Falk Gastro Review

1/19

Contents

Editorial .................................................. 2

Esophagus
Stomach
Duodenum .................................................. 3–8

Intestine .................................................... 9–18

Congress News in Brief

Falk Seminar
“IBD controversies”
Hamburg (Germany), June 16, 2018 ........... 19–20

Pancreas .................................................. 22–26

Liver
Bile ......................................................... 28–38

New Books ............................................... 35

International Gastroenterological
Congresses 2019 ........................................ 40
Dear colleagues,

Recurrent peptic ulcer bleeding following primarily successful endoscopic hemostasis is typically associated with a complicated disease course, which is why treating it endoscopically is greatly important. Within the context of the first direct comparison between conventional hemostasis procedures and over-the-scope clips (OTSC), Schmidt and colleagues were able to show that the OTSC treatment is significantly superior to conventional hemostasis and that it should be employed in cases of recurrent peptic ulcer bleeding (page 6). The question arises as to how frequently follow-up examinations should be conducted after successful endoscopic treatment of dysplastic Barrett’s esophagus. Evaluation of long registers of cases of Barrett’s esophagus compiled by Cotton and colleagues has proven that endoscopic follow-ups suffice 1, 3 and 5 years after successful eradication of Barrett’s esophagus with low-grade intraepithelial neoplasia, whereas the follow-up examinations to the eradication of high-grade neoplasia or intramucosal adenocarcinoma should initially occur after a quarter, a half and a full year and subsequently on an annual basis (page 4). Immunotherapy has revolutionized the oncologic treatment of numerous tumor entities in the past years and the identification of the underlying molecular mechanisms was awarded this year’s Nobel Prize. Thus, many patients place hope in immunotherapy with PD-1 inhibitors when first-line chemotherapy fails to work. In a phase 3 trial on the treatment of advanced gastric or gastroesophageal junction cancer, a course of treatment with the PD-1 inhibitor pembrolizumab did not prove superior to chemotherapy with paclitaxel within the context of a second-line therapy, but it did have a better safety profile (Shitara et al., page 5) and could therefore represent a valid option for second-line therapy.

Uncomplicated acute diverticulitis does not need to be treated with antibiotics. The long-term results of the DIABOLO study, 2 years later, prove that forgoing antibiotic treatment is not associated with a higher risk of complications and recurring diverticulitis or higher rates of sigmoid resections (van Dijk et al., page 18). Treating chronic constipation often constitutes a major medical challenge, which could potentially be addressed by a new medication treatment using elobixibat. The results of a phase 3 trial reveal that this locally acting ileal bile acid transporter inhibitor is effective for treating functional constipation in the short term and is well tolerated in the long term (Nakajima et al., page 15). For many decades, immunomodulators such as azathioprine have been used for treating inflammatory bowel disease. However, their clinical benefit is frequently called into question in light of their potentially limited efficacy in comparison with biologic therapy and their significant long-term side effects. Evaluations of a large population-based cohort study in Canada have shown that, in a wider clinical setting, nearly half of patients with Crohn’s disease or ulcerative colitis receive monotherapy with immunomodulators, and approximately one third of each group achieves a permanent response over 5 years (Targownik et al., page 10).

Fully covered lumen-apposing metal stents (LAMS) have technically simplified the endoscopic treatment of fluid collections and walled-off necrosis (WON) of the pancreas considerably. However, in addition to higher material costs, LAMS are potentially associated with increased bleeding complications. The first direct comparison of LAMS and plastic stents in the treatment of WON did reveal that the technical success rate of the two treatment methods is comparable, but LAMS are accompanied by higher treatment costs and a significantly greater risk of bleeding in the long term, which is why they should be removed again after 3 weeks, if possible (Bang et al., page 22).

Acute hepatitis E continues to be diagnosed with much greater frequency in Germany and other European and North American countries from year to year, but a retrospective analysis of laboratory data shows that this effect is to be ascribed to a rise in awareness and not a rise in incidence or prevalence. Indeed, the seroprevalence of hepatitis E (positive HEV IgG) in Germany in the last 10 years has receded from 19% to 15% (Faber et al., page 29). Using a new score, patients with primary biliary cholangitis (PBC) can be identified who are unlikely to respond sufficiently to monotherapy with ursodeoxycholic acid. These patients could thus benefit from primary combination therapy or an early therapy supplement with another specimen (Carbone et al., page 33). Human serum albumin is currently being employed in patients with decompensated cirrhosis, primarily in the context of large-volume paracentesis or for treating hepatorenal syndrome. However, a current study also shows that long-term administration of human serum albumin creates a survival advantage for patients with decompensated cirrhosis (Caraceni et al., page 34). The coming months are sure to see heated debate over whether human serum albumin should be widely used in patients with decompensated cirrhosis on the basis of these findings.

We wish you a very merry Christmas and all the best for 2019!

Sincerely,

Christoph Neumann-Haefelin and Peter Hasselblatt
Department of Internal Medicine II, Medical University Clinic of Freiburg (Germany)
Wheat intolerance and chronic gastrointestinal symptoms in an Australian population-based study: Association between wheat sensitivity, celiac disease and functional gastrointestinal disorders

Objectives: Wheat avoidance in the absence of celiac disease is common but occurrence of concurrent functional gastrointestinal disorders (FGIDs) in this group is uncertain. The aims of this study were to determine the prevalence of self-reported wheat or gluten sensitivity and doctor-diagnosed celiac disease in an Australian population, to define the associated gastrointestinal (GI) symptoms and FGIDs, and to determine the relationship between self-reported wheat sensitivity, demographic and medical factors.

Methods: A total of 3542 people randomly selected from the Australian population returned a mail survey which contained questions on wheat avoidance, GI symptoms, demographic, medical, and lifestyle factors. The authors defined self-reported wheat sensitivity as people who reported GI symptoms on ingestion of wheat-based foods, but did not suffer from celiac disease, inflammatory bowel disease or colorectal cancer. Functional dyspepsia (FD) and irritable bowel syndrome (IBS) were diagnosed by Rome III criteria. Celiac disease status was self-reported.

Results: The prevalence of self-reported wheat sensitivity in this cohort was 14.9% (95% confidence interval [CI]: 13.7–16.2). The prevalence of celiac disease was 1.2% (95% CI: 0.8–1.6). Doctor-diagnosed celiac disease was significantly associated with a diagnosis of FD (odds ratio [OR] = 3.35, 95% CI: 1.72–6.52) and IBS (OR = 2.28, 95% CI: 1.08–4.81). Those with self-reported wheat sensitivity were more likely to report multiple abdominal symptoms (of the 18 assessed) than those without (3.9 symptoms with self-reported wheat sensitivity vs. 1.6 without, p = 0.0001). In a multivariate analysis, self-reported wheat sensitivity was independently associated with IBS (OR = 3.55, 95% CI: 2.71–4.65) and FD (OR = 1.48, 95% CI: 1.13–1.94).

Conclusions: Self-reported wheat sensitivity is common, with a prevalence of 14.9% in this cohort. There is a strong association between both celiac disease and self-reported wheat sensitivity, and chronic gastrointestinal symptoms, as well as a diagnosis of functional dyspepsia and irritable bowel syndrome.

Dr. M.D.E. Potter, Faculty of Health and Medicine, University of Newcastle, Hunter Medical Research Institute Building, Kookaburra Circuit, New Lambton Heights, NSW 2305, Australia, E-Mail: michael.potter@newcastle.edu.au

Effects of Helicobacter pylori treatment on incidence of gastric cancer in older individuals

Background and aims: Although eradication of Helicobacter pylori infection reduces the risk of gastric cancer, few data are available on its effects in older subjects. The authors compared the age-specific risk of gastric cancer in a large cohort of subjects who received H. pylori eradication therapy versus a matched general population.

Methods: They searched the Hospital Authority database of Hong Kong to identify individuals with H. pylori infection who had received a course of clarithromycin-containing eradication therapy from January 2003 through December 2012. The gastric cancer incidence in this cohort was compared with the expected incidence for the local general population by retrieving the gastric cancer incidence of the age- and sex-matched population from 2003 through 2014 (the latest available year) from the Hong Kong Cancer Registry. The primary outcome was the incidence of gastric cancer development in the cohort treated for H. pylori infection versus the expected number of gastric cancer cases in the general population. Analyses were conducted by a priori age groups of > 40 years, 40–59 years, and ≥ 60 years.

Results: Among 73,237 subjects infected with H. pylori who received eradication therapy, 200 (0.27%) developed gastric cancer during a median follow-up time of 7.6 years. Compared with the matched general population, the gastric cancer risk was significantly lower in subjects ≥ 60 years who had received H. pylori eradication therapy versus a matched general population. Analyses were conducted by a priori age groups of > 40 years, 40–59 years, and ≥ 60 years.

Conclusions: In an analysis of data from a public hospital database on Hong Kong, the treatment of Helicobacter pylori infection was associated with a lower risk of gastric cancer, particularly in older subjects, ≥ 10 years after treatment.

Dr. W.K. Leung, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, E-Mail: waikleung@hku.hk
Objectives: Rising trends in eosinophilic esophagitis (EoE) have been repeatedly linked to declining Helicobacter pylori infection, mostly in retrospective studies. The authors aimed to prospectively evaluate this inverse association.

Methods: Prospective case-control study conducted in 23 centers. Children and adults naïve to eradication therapy for H. pylori were included. Cases were EoE patients, whereas controls were defined by esophageal symptoms and < 5 eos/HPF (eosinophils/high power field) on esophageal biopsies. H. pylori status was diagnosed by non-invasive (excluding serology) or invasive testing of proton-pump inhibitor (PPI) therapy for 2 weeks. Atopy was defined by the presence of immunoglobulin E-mediated conditions diagnosed by an allergist.

Results: 808 individuals, including 404 cases and 404 controls (170 children) were enrolled. Overall H. pylori prevalence was 38% (45% children vs. 37% adults, p = 0.009) and was not different between cases and controls (37% vs. 40%, p = 0.3; odds ratio [OR] = 0.97; 95% confidence interval [CI]: 0.73–1.30), neither in children (42% vs. 46%, p = 0.11) nor in adults (36% vs. 38%, p = 0.4). Atopy (OR = 0.85; 95% CI: 0.75–0.98) and allergic rhinitis (OR = 0.81; 95% CI: 0.68–0.98) showed a borderline inverse association with H. pylori infection in EoE patients. This trend was not confirmed for asthma or food allergy.

Conclusions: Helicobacter pylori infection was not inversely associated with eosinophilic esophagitis (EoE), neither in children nor in adults. A borderline inverse association was confirmed for atopy and allergic rhinitis, but not asthma of food allergy. These findings question a true protective role of H. pylori infection against allergic disorders, including EoE.

Dr. J. Molina-Infante, Department of Gastroenterology, Hospital Universitario San Pedro de Alcántara, Calle Pablo Naranjo s/n, 10003 Cáceres, Spain, E-Mail: xavi_molina@hotmail.com

Lancet. 2018;392(10145):400–8


Esomeprazole and aspirin in Barrett’s esophagus (AspECT): A randomized factorial trial

Background: Esophageal adenocarcinoma is the sixth most common cause of cancer death worldwide and Barrett’s esophagus (BE) is the biggest risk factor. The authors aimed to evaluate the eradication of intestinal metaplasia (CEIM). The frequency of surveillance is informed only by expert opinion. The authors aimed to model the incidence of neoplastic recurrence, validate the model in an independent cohort, and propose evidence-based surveillance intervals.

Methods: They collected data from the United States Radiofrequency Ablation Registry (US RFA, 2004–2013) and the United Kingdom National Halo Registry (UK NHR, 2007–2015) to build and validate models to predict the incidence of neoplasia recurrence after initially successful RFA. The authors developed 3 categories of risk and modeled intervals to yield 0.1% risk of recurrence with invasive adenocarcinoma. They fit Cox proportional hazards models assessing discrimination by C statistic and 95% confidence limits.

Results: The incidence of neoplastic recurrence was associated with most severe histologic grade before CEIM, age, endoscopic mucosal resection, sex, and baseline BE segment length. In multivariate analysis, a model based solely on most severe pre-CEIM histology predicted neoplastic recurrence with a C statistic of 0.892 (95% confidence limit: 0.863–0.921) in the US RFA registry. This model also performed well when the authors used data from the UK NHR. This model divided patients into 3 risk groups based on baseline histologic grade: non-dysplastic BE; indefinite for dysplasia, low-grade dysplasia, and high-grade dysplasia; or intramucosal adenocarcinoma. For patients with low-grade dysplasia, they propose surveillance endoscopy at 1 and 3 years after CEIM; for patients with high-grade dysplasia or intramus-}

Barrett’s Esophagus, Esophageal and Gastric Cancer


Cotton CC, Haidry R, Thrift AP, Lovat L, Shaheen NJ

Development of evidence-based surveillance intervals after radiofrequency ablation of Barrett’s esophagus

Background and aims: Barrett’s esophagus (BE) recurs in ≥ 25% of patients treated successfully with radiofrequency ablation (RFA), so surveillance endoscopy is recommended after complete eradication of intestinal metaplasia (CEIM). The frequency of surveillance is informed only by expert opinion. The authors aimed to model the incidence of neoplastic recurrence, validate the model in an independent cohort, and propose evidence-based surveillance intervals.

Methods: They collected data from the United States Radio-frequency Ablation Registry (US RFA, 2004–2013) and the United Kingdom National Halo Registry (UK NHR, 2007–2015) to build and validate models to predict the incidence of neoplasia recurrence after initially successful RFA. The authors developed 3 categories of risk and modeled intervals to yield 0.1% risk of recurrence with invasive adenocarcinoma. They fit Cox proportional hazards models assessing discrimination by C statistic and 95% confidence limits.

Results: The incidence of neoplastic recurrence was associated with most severe histologic grade before CEIM, age, endoscopic mucosal resection, sex, and baseline BE segment length. In multivariate analysis, a model based solely on most severe pre-CEIM histology predicted neoplastic recurrence with a C statistic of 0.892 (95% confidence limit: 0.863–0.921) in the US RFA registry. This model also performed well when the authors used data from the UK NHR. This model divided patients into 3 risk groups based on baseline histologic grade: non-dysplastic BE; indefinite for dysplasia, low-grade dysplasia, and high-grade dysplasia; or intramucosal adenocarcinoma. For patients with low-grade dysplasia, they propose surveillance endoscopy at 1 and 3 years after CEIM; for patients with high-grade dysplasia or intramus-
eficacy of high-dose esomeprazole proton-pump inhibitor (PPI) and aspirin for improving outcomes in patients with BE.

Methods: The Aspirin and Esomeprazole Chemoprevention in Barrett’s metaplasia Trial had a 2 x 2 factorial design and was done at 84 centers in the UK and 1 in Canada. Patients with BE of ≥ 1 cm were randomized 1:1:1 using a computer-generated schedule held in a central trials unit to receive high-dose (40 mg twice daily) or low-dose (20 mg once daily) PPI, with or without aspirin (300 mg/day in the UK, 325 mg/day in Canada) for at least 8 years, in an unblinded manner. Reporting pathologists were masked to treatment allocation. The primary composite end point was time to all-cause mortality, esophageal adenocarcinoma, or high-grade dysplasia, which was analyzed with accelerated failure time modelling adjusted for minimization factors (age, BE length, intestinal metaplasia) in all patients in the intention-to-treat population.

Findings: Between March 10, 2005, and March 1, 2009, 2557 patients were recruited. 705 patients were assigned to low-dose PPI and no aspirin, 704 to high-dose PPI and no aspirin, 571 to low-dose PPI and aspirin, and 577 to high-dose PPI and aspirin. Median follow-up and treatment duration was 8.9 years (IQR = 8.2–9.8), and 20,095 follow-up years and 99.9% of planned data were collected. 313 primary events occurred. High-dose PPI (139 events in 1270 patients) was superior to low-dose PPI (174 events in 1265 patients; time ratio [TR] = 1.27, 95% confidence interval [CI]: 1.01–1.58, p = 0.038). Aspirin (127 events in 1138 patients) was not significantly better than no aspirin (154 events in 1142 patients; TR = 1.24, 95% CI: 0.98–1.57, p = 0.068). If patients using non-steroidal anti-inflammatory drugs were censored at the time of first use, aspirin was significantly better than no aspirin (129 events in 1142 patients; TR = 1.29, 95% CI: 1.01–1.66, p = 0.043; n = 2236). Combining high-dose PPI with aspirin had the strongest effect compared with low-dose PPI without aspirin (TR = 1.59, 95% CI: 1.14–2.23, p = 0.0068). The numbers needed to treat were 34 for PPI and 43 for aspirin. Only 28 (1%) participants reported study-treatment-related serious adverse events.

Interpretation: High-dose proton-pump inhibitor and aspirin chemoprevention therapy, especially in combination, significantly and safely improved outcomes in patients with Barrett’s esophagus.

