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Outcomes and factors associated with reduced symptoms in gastroparesis

**Abbraviations used in this issue:**

CRC = colorectal cancer; HR = hazard ratio; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; OR = odds ratio; RFA = radiofrequency ablation; TNF = tumour necrosis factor

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**Welcome** to issue 29 of Gastroenterology Research Review.

The year begins with two papers looking at various effects of thiopurine therapy, one reporting an increased risk of urinary tract cancers, and the other reporting less colorectal neoplasias in patients with UC. UC researchers have reported on the incidence of oesophageal adenocarcinoma and its associated mortality following RFA (radiofrequency ablation) for Barrett’s oesophagus, and Australian researchers have reported long-term outcomes following primary complete endoscopic resection for Barrett’s oesophagus with high-grade dysplasia and early oesophageal adenocarcinoma. Research on the efficacy and safety of seasonal influenza vaccines in patients with IBD revealed high seroprotection rates, but with reduced persistence in anti-TNF therapy recipients.

I hope the papers selected for the first 2016 issue inspire you. Please keep sending your comments and feedback.

Kind Regards,

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**Excess risk of urinary tract cancers in patients receiving thiopurines for inflammatory bowel disease**

Authors: Bournier A et al., and the CESAME study group

**Summary:** The risk of urinary tract cancers in patients receiving thiopurines for IBD was assessed in 19,486 participants from the prospective CESAME observational cohort; 30.1% were thiopurine recipients. During median 33 months follow-up, ten participants developed kidney cancer and six developed bladder cancer. The respective incidence rates of urinary tract cancer among thiopurine recipients, participants who had discontinued thiopurines and participants who had never received thiopurine therapy were 0.48, 0.10 and 0.30 per 1000 patient-years, and the respective standardised incidence ratios were 0.40, 0.64 and 1.17. A multivariate analysis revealed that thiopurine recipients were significantly more likely to develop urinary tract cancer than nonrecipients (adjusted HR 2.82 [95% CI 1.04–7.68]), as were male participants (3.38 [1.12–14.10]) and those aged >65 vs. <50 years (13.26 [3.52–50.03]).

**Comment:** The thiopurines are commonly used in IBD to achieve and maintain remission. However, long-term use of thiopurines in IBD has been associated with increased risks for lymphoma, lymphoproliferative disease, hepatosplenic lymphoma and nonmelanoma skin cancers. Recently, thiopurines have also been associated with urinary tract cancers in organ transplant recipients, thus raising concern about similar risks in patients with IBD. This study is the first prospective cohort study describing the incidence of urinary tract cancers in IBD patients and showing an increased risk with prolonged exposure to thiopurines. Importantly, the risk seems to decrease again with cessation of thiopurine therapy. Data on smoking status were available only in 10% of the cohort (and did not increase risk in these) and thus could not be adjusted for. However, all patients with bladder cancer and half the patients with kidney cancer were active smokers. Notably, male gender and age >65 years presented an increased risk of urinary tract cancer in thiopurine-treated patients (incidence of 9.6 vs. 3.5 per 1000 patient-years in patients never exposed to thiopurines). The incidence for urinary tract cancers was close to that of lymphoma in the high-risk group of elderly men (7.2 per 1000 patient-years), and thus should be taken into consideration when treating particularly elderly men.

**Reference:** Aliment Pharmacol Ther 2016;43(2):252–61

[Abstract]

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**Thiopurine therapy reduces the incidence of colorectal neoplasia in patients with ulcerative colitis**

Authors: Gordillo J et al., on behalf of The ENEIDA Project of the Spanish Working Group in Crohn’s Disease and Ulcerative Colitis (GITECCU)

**Summary:** Retrospective registry data were reviewed to determine the incidence of dysplasia, CRC and related risk factors among 831 Spanish patients with UC. CRC was seen in 26 patients, and 24 had 29 cases of high-grade dysplasia, accounting for 45 patients with 55 advanced neoplasia diagnoses, one-third of which occurred within 8 years of UC diagnosis. The respective 10-, 20- and 30-year cumulative risks of advanced neoplasia were 2%, 5.3% and 14.7%. Independent risk factors for the development of advanced neoplasia were concomitant primary sclerosing cholangitis (OR 10.00 [95% CI 3.75–31.76]), extensive UC (2.10 [1.01–4.38]), older age at UC diagnosis (2.23 [1.03–4.83] and appendectomy prior to UC diagnosis (2.66 [1.06–6.71]), and the risk was reduced by thiopurine use (0.21 [0.06–0.74]) and enrolment in a surveillance colonoscopy programme (0.33 [0.16–0.67]).

