥50 points (p=0.72).

Comment: IBS remains a difficult entity to treat, partially because the pathogenesis and risk factors are still only partially understood and because it is a functional disorder. However, most patients with IBS can identify certain foods as triggers, and thus dietary interventions are commonly recommended despite the lack of large controlled trials. Low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) diets, first described by Peter Gibson and Susan Shepherd, have been shown to improve IBS symptoms, but randomised controlled trials of FODMAP diet versus traditional dietary recommendations are lacking. The current study compared these two approaches over 4 weeks in 67 patients meeting Rome III criteria for IBS, comparing the effect of 4 weeks of a low-FODMAP diet with traditional dietary advice on symptoms of IBS. The study measured a significant difference in symptom severity as compared with baseline, but not between both treatment groups. Thus, both treatment options were successful and neither clearly superior. However, the patient numbers were small and while Rome III criteria allow subclassification of patients there remains a certain heterogeneity. Notably, an unexpected result was low-calorie intake irrespective of treatment arm. While unlikely to be relevant in the short term, this does raise concern about the long-term impact of these diets on patients’ nutrition intake.


Abstract

Colectomy for constipation: time trends and impact based on the US Nationwide Inpatient Sample, 1998–2011

Authors: Dudekula A et al.

Summary: These researchers analysed data from two comparable US inpatient databases. Their analysis of Nationwide Inpatient Sample data found that the colectomy rate for constipation increased from 1.2% of all annual colectomies in 1994 to 2.4% up to 2010, but the perioperative complication rate during the index hospitalisation was 42.7%. Longitudinal data from 181 patients in the State Inpatient Database revealed a similar perioperative complication rate and a readmission rate of 28.9% within 30 days of index hospitalisation. Resource utilisation data for a 2-week period before and after colectomy showed no change in the median number of emergency department visits (2 vs. 2 [p=0.21]), but an increase in the median number of hospitalisations (1 vs. 2 [p=0.003]).

Comment: Constipation is a common gastrointestinal symptom resulting in significant morbidity and increased hospitalisations and healthcare costs. Current guidelines for constipation unresponsive or refractory to medical therapy in the context of slow transit constipation also include subtotal colectomy or ileorectal anastomosis as treatment options. The current study shows an increasing number of surgical interventions performed for constipation. Importantly, complication rates were high at 40% and surgery did not translate into fewer emergency department presentations and admissions. While this study has some weaknesses, it highlights that surgical options for treatment of refractory constipation should be approached only cautiously.

Reference: Aliment Pharmacol Ther 2015;42(11–12):1281–93

Abstract

Frequency of progression from acute to chronic pancreatitis and risk factors

Authors: Sankaran SJ et al.

Summary: This was a meta-analysis of 14 studies (n=8492) reporting data on progression from acute to chronic pancreatitis. The respective pooled prevalences of recurrent acute pancreatitis and chronic pancreatitis were 22% and 10%, and the respective pooled prevalences of chronic pancreatitis after a first occurrence and after recurrent acute pancreatitis were 10% and 36%. Alcohol use and smoking were the strongest risk factors for developing chronic pancreatitis, with respective pooled prevalences of 65% and 61%. Progression from acute to chronic pancreatitis was more likely in men than women.

Comment: Acute pancreatitis is usually considered a self-limiting condition and transition rates to chronic pancreatitis are ill-defined. Furthermore, it is unclear what risk factors predispose to transition from acute pancreatitis to chronic pancreatitis. This meta-analysis of 14 published studies included >6000 patients and showed a prevalence of recurrent acute pancreatitis of 22% and chronic pancreatitis of 10%. Alcohol use and smoking were the main risk factors and male gender increased the risk for transition to chronic pancreatitis. While the results of this meta-analysis are not unexpected, it suggests increased vigilance for males with alcohol intake and smoking. Whether cessation of alcohol will reduce transition rates down the track is currently unknown and requires further investigations.

Reference: Gastroenterology 2015;149(6):1490–500

Abstract

Inflammatory bowel disease patients are at increased risk of invasive pneumococcal disease

Authors: Kants B et al.

Summary: The risk of invasive pneumococcal disease before and after an IBD diagnosis was investigated in this Danish population-based cohort study of 74,156 patients with IBD and 1,482,363 controls without IBD followed over 1977–2013. The risk of invasive pneumococcal disease within the first 6 months of an IBD diagnosis was significantly increased by a factor of >3, after which it decreased and remained significantly increased for CD diagnoses (HR 1.99 [95% CI 1.59–2.49]) but not UC. Medications for IBD, including anti-TNF-α agents, did not significantly affect the risk of invasive pneumococcal disease, with the exception of azathioprine ever-use, which was associated with a significantly increased risk in patients with UC (HR 2.38 [95% CI 1.00–5.67]). The risk of invasive pneumococcal disease was significantly increased up to 4 years prior to diagnoses of CD and UC (respective HRs 1.79 [95% CI 1.05–3.03] and 1.51 [1.05–2.17]).

Comment: Invasive pneumococcal disease is a condition defined by infection with Streptococcus pneumoniae, septicaemia, meningitis and pneumonia. Previously, invasive pneumococcal disease has been associated with IBD in a retrospective cohort study. The current population-based study found a 3-fold increased risk for invasive pneumococcal disease in IBD patients within the first 6 months of diagnosis and a persistent 2.4-fold increased risk in CD but not UC patients. Use of azathioprine among UC, but not CD, patients resulted in a 2.4-fold increased risk for invasive pneumococcal disease. Mesalazine (5-ASA)/sulfasalazine, topical or oral steroids and anti-TNF agents did not significantly change the risk for invasive pneumococcal disease. Notably, the risk for invasive pneumococcal disease was already increased prior to UC diagnosis (3.3-fold for 0–1 years prior; 1.5-fold for 2–4 years prior). Of note, this trend persisted in 2011. No correlation found between vaccinations. The cause for the predisposition to invasive pneumococcal disease in patients with IBD or even prior to diagnosis remains unclear. However, it highlights the need to maintain an index of suspicion for invasive pneumococcal disease in such patients and consider appropriate vaccination.


Abstract

Independent commentary by Associate Professor Golo Ahlenstiel

Gastroenterologist and Hepatologist at Westmead Hospital, Sydney. After completing his medical and doctoral degrees at the University of Bonn, Germany, Golo Ahlenstiel received research fellowship awards from the National Institutes of Health (NIH, USA) and the German Research Foundation (DFG, Germany) to work in the Rehermann laboratory at the NIH on the immunopathogenesis of viral hepatitis. Apart from his clinical duties, he also leads a Liver Immunology group at Westmead Millennium Institute.