Risk of oral and upper gastrointestinal cancers in persons with positive results from a fecal immunochemical test in a colorectal cancer screening program

Background and aims: European guidelines recommend screening for colorectal cancer (CRC) using the fecal immunochemical test (FIT), with follow-up colonoscopies for individuals with positive test results. However, more than half of participants with positive results from the FIT are not found to have advanced neoplasia in the colonoscopy examination. Fecal occult blood might also come from the upper gastrointestinal (GI) tract, so perhaps one should consider esophagogastro-duodenoscopy (EGD), to detect upper GI cancers. The authors aimed to determine how many individuals are found to have oral or upper GI cancers (oral cavity, throat, esophageal, gastric, or small bowel cancer) within 3 years after a positive or negative result from a FIT in a CRC screening program.

Methods: They performed a retrospective analysis of data from a pilot study of 3 rounds of biennial FIT-based screening for CRC in 2 regions in the west of the Netherlands, from 2006 through October 2012. Participants who developed oral or upper GI cancers were identified through linkage with the National Cancer Registry. These cancers were classified into 3 groups: those that developed in individuals with a positive result from a FIT but negative findings from colonoscopy (no advanced neoplasia), those that developed in individuals with a positive result from a FIT and a positive finding from colonoscopy (advanced neoplasia), and those that developed in individuals with negative results from a FIT. Oral and upper GI cancer incidence was compared among groups.

Results: Among 16,165 screening participants, linkage identified 52 persons who developed an oral or upper GI cancer within 3 years after a FIT. No significant difference were found in incidence values between individuals with a positive versus a negative FIT result: 8 cancers developed in individuals with a positive result from a FIT (0.37%; 95% confidence interval [CI]: 0.19–0.76) and 44 developed in individuals with a negative result from a FIT (0.31%; 95% CI: 0.23–0.42; p = 0.65). Of the 8 individuals with a positive result from a FIT and an oral or upper GI cancer, 6 were diagnosed after negative findings from colonoscopy and 2 after positive findings from colonoscopy. It was found that only 0.14% of all persons with a positive result from a FIT were diagnosed with a gastric or esophageal cancer within 3 years.

Conclusion: In a study of individuals in the Netherlands undergoing screening for colorectal cancer by fecal immunochemical test (FIT), fewer than 1% of patients with a positive result from the FIT were found to receive a diagnosis of upper gastrointestinal cancers within 3 years. Routine esophagogastro-duodenoscopy investigation of individuals with positive results from a FIT and negative findings from colonoscopy is therefore not recommended.

van der Vlug M, Grobbee EJ, Bossuyt PM, Bos ACRK, Kuipers EJ, Lansdorp-Vogelaar I, Spaander MCW, Dekker E

Clin Gastroenterol Hepatol. 2018;16(8):1237–43.e2

van der Vlug M, Grobbee EJ, Bossuyt PM, Bos ACRK, Kuipers EJ, Lansdorp-Vogelaar I, Spaander MCW, Dekker E

Risk of oral and upper gastrointestinal cancers in persons with positive results from a fecal immunochemical test in a colorectal cancer screening program

Background and aims: European guidelines recommend screening for colorectal cancer (CRC) using the fecal immunochemical test (FIT), with follow-up colonoscopies for individuals with positive test results. However, more than half of participants with positive results from the FIT are not found to have advanced neoplasia in the colonoscopy examination. Fecal occult blood might also come from the upper gastrointestinal (GI) tract, so perhaps one should consider esophagogastro-duodenoscopy (EGD), to detect upper GI cancers. The authors aimed to determine how many individuals are found to have oral or upper GI cancers (oral cavity, throat, esophageal, gastric, or small bowel cancer) within 3 years after a positive or negative result from a FIT in a CRC screening program.

Methods: They performed a retrospective analysis of data from a pilot study of 3 rounds of biennial FIT-based screening for CRC in 2 regions in the west of the Netherlands, from 2006 through October 2012. Participants who developed oral or upper GI cancers were identified through linkage with the National Cancer Registry. These cancers were classified into 3 groups: those that developed in individuals with a positive result from a FIT but negative findings from colonoscopy (no advanced neoplasia), those that developed in individuals with a positive result from a FIT and a positive finding from colonoscopy (advanced neoplasia), and those that developed in individuals with negative results from a FIT. Oral and upper GI cancer incidence was compared among groups.

Results: Among 16,165 screening participants, linkage identified 52 persons who developed an oral or upper GI cancer within 3 years after a FIT. No significant difference were found in incidence values between individuals with a positive versus a negative FIT result: 8 cancers developed in individuals with a positive result from a FIT (0.37%; 95% confidence interval [CI]: 0.19–0.76) and 44 developed in individuals with a negative result from a FIT (0.31%; 95% CI: 0.23–0.42; p = 0.65). Of the 8 individuals with a positive result from a FIT and an oral or upper GI cancer, 6 were diagnosed after negative findings from colonoscopy and 2 after positive findings from colonoscopy. It was found that only 0.14% of all persons with a positive result from a FIT were diagnosed with a gastric or esophageal cancer within 3 years.

Conclusion: In a study of individuals in the Netherlands undergoing screening for colorectal cancer by fecal immunochemical test (FIT), fewer than 1% of patients with a positive result from the FIT were found to receive a diagnosis of upper gastrointestinal cancers within 3 years. Routine esophagogastro-duodenoscopy investigation of individuals with positive results from a FIT and negative findings from colonoscopy is therefore not recommended.

Dr. Dr. E. Dekker, Department of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands, E-Mail: e.dekker@amc.uva.nl

Lancet. 2018;392(10142):123–33


Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastroesophageal junction cancer (KEYNOTE-061): A randomized, open-label, controlled, phase 3 trial

Background: Patients with advanced gastric or gastroesophageal junction cancer that progresses on chemotherapy have poor outcomes. The authors compared pembrolizumab with paclitaxel
in patients with advanced gastric or gastroesophageal junction cancer that progressed on first-line chemotherapy with a platinum and fluoropyrimidine.

Methods: This randomized, open-label, phase 3 study was done at 148 medical centers in 30 countries. Eligible patients were randomized (1:1) in blocks of 4 per stratum with an interactive voice-response and integrated web-response system to receive either pembrolizumab 200 mg every 3 weeks for up to 2 years or standard-dose paclitaxel. Primary end points were overall survival and progression-free survival in patients with a programmed cell death ligand 1 (PD-L1) combined positive score (CPS) of ≥ 1. Safety was assessed in all patients, irrespective of CPS. The significance threshold for overall survival was p = 0.0135 (1-sided).

Findings: Between June 4, 2015, and July 26, 2016, 592 patients were enrolled. Of the 395 patients who had a PD-L1 CPS of ≥ 1, 196 patients were assigned to receive pembrolizumab and 199 patients were assigned to receive paclitaxel. As of October 26, 2017, 326 patients in the population with CPS of ≥ 1 had died (151/196 patients [77%] in the pembrolizumab group and 175/199 patients [88%] in the paclitaxel group). Median overall survival was 9.1 months (95% confidence interval [CI]: 6.2–10.7) with pembrolizumab and 8.3 months (95% CI: 7.6–9.0) with paclitaxel (hazard ratio [HR] = 0.82, 95% CI: 0.66–1.03; 1-sided p = 0.0421). Median progression-free survival was 1.5 months (95% CI: 1.4–2.0) with pembrolizumab and 4.1 months (95% CI: 3.1–4.2) with paclitaxel (HR = 1.27, 95% CI: 1.03–1.57). In the total population, grade 3–5 treatment-related adverse events occurred in 42 (14%) of the 294 patients treated with pembrolizumab and 96 (35%) of the 276 patients treated with paclitaxel.

Interpretation: Pembrolizumab did not significantly improve overall survival compared with paclitaxel as second-line therapy for advanced gastric or gastroesophageal junction cancer with a programmed cell death ligand 1 combined positive score of ≥ 1. Pembrolizumab had a better safety profile than paclitaxel. Additional trials of pembrolizumab in gastric and gastroesophageal cancer are ongoing.

Dr. K. Shitara, Department of Experimental Therapeutics (and Gastrointestinal Oncology), National Cancer Center Hospital East, Kashiwa-Shi 277-0882, Japan, E-Mail: kshitara@east.ncc.go.jp

Upper Gastrointestinal Bleeding

Gastroenterology. 2018;155(3):674–86.e6


Over-the-scope clips are more effective than standard endoscopic therapy for patients with recurrent bleeding of peptic ulcers

Background and aims: Endoscopic hemostasis is effective in treatment of bleeding peptic ulcers. However, rebleeding is difficult to treat and associated with substantial morbidity and mortality. A prospective randomized trial was performed to determine whether over-the-scope clips (OTSCs) are more effective than standard treatment of severe recurrent upper gastrointestinal bleeding.

Methods: The authors performed this study at 9 academic referral centers (in Germany, Switzerland, and Hong Kong) from March 2013 through September 2016. Adult patients with recurrent peptic ulcer bleeding following initially successful hemostasis (66 patients in the intent-to-treat analysis) were randomly assigned to groups (1:1) that underwent hemostasis with either OTSC or standard therapy. Standard therapy was defined as hemostasis with through-the-scope clips (TTSC, n = 31) or thermal therapy plus injection with diluted adrenaline (n = 2). The primary end point was further bleeding (a composite end point of a persistent bleeding despite endoscopic therapy according to the protocol or recurrent bleeding with 7 days after successful hemostasis). Patients with further bleeding were allowed to cross over to OTSC therapy. Main secondary end points were mortality, necessity of surgical or angiographic salvage therapy, duration of stay in the hospital or intensive care, number of blood units transfused, and complications associated with endoscopic therapy.

Results: Persistent bleeding after per-protocol hemostasis was observed in 14 patients (42.4%) in the standard therapy group and 2 patients (6.0%) in the OTSC group (p = 0.001). Recurrent bleeding within 7 days occurred in 5 patients (16.1%) in the standard therapy group versus 3 patients (9.1%) in the OTSC group (p = 0.468). Further bleeding occurred in 19 patients (57.6%) in the standard therapy group and in 5 patients (15.2%) in the OTSC group (absolute difference 42.4%; 95% confidence interval: 21.6–63.2; p = 0.001) Within 30 days of follow-up, 1 patient in the standard therapy group (3.0%) and 1 patient in the OTSC group (3.0%) required surgical therapy (p = 0.999). Within 30 days of the procedure, 2 patients died in the standard therapy group (6.3%) and 4 patients died in the OTSC group (12.1%) (p = 0.672). There were no significant differences in the other secondary end points.

Conclusions: In this prospective randomized trial, endoscopic treatment with over-the-scope clips was found to be superior to standard therapy with through-the-scope clips for patients with recurrent peptic ulcer bleeding.

Prof. Dr. K. Caca, Medizinische Klinik I, Klinikum Ludwigsburg, Posilipostr, 1–4, 71640 Ludwigsburg, Germany, E-Mail: karelcaca@klinikum-lb.de

Gut. 2018;67(10):1805–12


Therapeutic endoscopy-related GI bleeding and thromboembolic events in patients using warfarin or direct oral anticoagulants: Results from a large nationwide database analysis

Objective: To compare the risks of postendoscopy outcomes associated with warfarin with direct oral anticoagulants (DOACs), taking into account heparin bridging and various types of endoscopic procedures.

Design: Using the Japanese Diagnosis Procedure Combination database, the authors identified 16,977 patients who underwent 13 types of high-risk endoscopic procedures and took preoperative warfarin or DOACs from 2014 to 2015. One-to-one propensity-
ty score matching was performed to compare postendoscopy gastrointestinal (GI) bleeding and thromboembolism between the warfarin and DOAC groups.

**Results:** In the propensity score-matched analysis involving 5046 pairs, the warfarin group had a significantly higher proportion of GI bleeding than the DOAC group (12.0% vs. 9.9%; p = 0.002). No significant difference was observed in thromboembolism (5.4% vs. 4.7%) or in-hospital mortality (5.4% vs. 4.7%). The risks of GI bleeding and thromboembolism were greater in patients treated with warfarin plus heparin bridging or DOACs plus bridging than in patients treated with DOACs alone. Compared with percutaneous endoscopic gastrostomy, patients who underwent endoscopic submucosal dissection, endoscopic mucosal resection and hemostatic procedures including endoscopic variceal ligation or endoscopic injection sclerotherapy were at the highest risk of GI bleeding among the 13 types of endoscopic procedures, whereas those who underwent lower polypectomy, endoscopic sphincterotomy or endoscopic ultrasound-guided fine needle aspiration were at moderate risk.

**Conclusion:** The risk of postendoscopy gastrointestinal bleeding was higher in warfarin than direct oral anticoagulant users. Heparin bridging was associated with an increased risk of bleeding and did not prevent thromboembolism. The bleeding risk varied by the type of endoscopic procedure.

Dr. N. Nagata, Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, I-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan, E-Mail: nnagata_ncgm@yahoo.co.jp

---

**EoE**

**Am J Gastroenterol. 2018;113(6):836–44**

Warners MJ, Oude Nijhuis RAB, de Wijkerslooth LRH, Smout AJPM, Bredenoord AJ

### The natural course of eosinophilic esophagitis and long-term consequences of undiagnosed disease in a large cohort

**Background:** Eosinophilic esophagitis (EoE) is a chronic esophageal inflammation that may lead to stricture formation. This narrowing can cause major complications including food impactions. Despite increasing interest in EoE accurate data on its natural course is scarce. Therefore, the authors aimed to investigate the natural course of EoE and to evaluate the association between undiagnosed disease and the occurrence of complications over 2 decades in a large cohort.

**Methods:** They retrospectively analyzed charts of patients diagnosed with EoE between 1996 and 2015, collected from 15 hospitals throughout the Netherlands. Histologic, clinical, and endoscopic characteristics were identified and stratified by age and diagnostic delay.

**Results:** The rates of postendoscopic infection after colonoscopy and esophagogastroduodenoscopy in ambulatory surgery centers in the USA

**Gut. 2018;67(9):1626–36**

Wang P, Xu T, Ngamruengphong S, Makary MA, Kalloo A, Hutless S

### Rates of infection after colonoscopy and esophagogastroduodenoscopy in ambulatory surgery centers in the USA

**Objective:** Over 15 million colonoscopies and 7 million esophagogastroduodenoscopies (EGDs) are performed annually in the USA. The authors aimed to estimate the rates of infections after colonoscopy and EGD performed in ambulatory surgery centers (ASCs).

**Design:** They identified colonoscopy and EGD procedures performed at ASCs in 2014 all-payer claims data from 6 states in the USA. Screening mammography, prostate cancer screening, bronchoscopy and cystoscopy procedures were comparators. They tracked infection-related emergency department visits and unplanned in-patient admissions within 7 and 30 days after the procedures, examined infection sites and organisms and analyzed predictors of infections. Case-mix adjusted variation in infection rates by ASC was investigated.

**Results:** The rates of postendoscopic infection per 1000 procedures within 7 days were 1.1 for screening colonoscopy, 1.6 for non-screening colonoscopy and 3.0 for EGD; all higher than screening mammography (0.6) but lower than bronchoscopy (15.6) and cystoscopy (4.4) (p < 0.0001). Predictors of postendoscopic infection included recent history of hospitalization or endoscopic procedure; concurrence with another endoscopic procedure; low procedure volume or non-freestanding ASC; younger or older age; black or Native American race and male sex. Rates of 7-day postendoscopic infections varied widely by ASC, ranging from 0–115 per 1000 procedures for screening colonoscopy, 0–132 for non-screening colonoscopy and 0–62 for EGD.

**Conclusion:** It was found that postendoscopic infections are more common than previously thought and vary widely by
facility. Although screening colonoscopy is not without risk, the risk is lower than diagnostic endoscopic procedures.

S. Hutfless, Ph.D., Assistant Professor of Medicine, Division of Gastroenterology and Hepatology, Johns Hopkins University, 600 N. Wolfe Street, Blalock Building 449, Baltimore, MD 21287, USA, E-Mail: shuttle1@jhmi.edu

United European Gastroenterol J. 2018;6(7):1015–21

Bauder M, Schmidt A, Caca K

Endoscopic full-thickness resection of duodenal lesions – A retrospective analysis of 20 FTRD cases

Background: Endoscopic resections in the duodenum harbor a significant risk of complications. The full-thickness resection device (FTRD) has shown favorable results concerning efficacy and safety in the resection of colorectal lesions. Data of its use in the duodenum are limited to a single, small case series (n = 4).

Methods: Data of all consecutive patients scheduled for endoscopic full-thickness resection (EFTR) of duodenal lesions by FTRD in the authors’ institution were collected and analyzed retrospectively. Primary end point was technical success.

Results: Between March 2014 and June 2017, EFTR of a duodenal lesion was planned in a total of 20 patients. Overall technical success was 17 of 20 (85.0%). Indication for EFTR was adenomas (n = 13, 7 treatment-naive, 6 pretreated), subepithelial tumors (n = 5) and T1 adenocarcinoma (n = 1). The FTRD could be advanced to the lesion in 19 of 20 cases (95.0%). R0-resection rate was 12 of 19 (63.2%). During follow-up after 3 and 12 months there were 2 recurrent adenomas that were successfully re-resected by FTRD. Minor bleedings occurred at the first postinterventional day in 3 of 19 patients (15.8%). There were no major bleedings and perforations.