**Comment:** The current study, despite being retrospective and mostly from tertiary centres, emphasises a few aspects about the risk for advanced neoplasia or CRC in UC. Firstly, UC extent and duration, prior appendectomy and co-existing primary sclerosing cholangitis increased the risk for advanced neoplasia and CRC. Secondly, the risk steadily increases after age 35 years and a substantial proportion of advanced neoplasias are being diagnosed within the first 8 years of UC evolution. In keeping with other recently published studies, the authors demonstrate a decreased risk for advanced neoplasia if a patient was commenced on thiopurines. Overall, the study highlights the importance of accurate staging, treating inflammation and careful screening of patients with UC.

**Reference:** J Crohns Colitis 2015;9(12):1063–70

[Abstract]
Risk of diabetes mellitus after first-attack acute pancreatitis

Authors: Shen H-N et al.

Summary: In this Taiwanese population-based study, the incidence of diabetes mellitus in 2,986 survivors of acute pancreatitis was compared with that of 11,884 matched controls. Compared with controls, acute pancreatitis survivors had higher incidences of diabetes in the period up to 3 months (60.8 vs. 8.0 per 1000 person-years; adjusted HR 5.90 [95% CI 3.57–10.54]) and also from 3 months (22.5 vs. 6.7 per 1000 person-years; 2.54 [2.13–3.04]) with the HR for this latter period significantly greater for men than women (3.21 vs. 1.58 [p=0.0004]). The risk of diabetes associated with mild acute pancreatitis did not differ significantly to the risk for any acute pancreatitis.

Comment: In a meta-analysis of 24 prospective studies in patients with acute pancreatitis not requiring surgery, a first episode of acute pancreatitis was associated with a new diagnosis of diabetes in 15% of patients within the first year and 40% within 5 years. However, this observation is controversial, and other studies have reported no increase in incidence after acute pancreatitis. The current study from Taiwan is the first population-level study matching patients and controls in a 1:4 ratio in a large cohort. The large number of controls is an important strength in this, as other studies often studied acute pancreatitis only without matched controls. The results are remarkable, in that the risk for diabetes with a first episode of acute pancreatitis was greatest in young males. Given that this study is based on insurance claim data, misclassification in terms of first versus recurrent episode as well as severity is a potential risk. Secondly, both groups differ significantly in terms of comorbidities, likely contributing to the risk of acute pancreatitis as well as the risk for diabetes. Irrespective however, this study highlights the need to carefully monitor patients with acute pancreatitis, whether mild or severe, for new onset of diabetes in subsequent years.


Abstratc

Incidence of esophageal adenocarcinoma and causes of mortality after radiofrequency ablation of Barrett’s esophagus

Authors: Wolf WA et al.

Summary: This analysis of outcome data from 4,982 registry patients who underwent RFA for Barrett’s esophagus found that over mean 2.7 years follow-up, the incidence of oesophageal adenocarcinoma was 7.8 per 1000 person-years, with an incidence of 0.5 per 1000 person-years among patients with nondysplastic Barrett’s oesophagus. The all-cause mortality incidence was 11.2 per 1000 person-years and the incidence of death from oesophageal adenocarcinoma was 0.7 per 1000 person-years. A multivariate logistic regression analysis revealed that predictors of oesophageal adenocarcinoma were Barrett’s oesophagus length at baseline (OR 1.1 for each cm) and histology at baseline (ORs 5.8 and 50.3 for low- and high-grade dysplasia, respectively). Six of the nine patients who died from oesophageal adenocarcinoma had baseline high-grade dysplasia and three had intramucosal oesophageal adenocarcinoma at baseline. Most deaths were due to CV causes (15%) and extra-oesophageal cancers (15%); none were associated with RFA.

Comment: Barrett’s oesophagus is a common problem, particularly in older male Caucasians, and is associated with an increased risk of oesophageal adenocarcinoma. RFA is a well-established therapy for Barrett’s oesophagus and related dysplasia, reducing the risk for subsequent oesophageal adenocarcinoma. The current study focuses on an area less well studied; i.e. oesophageal adenocarcinoma incidence and mortality after RFA are not well known. Importantly, the registry recruited patients not only from academic centres (n=35) but also community-based centres (n=113). Oesophageal adenocarcinoma incidence with 7.8 per 1000 patient-years was less than previously predicted and associated with baseline histology and length of Barrett’s oesophagus segment. This suggests that RFA, even when performed in nonacademic settings, can successfully decrease oesophageal adenocarcinoma risk and the risk of oesophageal adenocarcinoma-

Reference: Gastroenterology 2015;148(7):1752–81

Abstract

Long-term outcomes of a primary complete endoscopic resection strategy for short-segment Barrett’s esophagus with high-grade dysplasia and/or early esophageal adenocarcinoma

Authors: Bahm FF et al.

Summary: This research reported long-term outcomes for 126 patients with high-grade dysplasia and 27 with early oesophageal adenocarcinoma in short-segment Barrett’s oesophagus (<3cm in circumferential length and <5cm in maximal length) who underwent staged complete endoscopic resection by multiband mucosectomy or the cap method; 138 participants met inclusion criteria. Technical success of complete endoscopic resection was achieved in all participants and was established after a median of two sessions. One participant had covert synchronous early oesophageal adenocarcinoma. The respective complete remission rates for high-grade dysplasia/early oesophageal adenocarcinoma, dysplasia and intestinal metaplasia were 98.5%, 89.1% and 71.0% at mean 40.7 months follow-up. Complete endoscopic resection led to down- and upstaging of pretreatment histological grades in 28.1% and 19.0% of participants, respectively. Oesophageal dilation was required in 36.8% of participants in a mean 2.5 sessions. Nil or minimal dysphagia was present in 96.4% of participants at the end of follow-up, and 90.6% reported that complete endoscopic resection was an acceptable treatment.

Comment: The aim of endoscopic therapy for high-grade dysplasia or early oesophageal cancer in the context of Barrett’s oesophagus is complete eradication of dysplastic areas and ultimately Barrett’s oesophagus. While RFA is relatively straightforward to use and has only few short-term complications, it does not allow complete staging of the lesion. The current two-centre study employed complete endoscopic resection instead in 153 patients with short-segment Barrett’s oesophagus and high-grade dysplasia or oesophageal cancer. Apart from its impressive outcomes, it is notable that complete endoscopic resection resulted in restaging of almost half of all patients, although only one covert oesophageal cancer was identified. Another aspect of this study is that it actually addressed whether the procedure and outcomes including complications made this approach acceptable. Notably, despite almost 40% of patients requiring dilatation due to stricture and dysphagia following complete endoscopic resection, >95% of patients reported no or only minimal dysphagia and >90% considered complete endoscopic resection acceptable at the end of study. Thus, despite its relatively short-term morbidity, the long-term outcomes of complete endoscopic resection are encouraging and seem to be acceptable from a patient’s point of view.

Reference: Gastrointest Endosc 2016;83(1):68–77

Randomised controlled trial of mesalazine in IBS

Authors: Barbara G et al.

Summary: In this phase 3 trial, 185 patients with IBS were randomised to receive mesalazine 800mg or placebo three times daily for 12 weeks and were followed for another 12 weeks. There was no significant difference between the mesalazine and placebo arms for the primary endpoint of satisfactory relief of abdominal pain/discomfort for at least half of the weeks during treatment in the primary analysis (68.6% vs. 67.4% [p=0.870]) or in exploratory supportive analyses that classified responders as participants with a percentage of affirmative answers of >75% or >75% of the study period. Mesalazine was associated with a 15.1% improvement over placebo for the secondary endpoint of overall symptoms when the >75% rule was applied (p=0.032).