Conclusion: This study confirmed the feasibility of duodenal endoscopic full-thickness resection and indicates good efficacy and safety. Larger studies are needed to further investigate this novel technique.

Dr. M. Bauder, Medizinische Klinik I, Klinikum Ludwigsburg, Posilipostr. 1–4, 71640 Ludwigsburg, Germany, E-Mail: markus.bauder@kliniken-lb.de
Postoperative morbidity and mortality of a cohort of steroid-refractory acute severe ulcerative colitis: Nationwide multicenter study of the GETECCU ENEIDA registry

Background: Despite the increased use of rescue medical therapies for steroid-refractory acute severe ulcerative colitis, mortality related to this entity still remains high. The authors aimed to assess the mortality and morbidity related to colectomy and their predictive factors in steroid-refractory acute severe ulcerative colitis, and to evaluate the changes in mortality rates, complications, indications of colectomy, and the use of rescue therapy over time.

Methods: They performed a multicenter observational study of patients with steroid-refractory acute severe ulcerative colitis requiring colectomy, admitted to 23 Spanish hospitals included in the ENEIDA registry (GETECCU) from 1989 to 2014. Independent predictive factors of mortality were assessed by binary logistic regression analysis. Mortality along the study was calculated using the age-standardized rate.

Results: During the study period, 429 patients underwent colectomy, presenting an overall mortality rate of 6.3% (range, 0–30%). The main causes of death were infections and postoperative complications. Independent predictive factors of mortality were: age ≥ 50 years (odds ratio [OR] = 23.34; 95% confidence interval [CI]: 4.66–141.36; p = 0.0001), undergoing surgery in a secondary care hospital (OR = 3.07; 95% CI: 1.01–9.35; p = 0.047), and in an emergency setting (OR = 10.47; 95% CI: 1.26–86.55; p = 0.029). Neither the use of rescue medical treatment nor the type of surgical technique used (laparoscopy vs. open laparotomy) influenced mortality. The proportion of patients undergoing surgery in an emergency setting decreased over time (p < 0.0001), whereas the use of rescue medical therapy prior to colectomy progressively increased (p > 0.001).

Conclusions: The mortality rate related to colectomy in steroid-refractory acute severe ulcerative colitis varies greatly among hospitals, reinforcing the need for a continuous audit to achieve quality standards. The increasing use of rescue therapy is not associated with a worse outcome and may contribute to reducing emergency surgical interventions and improve outcomes.

Dr. Dr. M. Esteve, Gastroenterology Department, Hospital Universitari Mútua Terrassa, Plaça del Doctor Robert, S, 08221 Terrassa, Barcelona, Spain, E-Mail: mariaesteve@mutuaterrassa.cat

No benefit of concomitant 5-aminosalicylates in patients with ulcerative colitis escalated to biologic therapy: Pooled analysis of individual participant data from clinical trials

Objectives: 5-aminosalicylates (5-ASA) are frequently continued in patients with moderate-to-severe ulcerative colitis (UC), even after escalation to biologic agents, without evaluation of the benefit of this approach. The authors conducted an individual participant data (IPD) pooled analysis of trials of infliximab and golimumab in UC, to evaluate whether concomitant use of 5-ASA modifies clinical outcomes among anti-tumor necrosis factor (TNF)-α-treated patients.

Methods: They included IPD from 5 trials of infliximab and golimumab in patients with moderate-to-severe UC (ACT-1 and -2, PURSUIT-SC, PURSUIT-M). Patients treated with infliximab or golimumab were categorized as receiving concomitant 5-ASA or not at time of trial entry. Primary outcome was clinical remission (Mayo Clinic Score < 3) at last follow-up for each trial; secondary outcomes were clinical response and mucosal healing. Using multivariable logistic regression analysis, the authors evaluated the association between concomitant 5-ASA and clinical remission, after adjusting for sex, smoking, baseline disease activity, disease extent, biochemical variables (C-reactive protein, albumin, hemoglobin), and concomitant prednisone and immunomodulators.

Results: They included 2183 infliximab-treated or golimumab-treated patients (7157 [78.6%] on 5-ASA). Concomitant use of 5-ASA was not associated with odds of achieving clinical remission (adjusted odds ratio [aOR] = 0.67; 95% confidence interval [CI]: 0.45–1.01; p = 0.06), clinical response (aOR = 0.89; 95% CI: 0.60–1.23; p = 0.58) or mucosal healing (aOR = 1.12; 95% CI: 0.82–1.51; p = 0.48). These results were consistent in trials of induction and maintenance therapy, and in trials of infliximab and golimumab.

Conclusion: Based on individual participant data pooled analysis, in patients with moderate-to-severe ulcerative colitis who are escalated to anti-tumor necrosis factor therapy, continuing 5-aminosalicylates does not improve clinical outcomes.

S. Singh, M.D., Assistant Professor of Medicine, Division of Gastroenterology, University of California San Diego, 9500 Gilman Drive #0956, La Jolla, CA 92093, USA, E-Mail: sis040@ucsd.edu
Persistence with immunomodulator monotherapy use and incidence of therapeutic ineffectiveness among users of immunomodulator monotherapy in IBD

Objectives: Immunomodulator (IM)-based monotherapy with thiopurines or methotrexate is being increasingly supplanted in the management of moderate-to-severe inflammatory bowel disease (IBD) by more efficacious biologic agents. However, given their low cost, IMs may still have a selective role in this setting.

Methods: The authors used a Canadian population-based data set of persons with IBD spanning from 1996 until 2014 to assess the initiation and continued use of IM monotherapy, the incidence of outcomes associated with ineffectiveness (defined as IBD-related hospitalization, IBD-resective surgery, systemic corticosteroid use, or the need for biologic therapy), and the demographic and disease-related characteristics associated with persistence on IM monotherapy and IBD-associated adverse outcomes.

Results: There were 3312 persons diagnosed with IBD (1480 Crohn’s disease [CD], 1832 ulcerative colitis [UC]) in the study period. The cumulative incidence of IM monotherapy use at 5 years was 46% for CD and 24.9% for UC. Approximately one-third remained on IM monotherapy continuously for ≥5 years. Roughly three-quarters of IM users with a history of corticosteroid use had at least a 50% reduction in corticosteroid exposure in the year following IM initiation. 35% of those with CD and 30% with UC had not developed evidence of therapeutic ineffectiveness within 5 years of IM initiation; people with no history of prior corticosteroid use, no IBD hospitalizations, and persons with CD initiating IM therapy after age 40 were less likely to have an episode of therapeutic ineffectiveness while on IM monotherapy.

Conclusions: Although the majority of persons who are initiated on immunomodulator monotherapy discontinue medications and/or have evidence of therapeutic ineffectiveness a significant minority remain free of these outcomes over many years of therapy.

Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases

Background and aims: The risk of infection associated with tumor necrosis factor antagonists (anti-TNF) and thiopurines (combination therapy) is uncertain. The authors assessed the risk of serious and opportunistic infections in patients with inflammatory bowel disease (IBD) treated with thiopurine monotherapy, anti-TNF monotherapy, or combination therapy in a large cohort of patients in France.

Methods: They performed a nationwide population-based study of patients (≥18 years) with a diagnosis of IBD in the French national health insurance database and collected data from January 1, 2009, until December 31, 2014. The risks of serious and opportunistic infections associated with exposure to combination therapy, anti-TNF, and thiopurine monotherapies were compared using marginal structural Cox proportional hazard models adjusted for baseline and time-varying sociodemographic characteristics, medications, and comorbidities.

Results: Among the 190,694 patients with IBD included in this analysis, 8561 serious infections and 674 opportunistic infections occurred. Compared with anti-TNF monotherapy, combination therapy was associated with increased risks of serious infection (hazard ratio [HR] = 1.23; 95% confidence interval [CI]: 1.05–1.45) and opportunistic infection (HR = 1.96; 95% CI: 1.32–2.91). Compared with thiopurine monotherapy, anti-TNF monotherapy was associated with increased risks of serious infection (HR = 1.17; 95% CI: 1.56–1.88), mycobacterial infection (HR = 1.98; 95% CI: 1.15–3.40), and bacterial infection (HR = 2.38; 95% CI: 1.23–4.58, respectively). Conversely, anti-TNF monotherapy was associated with decreased risk of opportunistic viral infection compared with thiopurine monotherapy (HR = 0.57; 95% CI: 0.38–0.87).

Conclusions: In a nationwide cohort study of patients with inflammatory bowel disease (IBD) in France, heterogeneity in risks of serious and opportunistic infections was found in patients treated with immunosuppressive regimens. These should be carefully considered and weighed against potential benefits for IBD treatment in patient management.

Gut. 2018;67(10):1824–35

Phase 2 evaluation of anti-MAdCAM antibody PF-00547659 in the treatment of Crohn’s disease: Report of the OPERA study

Objective: This phase 2, randomized, double-blind, placebo-controlled clinical trial was designed to evaluate the efficacy and safety of PF-00547659, a fully human monoclonal antibody that binds to human mucosal addressin cell adhesion molecule (MAdCAM) to selectively reduce lymphocyte homing to the intestinal tract, in patients with moderate-to-severe Crohn’s disease (CD).

Design: Eligible adults were aged 18–75 years, with active moderate-to-severe CD (Crohn’s Disease Activity Index [CDAI] 220–450), a history of failure or intolerance to anti-tumor necrosis factor and/or immunosuppressive agents, high-sensitivity C-reactive protein > 3.0 mg/l and ulcers on colonoscopy. Patients were randomized to PF-00547659 225 mg, 75 mg or 225 mg or placebo. The primary end point was CDAI 70-point decrease from baseline (CDAI-70) at week 8 or 12.
Results: In all, 265 patients were eligible for study entry. Although CDAI-70 response was not significantly different with placebo versus PF-00547659 treatment at weeks 8 or 12, remission rate was greater in patients with higher baseline C-reactive protein (> 5 mg/l vs. > 18.8 mg/l, respectively). Soluble MAdCAM decreased significantly from baseline to week 2 in a dose-related manner and remained low during the study in PF-00547659-treated patients. Circulating \( \beta^\uparrow \) CD4\(^+\) central memory T-lymphocytes increased at weeks 8 and 12 with PF-00547659 treatment. No safety signal was seen.

Conclusions: Clinical end point differences between PF-00547659 and placebo did not reach statistical significance in patients with moderate-to-severe Crohn's disease. PF-00547659 was pharmacologically active, as shown by a sustained dose-related decrease in soluble mucosal addressin cell adhesion molecule and a dose-related increase in circulating \( \beta^\uparrow \) central memory T cells.

W.J. Sandborn, M.D., Professor of Medicine, Division of Gastroenterology, University of California San Diego, 9500 Gilman Drive, MC 0956, La Jolla, CA 92093, USA, E-Mail: wsandborn@ucsd.edu

---

Incidence of psoriasiform diseases secondary to tumor necrosis factor antagonists in patients with inflammatory bowel disease: A nationwide population-based cohort study


Aliment Pharmacol Ther. 2018;48(2):196–205

Background: There are increasing reports of paradoxical psoriasiform diseases secondary to anti-tumor necrosis factor (TNF) agents.

Aims: To determine the risks of paradoxical psoriasiform diseases secondary to anti-TNF agents in patients with inflammatory bowel disease (IBD).

Methods: A nationwide population study was performed using the Korea National Health Insurance Claim Data. A total of 50,502 patients with IBD were identified between 2007 and 2016. The authors compared 5428 patients who were treated with any anti-TNF agent for more than 6 months (anti-TNF group) and 10,856 matched controls who had never taken anti-TNF agents (control group).

Results: Incidence of psoriasis was significantly higher in the anti-TNF group (36.8/10,000 person-years) compared to the control group (14.5/10,000 person-years) (hazard ratio [HR] = 2.357, 95% confidence interval [CI]: 1.668–3.331). Palmoplastic pustulosis (HR = 9.355, 95% CI: 2.754–31.780) and psoriatic arthritis (HR = 2.926, 95% CI: 1.640–5.218) also showed higher risks in the anti-TNF group. In subgroup analyses, HRs for psoriasis by IBD subtype were 2.549 (95% CI: 1.658–3.920) in Crohn’s disease and 2.105 (95% CI: 1.155–3.836) in ulcerative colitis. Interestingly, men and younger (10–39 years) patients have significantly higher risks of palmoplastic pustulosis (HR = 19.682, 95% CI: 5.627–69.315), and HR = 14.318, 95% CI: 2.915–70.315, respectively), whereas women and older (≥ 40 years) patients showed similar rates between the 2 groups.

Conclusions: The risks of psoriasiform diseases are increased by anti-tumor necrosis factor agents in patients with inflammatory bowel disease. Among psoriasiform diseases, the risk of palmoplastic pustulosis shows the biggest increase particularly in male and younger patients.

Prof. Dr. B.-I. Lee, Division of Gastroenterology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222, Banpo-daero, Seocho-gu, Seoul, South Korea, E-Mail: gidoc4u@gmail.com

and

Prof. Dr. K.-M. Lee, Division of Gastroenterology, Department of Internal Medicine, St. Vincent’s Hospital, College of Medicine, The Catholic University of Korea, 93, Jungbu-daero, Paldal-gu, Suwon-si, Gyeonggi-do, South Korea, E-Mail: drmaloman@catholic.ac.kr

---

Andecaliximab (anti-matrix metalloproteinase-9) induction therapy for ulcerative colitis: A randomized, double-blind, placebo-controlled, phase 2/3 study in patients with moderate-to-severe disease

Bhandari BR, Randall C, Younes ZH, Romanczyk T, Xin Y, Wendt E, Chai H, McKevitt M, Zhao S, Sundy JS, Keshav S, Danese S

J Crohns Colitis. 2018;12(9):1021–9

Background and aims: Matrix metalloproteinase-9 (MMP9) is implicated in the pathogenesis of ulcerative colitis (UC) via disruption of intestinal barrier integrity and function. A phase 2/3 combined trial was designed to examine the efficacy, safety, and pharmacokinetics of the anti-MMP9 antibody andecaliximab (formerly GS-5745) in patients with moderately-to-severely active UC.

Methods: Patients were randomized (1:1:1) to receive placebo, 150 mg andecaliximab every 2 weeks (Q2W), or 150 mg andecaliximab weekly (QW), via subcutaneous administration. The primary end point was endoscopy/bleeding/stool (EBS)-defined clinical remission (endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1-point decrease from baseline in stool frequency to achieve a subscore of 0 or 1) at week 8. The phase 2/3 trial met prespecified futility criteria and was terminated before completion. This study describes results from the 8-week induction phase.

Results: Neither 150 mg andecaliximab Q2W or QW resulted in a significant increase versus placebo in the proportion of patients achieving EBS clinical remission at week 8. Remission rates (95% confidence interval [CI]): 7.3% (95% CI: 2.0–17.6%), 7.4% (95% CI: 2.1–17.9%), and 1.8% (95% CI: 0.0–9.6%) in the placebo, andecaliximab Q2W, and andecaliximab QW groups, respectively. Similarly, Mayo Clinic Score response, endoscopic response, and mucosal (histological) healing did not differ among groups. Rates of adverse events were comparable among andecaliximab and placebo.

Conclusions: Eight weeks of induction treatment with 150 mg andecaliximab in patients with ulcerative colitis did not influence clinical remission or response. Andecaliximab was well tolerated in the study.
AutoLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CROHN’S DISEASE: A RETROSPECTIVE SURVEY OF LONG-TERM OUTCOMES FROM THE EUROPEAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION

Background and aims: Autologous hematopoietic stem cell transplantation (AH SCT) is a therapeutic option for patients with severe, treatment-refractory Crohn’s disease (CD). The evidence base for AH SCT for CD is limited, with one randomized trial (ASTIC) suggesting benefit. The aim of this study was to evaluate safety and efficacy for patients undergoing AH SCT for CD in Europe outside the ASTIC trial.

Methods: The authors identified 99 patients in the European Society for Blood and Marrow Transplantation (EBMT) registry who were eligible for inclusion. Transplant and clinical outcomes were obtained for 82 patients from 19 centers in 7 countries.

Results: Median patient age was 30 years (range, 20–65). Patients had failed or been intolerant to a median of 6 lines of drug therapy; 61 of 82 patients (74%) had had surgery. Following AH SCT, 53 of 78 patients (68%) experienced complete remission or significant improvement in symptoms at a median follow-up of 41 months (range, 6–174); 22 of 82 patients (27%) required no medical therapy at any point post-AH SCT. In patients who had restarted medical therapy at last follow-up, 57% (24/42) achieved remission or significant symptomatic improvement with therapies to which they had previously lost response or been non-responsive. Treatment-free survival at 1 year was 54%. On multivariate analysis, perianal disease was associated with adverse treatment-free survival (hazard ratio = 2.34, 95% CI: 1.14–4.83; p = 0.02). One patient died due to infectious complications (cytomegalovirus disease) at day +56.

Conclusions: In this multicenter retrospective analysis of European centers, autologous hematopoietic stem cell transplantation was relatively safe and appeared to be effective in controlling otherwise treatment-resistant Crohn’s disease. Further prospective randomized controlled trials against standard-of-care are warranted.

Dr. C.K. Brierley, Department of Hematology, Oxford University Hospitals NHS Foundation Trust, Churchill Hospital, Oxford OX3 7LE, UK, E-Mail: charlotte.brierley@ouh.nhs.uk

A PHASE 2, RANDOMIZED, PLACEBO-CONTROLLED STUDY EVALUATING MATRIX METALLOPROTEINASE-9 INHIBITOR, ANDECALIXIMAB, IN PATIENTS WITH MODERATELY-TO-SEVERELY ACTIVE CROHN’S DISEASE

Background and aims: Matrix metalloproteinase-9 (MMP9) is implicated in the pathogenesis of Crohn’s disease and may serve as a potential biomarker. A phase 2 trial was conducted to examine the efficacy and safety of the anti-MMP9 antibody andecaliximab (GS-5745) in patients with moderately-to-severely active Crohn’s disease.

Methods: Patients were randomized 1:2:2 to receive subcutaneous injections of placebo weekly (QW), andecaliximab 150 mg every 2 weeks (Q2W), andecaliximab 150 mg QW, or andecaliximab 300 mg QW. The co-primary study efficacy end points were evaluation of a clinical response, defined as liquid or very soft stool frequency and abdominal pain composite (from Patient-Reported Outcome 2) score ≤ 8 at week 8, and an endoscopic response, defined as a ≥ 50% reduction from baseline in the Simple Endoscopic Score for Crohn’s Disease, following 8 weeks of treatment.

Results: A total of 187 participants were randomized to treatment; 53 participants were randomized to each andecaliximab treatment group and 28 participants were randomized to placebo. Proportions of patients receiving andecaliximab were not different from proportions of patients receiving placebo based on clinical and endoscopic response and Crohn’s Disease Activity Index-defined remission at week 8. Rates of adverse events were comparable among the andecaliximab and placebo groups.

Conclusions: Eight weeks of induction treatment with 150 mg andecaliximab every 2 weeks, 150 mg andecaliximab weekly, or 300 mg andecaliximab weekly in patients with Crohn’s disease did not induce a clinically meaningful symptomatic or endoscopic response. Andecaliximab was well tolerated.

Prof. Dr. S. Schreiber, Klinik für Innere Medizin I, Universitätshospital Schleswig-Holstein, Campus Kiel, Arnold-Heller-Str. 3, Haus 6, Nebengebäude Haus S, 24105 Kiel, Germany, E-Mail: s.schreiber@mucosa.de

THERAPEUTIC DRUG MONITORING IS MORE COST-EFFECTIVE THAN A CLINICALLY-BASED APPROACH IN THE MANAGEMENT OF LOSS OF RESPONSE TO INFlixIMAB IN INFLAMMATORY BOWEL DISEASE: AN OBSERVATIONAL MULTICENTER STUDY

Background and aims: Empirical dose intensification and therapeutic drug monitoring (TDM) of infliximab (IFX) trough levels (ITLs) and antibody to infliximab (ATI) assays are recognized...
approaches for managing loss of response (LoR) in patients with inflammatory bowel disease (IBD). The aim of this study was to compare these 2 interventions in a clinical setting, in terms of effectiveness and cost savings.

**Methods:** Consecutive IBD patients experiencing LoR were clinically managed according to a TDM algorithm. A historical group of empirically treated patients, for whom sera for ITLs and ATI assays had been collected, served as the control group. Clinical outcomes 12 weeks after the therapeutic interventions were compared between the 2 groups. A cost-minimization analysis was performed to compare the economic impact of these 2 approaches.

**Results:** 96 patients were enrolled prospectively and compared with 52 controls. The 2 cohorts were similar in characteristics and in the distribution of TDM results. In the prospective cohort, however, the authors observed less IFX dose escalations compared with the controls (45% vs. 71%, p = 0.003). Also, more patients were switched to a different anti-tumor necrosis factor (TNF)-α in the prospective cohort than in the control cohort (25% vs. 4%, p = 0.001). The percentages of patients achieving a clinical response at 12 weeks were 52% and 54% for the prospective and control groups, respectively. By cost analysis, savings of 15% were estimated if the TDM algorithm was applied.

**Conclusions:** The use of a TDM algorithm resulted in decreased IFX dose escalations, without loss of efficacy, compared with empirical adjustment. In addition, the TDM approach was cost-effective.

Dr. L. Guidi, Medicina Interna e Gastroenterologia Columbus, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Largo Agostino Gemelli, 8, 00168 Rome, Italy, E-Mail: luisa.guidi@unicatt.it

---

### Microscopic Colitis

**Aliment Pharmacol Ther. 2018;48(6):618–25**

Bonderup OK, Nielsen GL, Dall M, Pottegård A, Hallas J

**Significant association between the use of different proton-pump inhibitors and microscopic colitis: A nationwide Danish case-control study**

**Background:** Microscopic colitis (MC) causes chronic watery diarrhea and has previously been associated with the use of proton-pump inhibitors (PPIs).

**Aim:** To explore the association between PPI use and MC, including its dependency on timing, dose and choice of PPI.

**Methods:** Within a 10-year period, the authors identified 10,652 patients with a first-time diagnosis of MC, including 6254 (59%) with collagenous colitis (CC) and 4398 (41%) with lymphocytic colitis (LC). All MC cases were histologically confirmed in the Danish Pathology Register. Information on PPI use was obtained from the Danish Prescription Register. In this case-control study, the adjusted odds ratios (aORs) for the association between PPI use and risk of MC were estimated using conditional logistic regression while adjusting for potential confounders.

**Results:** Strong associations were found between current PPI use and both CC (aOR = 6.98; 95% confidence interval [CI]: 6.45–7.55) and LC (aOR = 3.95; 95% CI: 3.60–4.33). This association was observed with all PPIs. The strongest association was with the current use of lansoprazole for both CC (aOR = 15.74; 95% CI: 14.12–17.55) and LC (aOR = 6.87; 95% CI: 6.00–7.86). When considering timing, ORs were highest for current use of PPIs and lower for recent or past exposure. No clear dose-response pattern was observed.

**Conclusions:** A strong association was found between microscopic colitis and ongoing use of proton-pump inhibitors, especially lansoprazole.

Dr. Dr. O.K. Bonderup, Diagnostic Center, Section of Gastroenterology, Silkeborg Regional Hospital, Falkevej 1, 8600 Silkeborg, Denmark, E-Mail: olebonde@rm.dk

---

### IBS

**Clin Gastroenterol Hepatol. 2018;16(7):1064–72.e4**

Litleskare S, Rortveit G, Eide GE, Hanevik K, Langeland N, Wensaa KA

**Prevalence of irritable bowel syndrome and chronic fatigue 10 years after Giardia infection**

**Background and aims:** Irritable bowel syndrome (IBS) is a complication that can follow gastrointestinal infection, but it is not clear if patients also develop chronic fatigue. The authors investigated the prevalence and odds ratio of IBS and chronic fatigue 10 years after an outbreak of Giardia lamblia, compared with a control cohort, and changes in prevalence over time.

**Methods:** They performed a prospective follow-up study of 1252 laboratory-confirmed cases of giardiasis (exposed), which developed in Bergen, Norway, in 2004. Statistics Norway provided them with information from 2504 unexposed individuals from Bergen, matched by age and sex (controls). Questionnaires were mailed to participants 3, 6, and 10 years after the outbreak. Results from the 3- and 6-year follow-up analyses have been published previously. The authors report the 10-year data and changes in prevalence over time points, determined by logistic regression using generalized estimating equations.

**Results:** The prevalence of IBS 10 years after the outbreak was 43% (n = 248) among 576 exposed individuals and 14% (n = 94) among 685 controls (adjusted odds ratio [aOR] for development of IBS in exposed individuals = 4.74; 95% confidence interval [CI]: 3.61–6.23). At this time point, the prevalence of chronic fatigue was 26% (n = 153) among 587 exposed individuals and 11% (n = 73) among 692 controls (aOR = 3.01; 95% CI: 2.22–4.08). The prevalence of IBS among exposed persons did not change significantly from 6 years after infection (40%) to 10 years after infection (43%; aOR for the change = 1.03; 95% CI: 0.87–1.22). However, the prevalence of chronic fatigue decreased from 31% at 6 years after infection to 26% at 10 years after infection (aOR for the change = 0.74; 95% CI: 0.61–0.90).

**Conclusion:** The prevalence of irritable bowel syndrome (IBS) did not change significantly from 6 years after an outbreak of Giardia lamblia infection in Norway to 10 years after. Howev-
er, the prevalence of chronic fatigue decreased significantly from 6 to 10 years afterward. IBS and chronic fatigue were still associated with giardiasis 10 years after the outbreak.

S. Litleskare, Department of Global Public Health and Primary Care, University of Bergen, Kalfarveien 31, 5018 Bergen, Norway, E-Mail: sverre.litleskare@uib.no

Lancet Gastroenterol Hepatol. 2018;3(9):603–13

Fukudo S, Endo Y, Hongo M, Nakajima A, Abe T, Kobayashi H, Nakata T, Nakajima T, Sameshima K, Kaku K; Mizagliflozin Study Group

Safety and efficacy of the sodium-glucose cotransporter 1 inhibitor mizagliflozin for functional constipation: A randomized, placebo-controlled, double-blind phase 2 trial

Background: Mizagliflozin is a novel oral sodium-glucose cotransporter 1 (SGLT1) inhibitor that increases luminal glucose and water. This study assessed the efficacy and safety of mizagliflozin in patients with functional constipation.

Methods: In this multicenter, randomized, double-blind phase 2 trial at 32 hospitals and community outpatient clinics in Japan, the authors enrolled patients with functional constipation or constipation-predominant irritable bowel syndrome, aged ≥ 20 years. Patients were randomly assigned (1:1:1), by use of an independent centralized registration system and dynamic allocation method, to receive mizagliflozin 5 mg, mizagliflozin 10 mg, or placebo, orally once daily for 4 weeks. Patients, investigators, staff, and the sponsor were blinded to the group assignments. The primary outcome was the change from baseline in the number of spontaneous bowel movements per week after 1 week. Efficacy analysis was done in all patients except those who deviated from good clinical practice, did not receive at least 1 dose of the study drug, withdrew before starting treatment, were ineligible, or for whom the primary outcome could not be assessed, and safety was assessed in all patients except those who deviated from good clinical practice, who did not receive the study drug, or who withdrew before receiving treatment.

Findings: Between October 15, 2014, and March 7, 2015, 258 patients with functional constipation were included in the full analysis population. 85 in the 5 mg mizagliflozin group, and 83 in the 10 mg mizagliflozin group were included in the full analysis population. 84 patients in the placebo group, 85 in the 5 mg mizagliflozin group, and 83 in the 10 mg mizagliflozin group were included in the full analysis population. Mean change from baseline in the number of spontaneous bowel movements per week after 1 week with mizagliflozin 5 mg (3.85, SD 3.96) and mizagliflozin 10 mg (5.85, SD 6.01) was significantly greater than those in the placebo group (1.80, SD 1.80; p < 0.0001 for both comparisons). The most common adverse events were nasopharyngitis (1/86 patients [1%] in the placebo group, 7/85 [8%] on mizagliflozin 5 mg, and 5/86 [6%] on mizagliflozin 10 mg), diarrhea (none on placebo, 4 patients [5%] on mizagliflozin 5 mg, and 8 [9%] on mizagliflozin 10 mg), and abdominal distention (3 [3%] on placebo, 4 [5%] on mizagliflozin 5 mg, and 7 [8%] on mizagliflozin 10 mg). Only diarrhea and abdominal distention were deemed to be related to mizagliflozin treatment, whereas nasopharyngitis might not be related to mizagliflozin treatment, on the basis of clinical evaluation.

Interpretation: The sodium-glucose cotransporter 1 inhibitor mizagliflozin showed favorable efficacy and tolerability at 5 mg and 10 mg doses in patients with functional constipation, providing a potential alternative therapy to available drugs.

Prof. Dr. S. Fukudo, Department of Behavioral Medicine, Tohoku University Graduate School of Medicine, Sendai 980-8575, Japan, E-Mail: sfukudo@med.tohoku.ac.jp

Am J Gastroenterol. 2018;113(8):1217–28


Association between ultraprocessed food consumption and functional gastrointestinal disorders: Results from the French NutriNet-Santé cohort

Objectives: Ultraprocessed foods (UPF) consumption has increased over the last decades and is raising concerns about potential adverse health effects. The objective of the present study was to assess the association between UPF consumption and 4 functional gastrointestinal disorders (FGIDs): irritable bowel syndrome (IBS), functional constipation (FC), functional diarrhea (FDh), and functional dyspepsia (FDy), in a large sample of French adults.

Methods: The authors analyzed dietary data of 33,343 participants from the web-based NutriNet-Santé cohort, who completed at least 3 24-hour food records, prior to a Rome III self-administered questionnaire. Proportion (in weight) of UPF in the diet (UPFp) was computed for each subject. The association between UPFp quartiles and FGIDs was estimated by multivariable logistic regression.

Results: Participants included in the analysis were mainly women (76.4%), and the mean age was 50.4 (SD 14.0) years. UPF accounted for 16.0% of food consumed in weight, corresponding to 33.0% of total energy intake. UPF consumption was associated with younger age, living alone, lower incomes, higher body mass index, and lower physical activity level (all p < 0.0001). A total of 3516 participants reported IBS (10.5%), 1785 FC (5.4%), 1303 FDy (3.9%), and 396 FDh (1.1%). After adjusting for confounding factors, an increase in UPFp was associated with a higher risk of IBS (adjusted odds ratio Q4 vs. Q1 = 1.25, 95% confidence interval: 1.12–1.39; p trend < 0.0001).

Conclusions: This study suggests an association between ultraprocessed food (UPF) consumption and irritable bowel syndrome. Further longitudinal studies are needed to confirm those results and understand the relative impact of the nutritional composition and specific characteristics of UPF in this relationship.

Dr. L. Schnabel, Département de santé publique, Hôpital Avicenne (AP-HP), 125, rue de Stalingrad, 93017 Bobigny, France, E-Mail: l.schnabel@eren.smbh.univ-paris13.fr
**Safety and efficacy of elobixibat for chronic constipation: Results from a randomized, double-blind, placebo-controlled, phase 3 trial and an open-label, single-arm, phase 3 trial**

**Background:** A subset of patients with constipation has reduced colonic bile acid concentrations, which are associated with slow colonic transit. In a previous study, elobixibat, a locally acting ileal bile acid transporter inhibitor, accelerated colonic transit in Japanese patients with functional constipation. In this study, the authors aimed to determine the efficacy of elobixibat for short-term treatment of chronic constipation, and safety, patient satisfaction, and quality of life with long-term treatment.

**Methods:** They did 2 phase 3 studies of patients aged 20–80 years in Japan with at least 6 months of chronic constipation, who satisfied Rome III criteria for functional constipation, including fewer than 3 spontaneous bowel movements per week. The first trial, including patients enrolled at 16 clinics, was a 2-week, randomized, double-blind, placebo-controlled study in which (after a 2-week run-in period) patients were randomly assigned (1:1) to either elobixibat 10 mg/day for 2 weeks or placebo. Randomization was done with permuted block method (block size 6) without stratification. Masking to treatment allocation was achieved with identical appearances of elobixibat and placebo, which were supplied in sealed, opaque containers. Group assignment was concealed from patients, investigators, and analysts. The second trial, including patients enrolled at 34 clinics or hospitals, was an open-label, 1-year study in which all patients received elobixibat; participants could titrate the dose to 5 mg/day or 15 mg/day, or maintain the 10 mg/day dose. In both studies, patients took the study drug as an oral tablet once per day before breakfast. The primary outcome of the 2-week randomized trial was the change from baseline (i.e., last week of the 2-week run-in) in the frequency of spontaneous bowel movements during week 1 of treatment. All efficacy analyses were based on the modified intention-to-treat (ITT) population without imputation for any missing data. Safety analyses included all patients who received at least 1 dose of study drug.

**Findings:** Between November 4, 2015, and June 11, 2016, 133 patients were assigned to treatment in the 2-week randomized trial; 70 to elobixibat (69 included in the modified ITT and safety populations) and 63 to placebo. The frequency of spontaneous bowel movements per week during week 1 of treatment was greater with elobixibat (least-squares mean 6.4, 95% confidence interval [CI]: 5.3–7.6) than with placebo (least-squares mean 1.7, 95% CI: 1.2–2.2; p < 0.0001). Between October 31, 2015, and March 15, 2017, 341 patients were allocated to 52 weeks of elobixibat (340 included in the modified ITT and safety populations). 163 patients (48%) in the 52-week trial had an adverse drug reaction, the most common of which were mild gastrointestinal disorders (in 135 patients [40%]). Inguinal hernia was reported in 1 patient with elobixibat in the 52-week study as a moderate adverse drug reaction. The most common adverse drug reactions in both trials were mild abdominal pain (13 patients [19%] with elobixibat and 1 patient [2%] with placebo in the 2-week randomized trial, and 82 patients [24%] in the 52-week trial) and diarrhea (9 patients [13%] with elobixibat and none with placebo in the 2-week randomized trial and 50 [15%] in the 52-week trial).