Comment: Low-grade inflammation has been previously observed in patients with IBS. Previous studies in IBS failed to show a response to steroids; mesalazine reduced the number of inflammatory cells in colon mucosa. The current phase 3 study assessed the clinical efficacy of mesalazine in 185 patients with IBS. Clinical efficacy of mesalazine could only be shown in patients with symptom relief for >75% of the study period (<75% rule) as compared with placebo. The study highlights common problems for clinical trials in IBS, i.e. that clinical symptoms are highly variable over time and placebo response rates are high; i.e., 67.4% of patients receiving placebo reported symptom relief for at least 50% of the study period. Given that mesalazine is usually used as an anti-inflammatory agent, it would have been useful to have data on colonic inflammation, which were not available. Overall, the results of this study suggest that anti-inflammatory drugs such as mesalazine may be a useful treatment in a subgroup of patients with IBS.

Reference: Gut 2016;65(1):82–90

http://gut.bmj.com/content/65/1/82.full
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**References:**

HCV=Hepatitis C Virus. RNA=Ribonucleic Acid. SVR=Sustained Virologic Response. GT1=Genotype 1. RBV=Ribavirin.

**Overall cure** rates in patients receiving the recommended dosing regimen in a pooled analysis of Phase III clinical trials1,2

97% (n=1062/1096) achieved SVR12

*Cure defined as <25 IU/mL HCV RNA 12 weeks post end-of-treatment (SVR12) in 97% HCV GT1 patients with or without cirrhosis (pooled analysis Phase III trial cohorts, n=1096)

**A NEW FACE OF CURE** IN CHRONIC HCV: INTRODUCING VIEKIRA PAK**1,2**
Increased risk of colorectal cancer among family members of all ages, regardless of age of index case at diagnosis

Authors: Samadder NJ et al.

Summary: These authors linked CRC (colorectal cancer) cases entered in the Utah Cancer Registry to pedigrees from the Utah Population Database, with age- and sex-matched controls without CRC used as comparators, to quantify CRC risk among the 18,208 index patients’ first-degree, second-degree and first-cousin relatives of index patients. Left-sided CRC who were diagnosed at age <40 years had the highest familial risk of CRC (HR 2.53 [95% CI 1.7–2.7]), although their risk was still increased even when the index patient was diagnosed at age >80 years (1.76 [1.59–1.94]). Familial cancer risk was affected by both the relatives’ and the index patient’s ages, with the highest risk seen in relatives aged <50 years of index patients with CRC diagnosed at <40 years (HR 7.0 [95% CI 2.6–17.0]).

Comment: The current study addressed the risk of CRC in relatives of patients with CRC. In contrast to most previous studies that focused on relatives of patients diagnosed with CRC at an older age, the current study shows clearly that there is a substantially increased risk of at least 1.7-fold for first-degree relatives of patients diagnosed even at older age. Furthermore, the authors conclude that earlier screening in first-degree relatives should be implemented if CRC was diagnosed at age <50 years, given an at least 2-fold increase in that subgroup. Finally, even second-degree relatives show a significantly increased risk at all ages, highlighting the need for a careful family history when determining when and how often to screen for CRC.


Immunogenicity and safety of influenza vaccine in inflammatory bowel disease patients treated or not with immunomodulators and/or biologics

Authors: Launay O et al.

Summary: The impact of immunosuppressants on serological response to 2-year influenza vaccination was prospectively evaluated in adults with IBD, including 31 receiving no immunosuppressants, 77 receiving immunosuppressants without anti-TNF therapy and 117 receiving anti-TNF therapy or without immunosuppressants. The seroprotection rates 3 weeks after first vaccine administration did not differ significantly among the three respective cohorts for strains A/HIN12007 (77%, 75% and 66%) and B (97%, 96% and 95%), but did strain A/H3N2 (77%, 68% and 52%) [p=0.014]; seroconversion rates for the three strains did not differ significantly among treatment groups. The seroprotection rates at 6 months were lower for anti-TNF recipients than for the other groups. Findings for the second vaccination year were comparable, and there was no detectable impact on the Harvey-Bradshaw or Mayo score.

Comment: Long-term immunosuppression in patients with IBD is often essential to achieve remission and avoid disease-related complications. Unfortunately, immunosuppression increases susceptibility to infectious agents, and thus vaccination against various infectious agents including influenza. The question, however, is whether vaccines work in immunosuppressed IBD patients. The current study shows that standard vaccines for influenza resulted in high antibody titres. In terms of safety, two out of 255 patients developed a flare after vaccination, with both patients suffering from Crohne’s disease and receiving anti-TNF therapy. These rates are similar to previously supported flare rates after vaccination for influenza. Notably, the study was not designed to assess whether observed antibody titres truly refer immunity to influenza given the low observed incidence of influenza in the years studied.