**Interpretation:** Elobixibat resolved constipation in the short-term, and was well tolerated with both short-term and long-term treatment. The evidence supports the use of this novel approach to increase intracolonic concentrations of endogenous bile acid for the treatment of chronic constipation.

M. Camilleri, M.D., Professor of Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA, E-Mail: camilleri.michael@mayo.edu

---

**Colorectal Cancer/Colorectal Cancer Screening**

Am J Gastroenterol. 2018;113(6):899–905

Jacobs ET, Gupta S, Baron JA, Cross AJ, Lieberman DA, Murphy G, Martínez ME

**Family history of colorectal cancer in first-degree relatives and metachronous colorectal adenoma**

**Objectives:** Little is known about the relationship between having a first-degree relative (FDR) with colorectal cancer (CRC) and risk for metachronous colorectal adenoma (CRA) following polypectomy.

**Methods:** The authors pooled data from 7 prospective studies of 7697 patients with previously resected CRAs to quantify the relationship between having a FDR with CRC and risk for metachronous adenoma.

**Results:** Compared with having no family history of CRC, a positive family history in any FDR was significantly associated with increased odds of developing any metachronous CRA (odds ratio [OR] = 1.14; 95% confidence interval [CI]: 1.01–1.29). Higher odds of CRA were observed among individuals with an affected mother (OR = 1.27; 95% CI: 1.05–1.53) or sibling (OR = 1.34; 95% CI: 1.11–1.62) as compared with those without, whereas no association was shown for individuals with an affected father. Odds of having a metachronous CRA increased with number of affected FDRs, with ORs (95% CIs) of 1.07 (0.93–1.23) for 1 relative and 1.39 (1.02–1.91) for ≥2. Younger age of diagnosis of a sibling was associated with higher odds of metachronous CRA, with ORs (95% CIs) of 1.66 (1.08–2.56) for diagnosis at < 54 years; 1.34 (0.89–2.03) for 55–64 years; and 1.10 (0.70–1.72) for > 65 years (p<sub>rend</sub> = 0.008). Although limited by sample size, results for advanced metachronous CRA were similar to those for any metachronous CRA.

**Conclusions:** A family history of colorectal cancer (CRC) is related to a modestly increased odds of metachronous colorectal adenoma. Future research should explore whether having a first-degree relative with CRC, particularly at a young age, should have a role in risk stratification for surveillance colonoscopy.

E.T. Jacobs, M.D., University of Arizona Cancer Center, 3838 N Campbell Ave, Tucson, AZ 85719, USA, E-Mail: jacobse@email.arizona.edu
**Endoscopy assistants influence the quality of colonoscopy**

**Background:** Colonoscopy performance varies between endoscopists, but little is known about the impact of endoscopy assistants on key performance indicators. The authors used a large prospective colonoscopy quality database to perform an exploratory study to evaluate differences in selected quality indicators between endoscopy assistants.

**Methods:** All colonoscopies reported to the Norwegian colonoscopy quality assurance register Gastronet can be used to trace individual endoscopy assistants. Key quality indicators (cecum intubation rate, polyp detection rate, colonoscopies rated as severely painful, colonoscopies with sedation or analgesia, and satisfaction with information) for colonoscopies performed between January 1, 2013, and December 31, 2014, were analyzed. Differences between individual assistants were analyzed by fitting multivariable logistic regression models, with the best performing assistant at each participating hospital as reference. All models were adjusted for the endoscopist.

**Results:** 63 endoscopy assistants from 12 hospitals assisted in 15,365 colonoscopies. Compared with their top performing peers from the same hospital, 1 assistant was associated with cecum intubation failure, 4 with poor polyp detection, 9 with painful colonoscopy, 16 with administration of sedation or analgesics during colonoscopy, and 3 with patient dissatisfaction about information given relating to the colonoscopy. The number of procedures during the study period or lifetime experience as an endoscopy assistant were not associated with any quality indicator.

**Conclusion:** In this exploratory study, there was little variation on important colonoscopy quality indicators between endoscopy assistants. However, there were differences among assistants that may be clinically important. Endoscopy assistants should be subject to quality surveillance similarly to endoscopists.

Dr. Dr. Ø. Holme, Sørlandet Hospital, Postboks 416, 4604 Kristiansand, Norway, E-Mail: oyvind.holme@medisin.uio.no

**Efficacy and safety of curcumin in treatment of intestinal adenomas in patients with familial adenomatous polyposis**

**Background and aims:** Familial adenomatous polyposis is an autosomal dominant disorder characterized by the development of hundreds of colorectal adenomas and eventually colorectal cancer. Oral administration of the spice curcumin has been followed by regression of polyps in patients with this disorder. The authors performed a double-blinded randomized trial to determine the safety and efficacy of curcumin in patients with familial adenomatous polyposis.

**Methods:** This study included 44 patients with familial adenomatous polyposis (18–85 years old) who had not undergone colectomy or had undergone colectomy with ileorectal anastomosis or ileal anal pouches, had at least 5 intestinal adenomas polyp, and had enrolled in Puerto Rico or the United States from September 2011 through November 2016. Patients were randomly assigned (1:1) to groups given 100% pure curcumin (1500 mg orally, twice per day) or identical-appearing placebo capsules for 12 months. The number and size of lower gastrointestinal tract polyps were evaluated every 4 months.

**Results:** Oral administration of curcumin was well tolerated and safe. A total of 36 patients completed 6 months of curcumin treatment. Curcumin significantly decreased the number (36% vs. 2% in placebo, P = 0.006) and size (33% vs. 0% in placebo, P = 0.040) of colorectal polyps. The authors recommend curcumin as an effective and safe treatment for the regression of colorectal polyps in patients with familial adenomatous polyposis.

Dr. A. Facciorusso, Division of Gastroenterology, University of Foggia, Viale Luigi Pinto, 1, 71121 Foggia, Italy, E-Mail: antonio.facciorusso@virgilio.it
Results: After 1 year of treatment, the average rate of compliance was 83% in the curcumin group and 91% in the placebo group. After 12 weeks, there was no significant difference in the mean number of polyps between the placebo group (18.6; 95% confidence interval [CI]: 9.3–27.8) and the curcumin group (22.6; 95% CI: 12.1–33.1; p = 0.58). No significant difference in mean polyp size was found between the curcumin group (2.3 mm; 95% CI: 1.8–2.8) and the placebo group (2.1 mm; 95% CI: 1.5–2.7; p = 0.76). Adverse events were few, with no significant differences between groups.

Conclusions: In a double-blinded randomized trial of patients with familial adenomatous polyposis, no difference in the mean number or size of lower intestinal tract adenomas was found between patients given curcumin 3000 mg/day and those given placebo for 12 weeks.

F.M. Giardiello, M.D., Professor of Medicine, Department of Gastroenterology and Hepatology, Johns Hopkins Hospital, 1830 East Monument Street, Room 431, Baltimore, MD 21205, USA, E-Mail: fgiardi@jhmi.edu

Effectiveness of a mailed colorectal cancer screening outreach program in community health clinics: The STOP CRC cluster randomized clinical trial

Importance: Approximately 24 million US individuals receive care at federally qualified health centers, which historically have low rates of colorectal cancer (CRC) screening. The US Preventive Services Task Force recommends routine CRC screening for individuals aged 50–75 years.

Objective: To determine the effectiveness of an electronic health record (EHR)-embedded mailed fecal immunochemical test (FIT) outreach program implemented in health centers as part of standard care.

Design, setting, and participants: This cluster randomized pragmatic clinical trial was conducted in 26 federally qualified health center clinics, representing 8 health centers in Oregon and California, randomized to intervention (n = 13) or usual care (n = 13). All participants were overdue for CRC screening during the accrual interval (February 4, 2014, to February 3, 2015).

Interventions: EHR-embedded tools to identify eligible adults and to facilitate implementation of a stepwise mailed intervention involving (1) an introductory letter, (2) a mailed FIT, and (3) a reminder letter; training, collaborative learning, and facilitation through a practice improvement process.

Main outcomes and measures: Effectiveness was measured as clinic-level proportions of adults who completed a FIT, and secondarily, any CRC screening within 12 months of accrual or by August 3, 2015. Implementation was measured as clinic-level proportions of adults who were mailed an introductory letter and ordered a FIT.

Results: 26 clinics with 41,193 adults (mean [SD] age, 58.5 [6.3] years; 22,994 women) were randomized to receive the direct mail colorectal screening intervention (13 clinics; 21,134 patients) or usual care (13 clinics; 20,059 patients). Compared with usual care clinics, intervention clinics had significantly higher adjusted clinic-level proportion of participants who completed a FIT (13.9% vs. 10.4%; difference, 3.4 percentage points; 95% confidence interval [CI]: 0.1–6.8%) and any CRC screening (18.3% vs. 14.5%; difference, 3.8 percentage points; 95% CI: 0.6–7.0%). Large variation was observed across health centers in effectiveness (FIT completion differences range, -7.4 percentage points to 17.6 percentage points) and implementation (proportion who were mailed a FIT range, 6.5–68.2%). The number needed to mail to achieve a completed FIT was 4.8 overall, and 4.0 in clinics that mailed a FIT reminder.

Conclusions and relevance: An electronic health record-embedded mailed fecal immunochemical test (FIT) outreach intervention significantly improved rates of FIT completion and rates of any colorectal cancer screening. Higher rates of colorectal cancer screening occurred in clinics that successfully implemented the mailed outreach program.

G.D. Coronado, Ph.D., Kaiser Permanente Center for Health Research, 3800 N Interstate Ave, Portland, OR 97227-1098, USA, E-Mail: gloria.d.coronado@kpchr.org

Effectiveness of colorectal cancer screening in detecting earlier-stage disease – A nationwide cohort study in Denmark

Background and aims: Most studies of the effectiveness of screening for colorectal cancer (CRC) using the fecal occult blood test (FOBT) tested the guaiac FOBT. However, the fecal immunochemical test (FIT) is now commonly used in screening. The authors aimed to evaluate the effectiveness of FIT-based screening for CRC on the number of incident CRC diagnoses and stage at diagnosis for individuals in Denmark who were invited for screening versus not yet invited.

Methods: They collected data for this register-based retrospective cohort study during the first 16 months of the prevalence round of a FIT-based CRC screening program (March 1, 2014, through June 30, 2015). A total of 402,826 residents of Denmark (50–72 years old) were randomly invited to undergo CRC screening within the study period, and 956,514 were invited thereafter. Information on CRC diagnosis, date, and stage at diagnosis was obtained from the Danish Colorectal Cancer Group database. Cancer incidence per 100,000 invited/not yet invited individuals was calculated, along with the relative risk (RR) of CRC among invited compared with not yet invited individuals.

Results: CRC incidence during the study period was 339.4/100,000 invited individuals and 169.6/100,000 not yet invited individuals. CRC incidence increased with age among invited and not yet invited individuals. For invited women compared with not yet invited women, the RR of being diagnosed with stage I CRC was 3.39 (95% confidence interval [CI]: 2.61–4.39), with stage II CRC was 2.16 (95% CI: 1.71–2.72), with stage III CRC was 1.37 (95% CI:
1.88 (95% CI: 1.53–2.30), and with stage IV CRC was 1.20 (95% CI: 0.95–1.52).

Conclusions: In analyzing data from a register-based cohort study in Denmark, it was found that inviting individuals to undergo fecal immunochemical test (FIT)-based colorectal cancer (CRC) screening led to detection of almost 2-fold more cases of CRC than not inviting participants. The significant increase of CRC incidence among those invited for screening indicates a need for awareness of treatment capacity in countries introducing FIT-based CRC screening.

Dr. M. Bach Larsen, Randers Regional Hospital, Skovlyvej 15, 8930 Randers NØ, Central Denmark Region, Denmark, E-Mail: metbacla@rm.dk

Short Bowel Syndrome


Randomized clinical trial: 2% taurolidine versus 0.9% saline locking in patients on home parenteral nutrition

Background: The catheter lock solutions 2% taurolidine and 0.9% saline are both used to prevent catheter-related bloodstream infections (CRBSIs) in home parenteral nutrition patients.

Aims: To compare the effectiveness and safety of taurolidine and saline.

Methods: This multicenter double-blinded trial randomly assigned home parenteral nutrition patients to use either 2% taurolidine or 0.9% saline for 1 year. Patients were stratified in a new catheter group and a pre-existing catheter group. Primary outcome was the rate of CRBSIs/1000 catheter days in the new catheter group and pre-existing catheter group, separately.

Results: The authors randomized 105 patients, of which 102 were analyzed as modified intention-to-treat population. In the new catheter group, rates of CRBSIs/1000 catheter days were 0.29 and 1.49 in the taurolidine and saline arm, respectively (relative risk [RR] = 0.20; 95% confidence interval [CI]: 0.04–0.71; p = 0.009). In the pre-existing catheter group, rates of CRBSIs/1000 catheter days were 0.39 and 1.32 in the taurolidine and saline arm, respectively (RR = 0.30; 95% CI: 0.03–1.82; p = 0.25). Excluding 1 outlier patient in the taurolidine arm, mean costs per patient were $1865 for taurolidine and $4454 for saline (p = 0.03). Drug-related adverse events were rare and generally mild.

Conclusions: In the new catheter group, taurolidine showed a clear decrease in the catheter-related bloodstream infection (CRBSI) rate. In the pre-existing catheter group, no superiority of taurolidine could be demonstrated, most likely due to underpowering. Overall, taurolidine reduced the risk for CRBSIs by more than 4 times. Given its favorable safety and cost profile, taurolidine locking should be considered as an additional strategy to prevent CRBSIs.

Diverticulitis

Am J Gastroenterol. 2018;113(7):1045–52

van Dijk ST, Daniels L, Ünlü Ç, de Korte N, van Dieren S, Stockmann HB, Vrouwenraets BC, Consten EC, van der Hoeven JA, Eijkbouts QA, Faneyte IF, Bemelman WA, Dijkgraaf MG, Boermeester MA; Dutch Diverticular Disease (3D) Collaborative Study Group

Long-term effects of omitting antibiotics in uncomplicated acute diverticulitis

Background: Traditionally uncomplicated acute diverticulitis was routinely treated with antibiotics, although evidence for this strategy was lacking. Recently, 2 randomized clinical trials (AVOD trial and DIABOLO trial) published short-term results of omitting antibiotics compared to routine antibiotic treatment. Both showed no significant differences regarding recovery from the initial episode, as well as rates of complicated or recurrent diverticulitis and sigmoid resection. However, both studies showed a trend of higher rates of sigmoid resection in the observational groups. Here, the long-term effects of omitting antibiotics in first episode uncomplicated acute diverticulitis were assessed.

Methods: A total of 528 patients with computed tomography-proven, primary, left-sided, uncomplicated acute diverticulitis were randomized to either an observational or an antibiotic treatment strategy (DIABOLO trial). Outcome measures were complicated diverticulitis, recurrent diverticulitis and sigmoid resection at 24 months’ follow-up. Differences between the groups were explored and risk factors were identified using multivariable logistic regression.

Results: Complete case analyses showed no difference in rates of recurrent diverticulitis (15.4% in the observational group vs. 14.9% in the antibiotic group; p = 0.885), complicated diverticulitis (4.8% vs. 3.3%; p = 0.403) and sigmoid resection (9.0% vs. 5.0%; p = 0.085). Young patients (< 50 years) and patients with a pain score at presentation of ≥ 8 on a visual analogue pain scale were at risk for complicated or recurrent diverticulitis. In this multivariable analysis, treatment type (with or without antibiotics) was not an independent predictor for complicated or recurrent diverticulitis.

Conclusion: Omitting antibiotics in the treatment of uncomplicated acute diverticulitis did not result in more complicated diverticulitis, recurrent diverticulitis or sigmoid resections at long-term follow-up. As the DIABOLO trial was not powered for these secondary outcome measures, some uncertainty remains whether (small) non-significant differences could be true associations.

Dr. S.T. van Dijk or Prof. Dr. M.A. Boermeester, Department of Surgery, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, Netherlands, E-Mail: stefanvandijk@amc.nl or E-Mail: m.a.boermeester@amc.nl
Despite alternatives, azathioprine and budesonide are firmly established as valuable treatments for inflammatory bowel disease

by Dr. Beate Fessler

A growing amount of active pharmaceutical ingredients are being made available to treat inflammatory bowel disease (IBD). This increases the need for discussion about when such typically expensive treatments are necessary and when proven treatment substances such as the topical steroid budesonide or the immunosuppressant azathioprine are indicated. The controversial discussions about the treat-to-target (T2T) strategy for IBD have also proven to be exciting. The seminar CED kontrovers (“IBD controversies”) offers a forum for this topic in an exciting training event format, created by the Falk Foundation, which has successfully established itself in the world of medical conferences. Well-known experts explicitly define the opposing positions on the basis of case reports to ultimately come to a consensus – something that does not always prove easy. Yet it became crystal clear that ‘old’ treatment methods are still ‘in’ when properly employed.

Should exacerbations during therapy with azathioprine or a biologic be treated with a steroid pulse? PD Dr. A. Pace, Friedrich Ebert Hospital, Neumuenster (Germany), spoke out against this. “Don’t just immediately reach for steroids. Look first at why the patient’s condition has worsened,” he stressed.

Flare-up during azathioprine therapy: treatment monitoring before administering a steroid pulse

Instead of administering a steroid pulse, he recommended initially monitoring treatment. “Azathioprine is frequently administered in an insufficient dosage,” he emphasized. Patients with high levels of 6-TGN (thioguanine nucleotide), an active metabolite of azathioprine, should be switched to a different class of active pharmaceutical ingredient (API) if treatment with the immunosuppressant fails. However, if the 6-TGN and 6-MMP (methylmercaptopurine) levels are low, it is recommended to question the patient regarding their compliance and raise the dosage if necessary. If 6-TGN levels are low and 6-MMP levels are high, A. Pace says there are three possible courses of action that can be taken: changing the API class, adding allopurinol or febuxostat, or splitting the dosage. One should not forget that combining azathioprine and tumor necrosis factor alpha inhibitors is also an option.

Topical steroid use – the best method of administration

Conversely, Prof. T. Kucharzik, Lueneburg General Hospital (Germany), emphasized the many years of experience with steroids, with which high remission rates can be reached in a short period of time. He referred to data from the GETAID study which states that within seven weeks, 92% of patients achieve a clinical remission with 29% of them attaining mucosal healing. According to T. Kucharzik, steroids are also very valuable when introducing a slow-acting immunosuppressive therapy, for instance with azathioprine. They are also highly effective in treating exacerbations in the short term, achieving high response rates in a short amount of time. Additionally, the initial response to prednisolone is a meaningful predictor of how IBD will progress. Non-responders suffer a recurrence more frequently than responders (92.5% vs. 51.1%), are more frequently hospitalized (75% vs. 23.4%) and must in more cases undergo a colectomy (22.5% vs. 4.3%). A consensus was reached that steroids should only be administered for remission induction and never for remission maintenance. A steroid pulse can also be administered in some individual cases in the event of secondary treatment failure when using biologics or immunosuppressants. The short-term side effects are estimated to be minimal. Topical steroids such as budesonide – available in assorted forms of delivery – should be used if possible. At a similar remission rate (56% vs. 55.2%), steroid side effects occur in far fewer patients when compared with prednisone (22.6% vs. 41.4%) [1].
Azathioprine use in cases of steroid dependency, except with EBV-seronegative patients

Prof. G. Rogler, University Hospital Zurich (Switzerland), stood up for the administration of azathioprine in cases of steroid dependency. According to the results of a post hoc analysis, azathioprine reduces moderate-to-severe flare-ups (CDAI > 220) in comparison to a placebo (11.8% vs. 30.2%) [2]. The risk of an initial surgical procedure is reduced by about 40% according to a meta-analysis [3]. The high relapse rate after discontinuation of azathioprine speaks for long-term usage [4]. “If azathioprine proves effective and is tolerated well, treatment should not be interrupted,” says G. Rogler. An alternative to azathioprine is vedolizumab, an integrin antagonist that is also effective in treating extraintestinal manifestations despite only targeting the intestine. Except for a potentially increased risk of postoperative complications, it has proven to be well tolerated, PD Dr. M. Blaeker of Hamburg said. It is a good alternative to azathioprine in patients who are seronegative for Epstein-Barr virus (EBV) and patients over the age of 65.

Treatment goal discussion: T2T or “I’m fine”?

There was also a lively debate around the question of how much remission is necessary, or rather, whether the absence of symptoms is enough or if specifically defined biomarkers need to be reached for T2T (treat to target). For Prof. C. Maaser, Lueneburg General Hospital (Germany), being “fine” is not good enough. He supports a treat-to-target strategy. Prof. M. Reinshagen, Braunschweig General Hospital (Germany), is of a different opinion. He referenced the REACT study, which compared 898 patients at conventional management medical practices and 1084 patients at early combined immunosuppression practices according to a predefined algorithm [5]. In the two-year course of treatment, no difference was detected in symptomatic remission even though the patients in the T2T group were treated more intensively. However, hospitalization, operations and severe complications were more common in patients undergoing conventional treatment (34.7% vs. 27.4%).

Follow-up with asymptomatic patients, too

Regular follow-up procedures (laboratory inflammation indicators, calprotectin, bowel sonography, endoscopy) should also be conducted with asymptomatic patients. The consensus was that therapy management based on clinical symptoms alone bears the risk of both under- and over-treatment. Every medical center should store algorithms, and decisions on treatment should be based on a combination of individual medical histories, clinical symptoms and findings, and not on a single value alone. Furthermore, there is no outcomes research on treatment management, including in reference to morphological imaging findings.

References:

Scientific organizers:

Prof. K. Fellermann, Hospitals in the District of Freudenstadt (Germany)
Prof. K. Herrlinger, Asklepios Clinic North – Heidberg, Hamburg (Germany)
Prof. T. Kucharzik, Lueneburg General Hospital (Germany)
Workshop and
35th Annual Meeting of the GASL

February 21–23, 2019
Heidelberg, Germany

Congress Venue
Hörsaalzentrum Chemie
Chemisches Institut
Im Neuenheimer Feld 252
69120 Heidelberg
Germany

February 21–22, 2019
Workshop
From Viral Hepatitis to Chronic Inflammation and Liver Cancer
Scientific Organization
R. Bartenschlager, Heidelberg (Germany)
M. Heikenwälder, Heidelberg (Germany)
P. Schirmacher, Heidelberg (Germany)

February 22–23, 2019
35th Annual Meeting of the German Association for the Study of the Liver (GASL)
President
R. Bartenschlager, Heidelberg (Germany)

Information:
Prof. Dr. Ralf Bartenschlager
Zentrum für Infektiologie, Molekulare Virologie
Universitätsklinikum Heidelberg
Im Neuenheimer Feld 344
69120 Heidelberg
Germany
**Acute/Chronic Pancreatitis**

*Gut. 2018 [in press]*


**Non-superiority of lumen-apposing metal stents over plastic stents for drainage of walled-off necrosis in a randomized trial**

**Objective:** Although lumen-apposing metal stents (LAMS) are increasingly used for drainage of walled-off necrosis (WON), their advantage over plastic stents is unclear. The authors compared efficacy of LAMS and plastic stents for WON drainage.

**Design:** Patients with WON were randomized to endoscopic ultrasound-guided drainage using LAMS or plastic stents. Primary outcome was comparing total number of procedures to achieve treatment success defined as symptom relief in conjunction with WON resolution on computed tomography (CT) at 6 months. Secondary outcomes were treatment success, procedure duration, clinical/stent-related adverse events, readmissions, length of hospital stay (LOS) and costs.

**Results:** 60 patients underwent LAMS (n = 31) or plastic stent (n = 29) placement. There was no significant difference in total number of procedures performed (median 2 [range, 2–7] LAMS vs. 3 [range, 2–7] plastic, $p = 0.192$), treatment success, clinical adverse events, readmissions, LOS and overall treatment costs between cohorts. Although procedure duration was shorter (15 vs. 40 min, $p < 0.001$), stent-related adverse events (32.3% vs. 6.9%, $p = 0.01$) and procedure costs ($12,155 vs. $6609, p < 0.001$) were higher with LAMS. Significant stent-related adverse events were observed ≥ 3 weeks postintervention in LAMS cohort. Interim audit resulted in protocol amendment where CT scan was obtained at 3 weeks postintervention followed by LAMS removal if WON had resolved. After protocol amendment, there was no significant difference in adverse events between cohorts.

**Conclusion:** Except for procedure duration, there was no significant difference in treatment outcomes between lumen-apposing metal stents (LAMS) and plastic stents. To minimize adverse events with LAMS, patients should undergo follow-up imaging and stent removal at 3 weeks if walled-off necrosis has resolved.

S. Varadarajulu, M.D., Center for Interventional Endoscopy, Florida Hospital, Orlando, 601 East Rollins Street, Orlando, FL 32803, USA, E-Mail: svaradarajulu@yahoo.com

---

**Recurrent acute pancreatitis significantly reduces quality of life even in the absence of overt chronic pancreatitis**


**Objectives:** The impact of recurrent acute pancreatitis (RAP) on quality of life (QOL) is unknown. The authors hypothesized that RAP would reduce QOL even in the absence of chronic pancreatitis (CP).

**Methods:** Data were pooled from 3 prospective, cross-sectional studies conducted across 27 US centers (the North American Pancreatitis Studies); these included subjects with chronic pancreatitis (n = 1086), RAP alone (n = 508), and non-disease controls (n = 1025). QOL was measured using the Short Form 12 (SF-12), generating a Physical Component Summary (PCS) and the Mental Component Summary score (MCS). Multivariable regression models were developed to measure the effect of RAP on QOL, the predictors of lower QOL in those with RAP, and the differential effect QOL predictors between CP and RAP.

**Results:** Compared to controls (51.0 ± 9.4), subjects with RAP (41.1 ± 11.4) and CP (37.2 ± 11.8) had lower PCS (p < 0.01). Subjects with CP had lower PCS compared to those with RAP (p < 0.01). Similarly, MCS was lower among RAP (44.6 ± 11.5) and CP (42.8 ± 12.2) subjects compared to controls (51.7 ± 9.1, p < 0.01). Subjects with CP had lower MCS compared to those with RAP (p < 0.01). After controlling for independent predictors of PCS, RAP was associated with lower PCS (estimate -8.45, p < 0.01) and MCS (estimate -6.45, p < 0.0001) compared to controls. The effect of endocrine insufficiency on PCS was differentially greater among subjects (-12.8 for CP vs. -4.9 for RAP, p = 0.0184).

**Conclusions:** Even in the absence of chronic pancreatitis (CP), subjects with recurrent acute pancreatitis (RAP) have lower physical and mental quality of life. This underscores the importance of identifying interventions to attenuate RAP before the development of overt CP.

G.A. Coté, M.D., Associate Professor of Medicine, Department of Medicine, College of Medicine, Medical University of South Carolina, 171 Ashley Ave, Charleston, SC 29425 USA, E-Mail: cotea@musc.edu

---

**Cholecystectomy during index admission for acute biliary pancreatitis lowers 30-day readmission rates**


**Objectives:** Few studies have evaluated national readmission rates after acute pancreatitis (AP) in the United States. The authors sought to evaluate modifiable factors impacting 30-day readmissions after AP hospitalizations.
Methods: They used the Nationwide Readmission Database (2013) involving all adults with a primary discharge diagnosis of AP. Multivariable logistic regression models assessed independent predictors for specific outcomes.

Results: Among 180,480 patients with AP index admissions, 41,094 (23%) had biliary AP, of which 10.5% were readmitted within 30 days. The 30-day readmission rate for patients who underwent same-admission cholecystectomy (CCY) was 6.5%, compared with 15.1% in those who did not (p < 0.001). Failure of index admission CCY increased the risk of readmissions (odds ratio [OR] = 2.27; 95% confidence interval [CI]: 2.04–2.56). Same-admission CCY occurred in 55% (n = 19,274) of patients without severe AP. Severe AP (OR = 0.73; 95% CI: 0.65–0.81), sepsis (OR = 0.63; 95% CI: 0.52–0.75), ≥ 3 comorbidities (OR = 0.74; 95% CI: 0.68–0.79), and admissions to small (OR = 0.76; 95% CI: 0.64–0.91) or rural (OR = 0.78; 95% CI: 0.65–0.95) hospitals were less likely to undergo same-admission CCY.

Conclusions: Same-admission cholecystectomy should be considered in patients with biliary acute pancreatitis (AP) when feasible. This national appraisal recognizes modifiable risk factors to reduce readmission in biliary AP and reinforces adherence to major society guidelines.

S.G. Krishna, M.D., Division of Gastroenterology, Hepatology and Nutrition, The Ohio State University, Wexner Medical Center, 2nd floor, 395 W 12th Ave, Columbus, OH 43210, USA, E-Mail: sgkrisshna@gmail.com

Pancreatic Tumors


Higher growth rate of branch-duct intraductal papillary mucinous neoplasms associates with worrisome features

Background and aims: For patients with branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs, cysts), it is a challenge to identify those at high risk for malignant lesions. The authors sought to identify factors associated with development of pancreatic cancer, focusing on neoplasm growth rate.

Methods: They performed a retrospective study of 189 patients with BD-IPMNs who underwent at least 2 contrast-enhanced cross-sectional imaging studies, 1 year or more apart, at a tertiary referral center from January 2003 through 2013. Patients with cysts that had Fukuoka worrisome or high-risk features were excluded. Two radiologists reviewed all images. Cyst size was recorded at the initial and final imaging studies and growth rate was calculated. Patient demographic data, cyst characteristics,
and clinical outcomes were collected; univariate logistic regression models were used to determine the odds of developing worrisome features. The primary outcomes were to determine growth rate of low-risk BD-IPMNs and to assess whether cyst growth rate correlates high-risk features of IPMNs.

**Results:** Based on image analyses, cysts were initially a median 11 mm (range, 3–31 mm) and their final size was 12.5 mm (range, 3–42 mm). After a median follow-up time of 56 months (range, 12–163 months), the median cyst growth rate was 0.29 mm/year. 12 patients developed worrisome features, no patients developed high-risk features, 4 patients had surgical resection, and no cancers developed. The rate of BD-IPMN growth was greater in patients who developed worrisome features than those who did not (2.84 mm/year vs. 0.23 mm/year; p < 0.001). The odds of developing worrisome features increased for each unit (mm) increase in cyst size (odds ratio = 1.149; 95% confidence interval: 1.035–1.276; p = 0.009).

**Conclusion:** In a retrospective analysis of images from patients with branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs), the authors found low-risk BD-IPMNs to grow at an extremely low rate (< 0.3 mm/year). BD-IPMNs in only about 6% of patients developed worrisome features, and none developed high-risk features or invasive cancers. BD-IPMNs that developed worrisome features were associated with a significantly higher rate of growth than lesions with low-risk features. Low risk BD-IPMNs that grow more than 2.5 mm/year might require surveillance.

C.J. DiMaio, M.D., Associate Professor of Medicine, Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1069, New York, NY 10029, USA, E-Mail: christopher.dimaio@mountsinai.org

---

**Clin Gastroenterol Hepatol. 2018;16(7):1123–30.e1**


**Risk of pancreatic cancer in patients with pancreatic cysts and family history of pancreatic cancer**

**Background and aims:** A diagnosis of pancreatic cancer (PC) in a first-degree relative increases an individual’s risk of this cancer. However, it is not clear whether this cancer risk increases in individuals with pancreatic cystic lesions who have a first-degree relative with PC. The Fukuoka criteria are used to estimate risk of PC for patients with pancreatic cystic lesions: Individuals with cysts with high risk or worrisome features (Fukuoka-positive) have a higher risk of PC than individuals without these features (Fukuoka-negative). The authors aimed to compare the risk of PC and surgery based on presence or absence of pancreatic cystic lesions and a first-degree relative with PC.

**Methods:** They performed a retrospective study of patients seen at the Mayo Clinic in Rochester, Minnesota, from January 1, 2000, through December 31, 2012, and identified individuals with pancreatic cystic lesions and first-degree relative with PC (group 1, n = 269), individuals with pancreatic cystic lesions but no first-degree relative with PC (group 2, n = 1195), and individuals without pancreatic cystic lesions but with a first-degree relative with PC (group 3, n = 720). They compared among groups, as well as among patients with cysts classified according to Fukuoka criteria, proportions of individuals who developed PC or underwent pancreatic surgery within a 5-year period.

**Results:** A significantly higher proportion of individuals in group 1 developed PC during the 5-year period than in group 2 (6.64% vs. 4.05%; p = 0.01). A 1-month longer median survival was observed in regular statin users compared with non-regular users. Regular statin use within the 2 years prior to cancer diagnosis was most strongly associated with longer survival. Regular statin use before diagnosis was similarly associated with survival in the Nurses’ Health Study (HR = 0.79; 95% CI: 0.64–0.97) and Health Professionals Follow-up Study (HR = 0.86; 95% CI: 0.63–1.15).

**Conclusions:** Regular statin use before diagnosis of pancreatic cancer was associated with modest increases in survival times in 2 large prospective cohort studies.

B.M. Wolpin, M.D., Associate Professor of Medicine, Department of Medical Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215, USA, E-Mail: bwolpin@partners.org

---

**Clin Gastroenterol Hepatol. 2018;16(8):1300–6.e3**


**Prediagnosis use of statins associates with increased survival times of patients with pancreatic cancer**

**Background and aims:** Statin medications, most commonly prescribed to reduce lipid levels and prevent cardiovascular disease, may be associated with longer survival times of patients with cancer. However, the association of statins with outcomes of patients with pancreatic adenocarcinoma is not clear.