Reference: J Crohns Colitis 2015;9(12):1096–107

Combined ursodeoxycholic acid (UDCA) and fenofibrate in primary biliary cholangitis patients with incomplete UDCA response may improve outcomes

Authors: Cheung AC et al.

Summary: These researchers evaluated biochemical profiles, liver-related outcomes and adverse events associated with fenofibrate therapy in a retrospective cohort of patients with primary biliary cholangitis who had an incomplete response to ursodeoxycholic acid; 46 patients had received fenofibrate for a median 11 months with ursodeoxycholic acid and 74 received ursodeoxycholic acid only. Compared with ursodeoxycholic acid alone, the addition of fenofibrate was associated with a significantly greater proportion of patients achieving the Toronto criteria for biochemical response (alkaline phosphatase level ≤1.2 times the upper limit of normal; 41% vs. 7% [p=0.0001]) and improved decompensation-free and transplant-free survival (HR 0.09 [95% CI 0.03–0.32]). However, a multivariate analysis revealed that fenofibrate use but not biochemical response was independently associated with improved outcomes (HR 0.40 [95% CI 0.17–0.93]). The rate of fenofibrate discontinuation due to adverse events (mostly abdominal pain and myalgias) was 22%, and fenofibrate and cirrhosis had a more rapid increase in bilirubin level (p=0.005).

Comment: The mainstay of therapy for primary biliary cholangitis is ursodeoxycholic acid. However, 30–40% of patients have an incomplete response to ursodeoxycholic acid (UOA). Fibrates are known to decrease hepatic alkaline phosphatase levels through an increase of biliary phospholipid excretion, which has been hypothesised to reduce bile toxicity. In this retrospective study, fenofibrate was associated with improved alkaline phosphatase level, and fenofibrate was an independent risk factor, apart from absence of cirrhosis, for transplant- and decompensation-free survival in patients with incomplete response to ursodeoxycholic acid alone. Interestingly, despite being retrospective, this study is by far the largest of its kind and best powered to detect an impact of fibrates on survival. Notably, most other studies have been done with bezafibrate. While these results are interesting, there remain some concerns of using fibrates in patients with advanced liver disease, and their potential will likely be outpaced by newer agents, such as obeticholic acid, that have shown promising results.


Outcomes and factors associated with reduced symptoms in patients with gastroparesis

Authors: Pasricha PJ et al.

Summary: This research involved 262 adults with diabetic or idiopathic gastroparesis treated according to standard care with prescribed medications or other therapies at seven US tertiary-care centres. Reductions in GCSI (Gastroparesis Cardinal Symptom Index) scores of ≥1 at 48 weeks were seen for 28% of the patients, but no significant symptom reductions were seen during weeks 48–192. Independent associations were seen between reduced symptoms at 48 weeks and age ≥50 years, initial infectious prodrome, antidepressant use and 4-hour gastric retention >20%: factors associated with no reduction in symptoms included overweight/obesity, smoking history, anxiolytic/pain modulator use, moderate-to-severe abdominal pain, more severe gastro-oesophageal reflux disease and moderate-to-severe depression.

Comment: In this study, the authors report on the clinical outcomes of a large cohort of patients with gastroparesis (68% idiopathic). Despite being treated at tertiary-care centres, only 28% reported improvement of symptom scores. The chances for clinical improvement were higher in patients aged more than 50 years or treated with antidepressants. Interestingly, more severe gastric emptying increased the likelihood of response, and response rates did not differ between patients with diabetic versus idiopathic gastroparesis. However, the results need to be considered with some caution, as all these patients were treated at tertiary-care centres, and likely represent a group of difficult-to-treat or otherwise complex patients to begin with. Nevertheless, this study provides some insights into which patients are likely to respond to therapeutic interventions and highlights the need for more research into this area to develop better interventions for gastroparesis.

Reference: Gastroenterology 2015;149(1):1782–74