**Methods:** The authors analyzed the association of statin use before a diagnosis of pancreatic cancer with survival times of 648 participants in the Nurses’ Health Study and Health Professionals Follow-up Study who were diagnosed with pancreatic adenocarcinoma from 2000 through 2013. They estimated hazard ratios (HRs) for overall mortality using Cox proportional hazards models with adjustment for potential confounders and assessed the temporal association between prediagnosis statin use and cancer survival by 2-year lag periods to account for a possible latency period between statin use and cancer survival.

**Results:** Regular statin use before diagnosis of pancreatic cancer was associated with modestly prolonged survival compared with non-regular use (adjusted HR = 0.82; 95% confidence interval [CI]: 0.69–0.97; p = 0.02). A 1-month longer median survival was observed in regular statin users compared with non-regular users. Regular statin use within the 2 years prior to cancer diagnosis was most strongly associated with longer survival. The authors observed no statistically significant effect modification by smoking status, body mass index, diabetes, or cancer stage (all p(Interaction) > 0.53). Regular statin use before diagnosis was similarly associated with survival in the Nurses’ Health Study (HR = 0.79; 95% CI: 0.64–0.97) and Health Professionals Follow-up Study (HR = 0.86; 95% CI: 0.63–1.15).
Conclusions: In a retrospective study of patients with pancreatic cysts and/or cancer, it was found that a family history of pancreatic cancer (PC) does not affect the 5-year risk of PC in patients with pancreatic cystic lesions. Despite this, among patients with Fukuoka-negative cysts, a higher proportion of those with a family history of PC underwent surgery than patients without family history of PC.

S.T. Chari, M.D., Professor of Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA, E-Mail: chari.suresh@mayo.edu

Pancreas. 2018;47(7):800–6

Conclusions: In a retrospective study of patients with pancreatic neuroendocrine tumors, a significant association between metformin use and longer progression-free survival was found.

Dr. S. Pusceddu, Department of Medical Oncology Unit-1, Fondazione IRCCS Istituto Nazionale dei Tumori and ENETS Center of Excellence, Via Venezian 1, 20133 Milan, Italy, E-Mail: sara.pusceddu@istitutotumori.mi.it

A multicenter open-label randomized controlled trial of pancreatic enzyme replacement therapy in unresectable pancreatic cancer

Objective: Exocrine pancreatic insufficiency may impair the nutritional status in pancreatic cancer (PC), but the role of pancreatic enzyme replacement therapy (PERT) is not fully evaluated. Therefore, the authors conducted this multicenter open-label randomized controlled trial to evaluate the role of PERT in PC patients.

Methods: Patients with unresectable PC receiving chemotherapy were randomly assigned to pancrelipase and non-pancrelipase groups. Patients in the pancrelipase group took oral pancrelipase of 48,000 lipase units per meal. N-benzoyl-tryrosyl para-aminobenzoic acid (NB-PABA) test was performed at baseline. The primary end point was change in body mass index (BMI) at 8 weeks. Secondary end points were change in other nutritional status at 8 weeks and overall survival.

Results: A total of 88 patients were enrolled between May 2014 and May 2016. The NB-PABA test was lower than the normal range in 90%. There were no significant differences in change in BMI at 8 weeks: 0.975 and 0.980 in the pancrelipase and the
non-pancrelipase groups, respectively (p = 0.780). The other nutritional markers were also comparable. The median overall survival was 19.0 and 12.0 months (p = 0.670).

Conclusions: In this randomized controlled trial, pancrelipase failed to improve the change in body mass index at 8 weeks in pancreatic cancer patients receiving chemotherapy.

Prof. Dr. H. Isayama, Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo Bunkyo-ku, Tokyo, 113-8655, Japan, E-Mail: isayama-tky@umin.ac.jp

Conclusions: In a long-term (16-year) follow-up study of individuals at high risk for pancreatic ductal adenocarcinoma (PDAC), most PDACs detected during surveillance (9/10) were found to be resectable, and 85% of these patients survived for 3 years. Radiologic features were identified to be associated with neoplastic progression.

M.I. Canto, M.D., Associate Professor of Medicine, Division of Gastroenterology, Department of Medicine, Johns Hopkins Medical Institutions, 1800 Orleans Street, Blalock 407, Baltimore, MD 21231, USA, E-Mail: mcanto@jhmi.edu

Gastroenterology. 2018;155(3):740–51.e2


Risk of neoplastic progression in individuals at high risk for pancreatic cancer undergoing long-term surveillance

Background and aims: Screening of individuals who have a high risk of pancreatic ductal adenocarcinoma (PDAC), because of genetic factors, frequently leads to identification of pancreatic lesions. The authors investigated the incidence of PDAC and risk factors for neoplastic progression in individuals at high risk for PDAC enrolled in a long-term screening study.

Methods: They analyzed data from 354 individuals at high risk for PDAC (based on genetic factors of family history), enrolled in Cancer of the Pancreas Screening cohort studies at tertiary care academic centers from 1998 through 2014 (median follow-up time, 5.6 years). All subjects were evaluated at study entry (baseline) by endoscopic ultrasonography and underwent surveillance with endoscopic ultrasonography, magnetic resonance imaging, and/or computed tomography. The primary end point was the cumulative incidence of PDAC, pancreatic intraepithelial neoplasm grade 3, or intraductal papillary mucinous neoplasm with high-grade dysplasia (HGD) after baseline. Multivariate Cox regression and Kaplan-Meier analyses were performed.

Results: During the follow-up period, pancreatic lesions with worrisome features (solid mass, multiple cysts, cyst size > 3 cm, thickened/enhancing walls, mural nodule, dilated main pancreatic duct > 5 mm, or abrupt change in duct caliber) or rapid cyst growth (> 4 mm/year) were detected in 68 patients (19%). Overall, 24 of 354 patients (7%) had neoplastic progression (14 PDACs and 10 HGDs) over a 16-year period; the rate of progression was 1.6%/year, and 93% had detectable lesions with worrisome features before diagnosis of the PDAC or HGD. Nine of the 10 PDACs detected during routine surveillance were resectable; a significantly higher proportion of patients with resectable PDACs survived 3 years (85%) compared with the 4 subjects with symptomatic, unresectable PDACs (25%), which developed outside surveillance (log rank p < 0.0001). Neoplastic progression occurred at a median age of 67 years; the median time from baseline screening until PDAC diagnosis was 4.8 years (interquartile range = 1.6–6.9 years).

Conclusions: In a long-term (16-year) follow-up study of individuals at high risk for pancreatic ductal adenocarcinoma...
IBD: From Pathophysiology to Personalized Medicine

March 29–30, 2019
Oxford, Great Britain

Congress Venue
Examination Schools
75-81, High Street
Oxford, OX1 4BG
Great Britain

Scientific Organization
A. Kaser, Cambridge (Great Britain)
M. F. Neurath, Erlangen (Germany)
F. Powrie, Oxford (Great Britain)
Significance of definitions of relapse after discontinuation of oral antivirals in HBeAg-negative chronic hepatitis B

Relapses are observed in most hepatitis B e antigen (HBeAg)-negative chronic hepatitis B patients who discontinue treatment with nucleos(t)ide analogues (NAs); however, the rates of relapse vary widely among studies, and whether all patients with relapse need retreatment is unclear. The aim of this study was to assess the impact of different definitions on the rates of post-treatment relapse and therefore on the probability of retreatment in patients who have discontinued effective long-term NA therapy. In total, 130 HBeAg-negative chronic hepatitis B patients without cirrhosis and before NA treatment were included. All had on-therapy virological remission for ≥ 24 months and close follow-up for ≥ 12 months after stopping NA treatment or until retreatment, which started on stringent predefined criteria. Relapse rates based on several predetermined definitions of virological and perhaps biochemical criteria were assessed. The median duration of therapy was 60 months and the median duration of on-therapy virological remission was 43 months. During a median off-NA follow-up of 15 months, no patient experienced liver decompensation or died. Cumulative relapse rates were 2–49%, 4–73%, 11–82%, and 16–90% at 3, 6, 12, and 24 months, respectively, whereas cumulative retreatment rates were 15%, 22%, and 40% at 6, 12, and 24 months, respectively, after discontinuation of NA therapy. No patient characteristic was independently associated with the probability of relapse based on at least 2 definitions or of retreatment.

Conclusion: In hepatitis B e antigen-negative chronic hepatitis B patients who discontinue therapy with nucleos(t)ide analogues (NAs), the definition of relapse has a great impact on off-NA relapse rates and potentially on the probability of retreatment. Regardless of definition, off-NA relapses cannot be easily predicted by patient characteristics. A substantial proportion of such patients may not require retreatment if stringent criteria are adopted.

Prof. Dr. G.V. Papatheodoridis, Department of Gastroenterology, National and Kapodistrian University of Athens Medical School, Laiko General Hospital, 17 Agiou Thoma Street, 11527 Athens, Greece, E-Mail: gepapath@med.uoa.gr

Efficacy of generic oral directly acting agents in patients with hepatitis C virus infection

Novel direct-acting antivirals (DAAs) are now the standard of care for the management of hepatitis C virus (HCV) infection. Branded DAAs are associated with high sustained virological response at 12 weeks post-completion of therapy (SVR12), but are costly. The authors aimed to assess the efficacy of generic oral DAAs in a real-life clinical scenario. Consecutive patients with known HCV infection who were treated with generic-oral DAA regimens (May 2015 to January 2017) were included. Demographic details, prior therapy and SVR12 were documented. 490 patients (mean age, 38.9 ± 12.7 years) were treated with generic DAAs in the study time period. Their clinical presentations included chronic hepatitis in 339 (69.2%) cases, compensated cirrhosis in 120 (24.48%) cases and decompensated cirrhosis in 31 (6.32%) cases. Genotype 3 was most common (n = 372, 75.9%) followed by genotype 1 (n = 97, 19.8%). Treatment-naïve and treatment-experienced (defined as having previous treatment with pegylated interferon and ribavirin) were 432 (88.2%) and 58 (11.8%) patients, respectively. Generic DAA treatment regimens included sofosbuvir in combination with ribavirin (n = 175), daclatasvir alone (n = 149), ribavirin and pegylated interferon (n = 80), ledipasvir alone (n = 43), daclatasvir and ribavirin (n = 37), and ledipasvir and ribavirin (n = 6). Overall SVR12 was 95.9% (470/490) for all treatment regimens. SVR12 for treatment-naïve and -experienced patients was 97.0% (419/432) and 87.9% (51/58), respectively (p = 0.005). High SVR12 was observed with various regimens, irrespective of genotype and underlying liver disease status. There were no differences in SVR12 with 12 or 24 weeks therapy. No major adverse event occurred requiring treatment stoppage.

Generic oral direct-acting antivirals are associated with high sustained virological response rates in patients with hepatitis C virus infection in a real-life clinical scenario.

Prof. Dr. Shalimar, Department of Gastroenterology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India, E-Mail: drshalimar@gmail.com

Persistently altered liver test results in hepatitis C patients after sustained virological response with direct-acting antivirals

Guidelines recommend evaluating persistent alteration of liver tests in hepatitis C virus (HCV)-infected patients after sustained virological response (SVR) and its influence on liver disease pro-
The efficacy of direct anti-HCV drugs improves early post-liver transplant survival and induces significant changes in waiting list composition

Background and aims: The efficacy of direct-acting antivirals (DAA) has dramatically changed the prognosis of patients with chronic hepatitis C. The authors aimed to evaluate the impact of DAA therapy on the composition of the liver transplant (LT) waiting list and the early post-transplant survival.

Methods: They evaluated all patients admitted to the waiting list for a primary LT between January 1, 2008, and December 31, 2016, in Catalonia, Spain. Time span was divided into 2 periods according to the availability of different antiviral therapies: 2008–2013 (interferon-based therapies) and 2014–2016 (DAA). Changes in the indications of LT and the etiology of liver disease, as well as post-LT patient survival, were evaluated according to the availability of different antiviral therapies: 2008–2013 (interferon-based therapies) and 2014–2016 (DAA).

Results: 1483 patients were included. Admissions in the waiting list for hepatitis C virus (HCV)-related liver disease decreased significantly, from 47% in 2008–2013 to 39% in 2014–2016 (p < 0.001), particularly because of a reduction in patients with decompensated cirrhosis. In contrast, non-alcoholic steatohepatitis (NASH)-related inclusions increased from 4% to 7% (p = 0.003). Three-year post-LT patient survival increased significantly in the second period in the whole cohort (82% vs. 91%, p = 0.002), because of better survival in anti-HCV-positive patients (76% vs. 91%, p = 0.001), but not in anti-HCV-negative patients (88% vs. 91%; p = 0.359). Anti-HCV-positive serology, the time period of 2008–2013 and higher donor age were independently associated with post-LT mortality in the whole cohort; while time period and donor age were independently associated with post-LT mortality in anti-HCV-positive recipients.

Conclusions: The high efficacy of direct-acting antivirals is associated with significant changes in the composition of the liver transplant waiting list and, more importantly, results in improved post-transplant survival.

Dr. G. Crespo or Dr. M.-C. Londoño, Liver Unit, Hospital Clinic de Barcelona, Villarroel, 170, 08036 Barcelona, Spain, E-Mail: gcrespo@clinic.cat or E-Mail: mlondono@clinic.cat

HEV

Hepatitis E virus seroprevalence, seroincidence and seroreversion in the German adult population

A steep rise in hepatitis E diagnoses is currently being observed in Germany and other European countries. The objective of this study was (i) to assess whether this trend mirrors an increase in infection pressure or is caused by increased attention and testing and (ii) estimate individual and population-based hepatitis E virus (HEV) seroconversion and seroreversion rates for Germany. The authors measured anti-HEV immunoglobulin G (IgG) prevalence in 10,407 adults participating in 2 linked, population-representative serosurveys (total n = 12,971) conducted in 1998 and 2010. In this period, they found a moderate but statistically significant decline of overall anti-HEV IgG prevalence from 18.6% to 15.3%. At both time points, seroconversion increased with age and peaked in persons born between 1935 and 1959 suggesting a past period of increased infection pressure. Paired samples of individuals participating in 1998 and 2010 (n = 2564) revealed respective seroconversion and seroreversion rates of 6.2% and 22.6% among seronegative and seropositive individuals during 12 years, or 5.2 and 2.9 per 1000 inhabitants per year. This corresponds to a total of 417,242 (95% CI: 344,363–495,971) new seroconversions per year in the German population.

While anti-hepatitis E virus seroprevalence has decreased in the last decade, infection pressure and seroincidence remains high in Germany. Continuously rising numbers of hepatitis E diagnoses in Europe are likely due to an increased

J Viral Hepat. 2018;25(6):752–8


J Hepatol. 2018;69(1):11–7


The efficacy of direct anti-HCV drugs improves early post-liver transplant survival and induces significant changes in waiting list composition

Dr. A. Olveira, Servicio de Aparato Digestivo, Hospital Universitario La Paz, Paseo de Castellana, 261, 28046 Madrid, Spain, E-Mail: aolveiram@gmail.com
HEV-positive blood donations represent a relevant infection risk for immunosuppressed recipients

Background and aims: Routine hepatitis E virus (HEV) testing of blood products has recently been implemented in Great Britain and the Netherlands. The relevance of transfusion-transmitted HEV infections is still controversially discussed in Europe.

Methods: All blood donations at the University Medical Center Hamburg-Eppendorf (Germany) were prospectively tested for HEV RNA by pooled polymerase chain reaction from October 2016 to May 2017. Reactive samples were individually retested. Additionally, stored samples from previous donations of positive donors were tested to determine the duration of HEV viremia. HEV RNA-positive donors and a control cohort were asked to answer a questionnaire.

Results: 23 out of 18,737 HEV RNA-positive donors were identified (0.12%). Only 2 of the positive donors (8.7%) presented with elevated aminotransferases at time of donation (alanine aminotransferase: 192 and 101 U/l). The retrospective analysis of all positive donors revealed that 4 asymptomatic donors had been HEV-viremic for up to 3 months with the longest duration of HEV viremia exceeding 4 months. Despite the HEV-testing efforts, 14 HEV RNA-positive blood products were transfused into 12 immunocompromised and 2 immunocompetent patients. One recipient of these products developed fatal acute-on-chronic liver failure complicated by Pseudomonas septicemia. The questionnaire revealed that HEV RNA-positive donors significantly more often consumed raw pork meat (12/18; 67%) than controls (89/256; 35%; p = 0.01). In 2 donors, undercooked pork liver dishes were identified as the source of infection. HEV genotyping was possible in 7 out of 23 HEV-viremic donors and 6 out of 7 isolates belonged to HEV genotype 3, group 2.

Conclusions: Prolonged hepatitis E virus (HEV) viremia can be detected at a relatively high rate in Northern German blood donors, leading to transfusion-transmitted HEV infections in several patients with the risk of severe and fatal complications. Eating raw pork tartare represented a relevant risk for the acquisition of HEV infection.


Corticosteroids reduce risk of death within 28 days for patients with severe alcoholic hepatitis, compared with pentoxifylline or placebo – A meta-analysis of individual data from controlled trials

Background and aims: The authors performed a meta-analysis of individual patient data from 11 randomized controlled trials (RCTs) comparing corticosteroids, pentoxifylline, or their combination in patients with severe alcoholic hepatitis. They compared the effects of the treatments on survival for 28 days or 6 months, and response to treatment based on the Lille model.

Methods: PubMed was searched for RCTs of pharmacologic therapy for severe alcoholic hepatitis. The final analysis comprised 11 studies, of 2111 patients. Four meta-analyses of the effects of corticosteroids versus placebo or control, corticosteroids versus pentoxifylline, corticosteroids and pentoxifylline versus corticosteroids and placebo or control, and pentoxifylline versus placebo were performed. In each meta-analysis, the effect of treatment on the primary outcome (overall survival at 28 days, defined as the period from the first day of assigned treatment to 28 days) was estimated using a Cox proportional hazards regression model, including trials as random effect.

Results: Corticosteroid treatment significantly decreased risk of death within 28 days compared with controls (hazard ratio [HR] = 0.64; 95% confidence interval [CI]: 0.48–0.86) or to pentoxifylline (HR = 0.64; 95% CI: 0.43–0.95). In multiple-imputation analyses, the effect of corticosteroids compared with controls remained significant. When corticosteroids were compared versus pentoxifylline, the corticosteroid effect remained significant in the complete case analysis (HR = 0.66; p = 0.04) but not in multiple-imputation analysis (HR = 0.71; p = 0.08). There was no difference in 28-day mortality when patients were given a combination of corticosteroids and pentoxifylline versus corticosteroids alone or between patients given pentoxifylline versus control. In the analysis of secondary outcomes, no significant differences were found in 6-month mortality when any treatments or controls were compared. Corticosteroids were significantly associated with increased response to therapy compared with controls (relative risk = 1.24; 95% CI: 1.10–1.41) or pentoxifylline (relative risk = 1.43; 95% CI: 1.20–1.68). No difference in response to therapy was found between patients given a combination of corticosteroids and pentoxifylline versus corticosteroids alone or pentoxifylline versus controls.

Conclusions: In a meta-analysis of 4 controlled trials, corticosteroid use was found to reduce risk of death within 28 days of treatment, but not in the following 6 months. This loss of efficacy over time indicates a need for new therapeutic strategies to improve medium-term outcomes.

Dr. P. Mathurin, Service Maladies de l'Appareil Digestif, Hôpital Claude Huriez, Rue Polonovski, 59037 Lille cedex, France, E-Mail: philippe.mathurin@chru-lille.fr
High BMI in late adolescence predicts future severe liver disease and hepatocellular carcinoma: A national, population-based cohort study in 1.2 million men

Objective: A high body mass index (BMI) is associated with an increased risk for severe liver disease. It is unclear if this risk differs across BMI categories, and if the association is partially attributed to development of type 2 diabetes mellitus (T2DM).

Design: The authors used register data from more than 1.2 million Swedish men enlisted for conscription between 1969 and 1996. Data regarding new events of severe liver disease and T2DM during follow-up were obtained by record-linkage of population-based registers. Cox regression was used to estimate adjusted hazard ratios (HRs) for future inpatient care and mortality.

Results: During a follow-up of more than 34 million person-years, 5281 cases of severe liver disease including 251 cases of HCC were identified. An association with severe liver disease was found for overweight (HR = 1.49, 95% confidence interval [CI]: 1.35–1.64) and for obese men (HR = 2.17, 95% CI: 1.82–2.59). Development of T2DM further increased the risk for severe liver disease across all BMI categories, for instance, men with obesity and T2DM had a higher risk of severe liver disease (HR = 3.28, 95% CI: 2.27–4.74) than men with obesity free of T2DM (HR = 1.72, 95% CI: 1.72–2.54).

Conclusions: A high body mass index (BMI) in late adolescent men was associated with an increased risk of future severe liver disease, including hepatocellular carcinoma. Development of type 2 diabetes mellitus during follow-up was associated with a further increased risk of severe liver disease, independent of baseline BMI.

A high body mass index (BMI) in late adolescent men was associated with an increased risk of future severe liver disease, including hepatocellular carcinoma. Development of type 2 diabetes mellitus during follow-up was associated with a further increased risk of severe liver disease, independent of baseline BMI.

Improved diet quality associates with reduction in liver fat, particularly in individuals with high genetic risk scores for non-alcoholic fatty liver disease

Background and aims: Dietary modification has been recommended for treatment of non-alcoholic fatty liver disease (NAFLD), although it is not clear whether improving diet quality can prevent its development. The authors performed a prospective study to examine the association between diet quality change and change in liver fat. They also examined the association between genetic risk score and liver fat change in individuals with different levels of diet quality change.

Methods: The present study included 1521 participants who attended the seventh and eighth examinations (1998–2001 and 2005–2008) of the second-generation cohort or attended the first and second examinations (2002–2005 and 2008–2011) of the third-generation cohort in the Framingham Heart Study. The self-administered semiquantitative 126-item Harvard food frequency questionnaire was used to determine dietary intake in the year leading up to an examination. Levels of liver fat were assessed using liver-phantom ratio (LPR) on computed tomography images from 2002 through 2005 and again from 2008 through 2011. LPR values are inversely related to liver fat: Increased LPR indicates decreased liver fat. The authors examined associations of changes in diet scores, the Mediterranean-style diet score (MDS) and Alternative Healthy Eating Index (AHEI), with changes in liver fat and new-onset fatty liver. They evaluated interactions between diet score change and a weighted genetic risk score for NAFLD, determined based on multiple single-nucleotide polymorphisms identified in genome-wide association studies of NAFLD. The primary outcome was change in LPR between baseline and follow-up measurement.

Results: For each 1 standard deviation increase in MDS, the LPR increased (mean liver fat decreased by 0.57 [95% confidence interval [CI]: 0.27–0.86; p < 0.001] and the odds for incident fatty liver decreased by 26% [95% CI: 10–39%; p = 0.002]. For each 1 standard deviation increase in AHEI, LPR increased by 0.56 (95% CI: 0.29–0.84; p < 0.001) and the odds for incident fatty liver decreased by 21% (95% CI: 5–35%; p = 0.02). Increased diet scores were also associated with reduced odds of developing more-advanced fatty liver. Higher genetic risk scores were associated with increased liver fat accumulation in participants who had decreased MDS (p < 0.001) or AHEI scores (p = 0.001), but not in those with stable or improved diet scores (p for gene-diet interaction < 0.001).

Conclusions: In an analysis of participants in the Framingham Heart Study, increasing diet quality, determined based Mediterranean-style diet score and Alternative Healthy Eating Index, is associated with less liver fat accumulation and reduced risk for new-onset fatty liver. An improved diet is particularly important for individuals with a high genetic risk for non-alcoholic fatty liver disease.
with non-drinkers. The authors collected data from adult participants in the Nonalcoholic Steatohepatitis (NASH) Clinical Research Network to evaluate the longitudinal association between modest use of alcohol and histology findings in patients with NAFLD, using paired liver biopsies collected more than 1 year apart.

Methods: They studied NASH Clinical Research Network participants 21 years or older, not receiving pharmacologic therapy, from whom ≥ 2 liver biopsies and data on alcohol use within 2 years of the initial biopsy were available. Alcohol consumption was evaluated at study entry using the Alcohol Use Disorders Identification Test and Skinner Lifetime Drinking History questionnaires. At each follow-up visit participants were asked about alcohol use frequency, number of drinks on a typical day, and frequency of heavy drinking. The association between baseline drinking status and changes in fibrosis stage, NASH histology, and the NAFLD Activity Score and its individual components were evaluated by analysis of covariance. The association between change in drinking status and change in histology was evaluated using adjusted logistic regression.

Results: Of 285 participants (82% white, 70% female, mean age, 47 years) meeting entry criteria, 168 (59%) were modest alcohol users (≤ 2 drinks/day) and the remaining 117 were abstinent. At baseline, a higher proportion of modest alcohol users were white (86% vs. 76% non-white; p = 0.04) and a lower proportion of modest alcohol users were diagnosed with definite NASH (57% vs. 74% without NASH; p = 0.01). During a mean follow-up period of 47 months between biopsies, non-drinkers had a greater mean reduction in steatosis grade (reduction, 0.49) than modest drinkers (reduction, 0.30; p = 0.04) and a greater reduction in mean level of aspartate transaminase (reduction, 7 U/l vs. an increase of 2 U/l in modest drinkers; p = 0.04). Modest drinkers had significantly lower odds of NASH resolution compared with non-drinkers (adjusted odds ratio = 0.32; p = 0.04) and a greater reduction in mean level of aspartate transaminase (reduction, 0.30; p = 0.04) and a greater reduction in mean level of aspartate transaminase (reduction, 7 U/l vs. an increase of 2 U/l in modest drinkers; p = 0.04). Modest drinkers had significantly lower odds of NASH resolution compared with non-drinkers (adjusted odds ratio = 0.32, 95% confidence interval: 0.11–0.92; p = 0.04) on adjusted analysis.

Conclusions: In a longitudinal analysis of liver biopsies from patients with non-alcoholic fatty liver disease not receiving pharmacologic therapy, modest alcohol use was associated with less improvement in steatosis and level of aspartate transaminase, as well as lower odds of non-alcoholic steato-hepatitis resolution, compared with no use of alcohol.

V. Ajmera, M.D., Assistant Professor of Medicine, University of California San Diego, 9500 Gilman Drive MC 0887, La Jolla, CA 92093, USA, E-Mail: v1ajmera@ucsd.edu


Inotersen treatment for patients with hereditary transthyretin amyloidosis

Background: Hereditary transthyretin amyloidosis is caused by pathogenic single-nucleotide variants in the gene encoding transthyretin (TTR) that induce transthyretin misfolding and systemic deposition of amyloid. Progressive amyloid accumulation leads to multiorgan dysfunction and death. Inotersen, a Z’-O-methoxymethyl-modified antisense oligonucleotide, inhibits hepatic production of transthyretin.

Methods: The authors conducted an international, randomized, double-blind, placebo-controlled, 15-month, phase 3 trial of inotersen in adults with stage 1 (patient is ambulatory) or stage 2 (patient is ambulatory with assistance) hereditary transthyretin amyloidosis with polyneuropathy. Patients were randomly assigned, in a 2:1 ratio, to receive weekly subcutaneous injections of inotersen (300 mg) or placebo. The primary end points were the change in the modified Neuropathy Impairment Score+7 (mNIS+7; range -22.3–346.3, with higher scores indicating poorer function; minimal clinically meaningful change, 2 points) and the change in the score on the patient-reported Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire (range, -4–136, with higher scores indicating poorer quality of life). A decrease in scores indicated improvement.

Results: A total of 172 patients (112 in the inotersen group and 60 in the placebo group) received at least 1 dose of a trial regimen, and 139 (81%) completed the intervention period. Both primary efficacy assessments favored inotersen: The difference in the least-squares mean change from baseline to week 66 between the 2 groups (inotersen minus placebo) was -19.7 points (95% confidence interval [CI]: -26.4 to -13.0; p < 0.001) for the mNIS+7 and -17.0 points (95% CI: -18.3 to -5.1; p < 0.001) for the Norfolk QOL-DN score. These improvements were independent of disease stage, mutation type, or the presence of cardiomyopathy. There were 5 deaths in the inotersen group and none in the placebo group. The most frequent serious adverse events in the inotersen group were glomerulonephritis (in 3 patients [3%]) and thrombocytopenia (in 3 patients [3%]), with 1 death associated with 1 of the cases of grade 4 thrombocytopenia. Thereafter, all patients received enhanced monitoring.

Conclusions: Inotersen improved the course of neurologic disease and quality of life in patients with hereditary transthyretin amyloidosis. Thrombocytopenia and glomerulonephritis were managed with enhanced monitoring.

Dr. T. Coelho, Hospital de Santo António – Centro Hospitalar do Porto, Largo Professor Abel Salazar, 4099-001 Porto, Portugal, E-Mail: tcoelho@netcabo.pt


Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis

Background: Patisiran, an investigational RNA interference therapeutic agent, specifically inhibits hepatic synthesis of transthyretin.

Methods: In this phase 3 trial, the authors randomly assigned patients with hereditary transthyretin amyloidosis with polyneu-
Autoimmune hepatitis (AIH) can present under clinical profile as acute hepatitis of unexplained cause. The authors analyzed clinical, therapeutic and prognostic implications of AIH presenting as acute hepatitis in a cohort of patients admitted to 3 referral centers in Italy. AIH onset was considered acute when transaminases were > 10 times the normal limit and/or bilirubin > 5 mg/ml (irrespectively from the histology, available only in 62% of cases). Among 479 patients diagnosed as AIH, 202 (43%) met the criteria of acute onset. This former group of patients on the basis of the histology has been subdivided in the “genuine” acute onset (83 patients) and acute-“on-chronic” onset (45 patients). At onset, clinical acute AIH showed significantly higher alanine aminotransferase (ALT), bilirubin and international normalized ratio (INR) levels (p < 0.001 for all), lower albumin values (p = 0.001), similar immunoglobulin G levels; response to treatment was similar between the 2 groups. The progression to liver cirrhosis or its complications was significantly less frequent in acute onset AIH (13% vs. 22%, p = 0.02). The “genuine” acute patients showed higher albumin serum levels (40 vs. 36, p = 0.001), lower INR levels (1.12 vs. 1.26, p = 0.002) and less tendency to the progression of liver disease (7% vs. 12%, p = n.s.) with respect to acute-“on-chronic” onset patients.

Clinical acute hepatitis represents a common presentation of autoimmune hepatitis, responds to standard immunosuppression regimen and seems to be correlated with a better long-term prognosis.

Pro. Dr. P. Muratori, Department of Medical and Surgical Sciences, University of Bologna, S. Orsola-Malpighi, University Hospital, Via Massarenti, 9, 40138 Bologna, Italy, E-Mail: paolo.muratori3@unibo.it

**AIH/PBC/PSC**


Clinical and prognostic implications of acute onset of autoimmune hepatitis: An Italian multicenter study

Autoimmune hepatitis (AIH) can present under clinical profile as acute hepatitis of unexplained cause. The authors analyzed clinical, therapeutic and prognostic implications of AIH presenting as acute hepatitis in a cohort of patients admitted to 3 referral centers in Italy. AIH onset was considered acute when...
and treated with UDCA in Italy. Additionally, they assessed correlations between model predictions and key histological features, such as biliary injury and fibrosis, on liver biopsy samples.

**Findings:** 2703 participants diagnosed with PBC between January 1, 1998, and May 31, 2015, were included in the UK-PBC cohort for derivation of the model. The following pretreatment parameters were associated with lower probability of UDCA response: higher alkaline phosphatase concentration (p < 0.0001), higher total bilirubin concentration (p = 0.0003), lower albumin concentration (p = 0.0012), younger age (p < 0.0001), longer interval from diagnosis to the start of UDCA treatment (treatment time lag, p < 0.0001), and worsening of alkaline phosphatase concentration from diagnosis (p < 0.0001). Based on these variables, the authors derived a predictive score of UDCA response. In the external validation cohort, 460 patients diagnosed with PBC were treated with UDCA, with follow-up data until May 31, 2016. In this validation cohort, the area under the receiver-operating characteristic curve (AUROC) for the score was 0.83 (95% confidence interval: 0.79–0.87). In 20 liver biopsy samples from patients with PBC, the UDCA response score was associated with ductular reaction (r = -0.556, p = 0.0130) and intermediate hepatocytes (probability of response was 0.90 if intermediate hepatocytes were absent vs. 0.51 if present).

**Interpretation:** The authors have derived and externally validated a model based on pretreatment variables that accurately predicts ursodeoxycholic acid response. Association with histological features provides face validity. This model provides a basis to explore alternative approaches to treatment stratification in patients with primary biliary cholangitis.

Dr. M. Carbone, Division of Gastroenterology and Hepatology, Department of Medicine and Surgery, University of Milan Bicocca, 20126 Milan, Italy, E-Mail: marco.carbone@unimib.it

**Liver Cirrhosis**

*Lancet. 2018;391(10138):2417–29*


**Long-term albumin administration in decompensated cirrhosis (ANSWER): An open-label randomized trial**

**Background:** Evidence is scarce on the efficacy of long-term human albumin (HA) administration in patients with decompensated cirrhosis. The human Albumin for the treatment of ascites in patients with Hepatic cirrhosis (ANSWER) study was designed to clarify this issue.

**Methods:** The authors did an investigator-initiated multicenter randomized, parallel, open-label, pragmatic trial in 33 academic and non-academic Italian hospitals. They randomly assigned patients with cirrhosis and uncomplicated ascites who were treated with anti-aldosterone drugs (≥ 200 mg/day) and furosemide (≥ 25 mg/day) to receive either standard medical treatment (SMT) or SMT plus HA (40 g twice weekly for 2 weeks, and then 40 g weekly) for up to 18 months. The primary end point was 18-month mortality, evaluated as difference of events and analysis of survival time in patients included in the modified intention-to-treat and per-protocol populations.

**Findings:** From April 2, 2011, to May 27, 2015, 440 patients were randomly assigned and 431 were included in the modified intention-to-treat analysis. 38 of 218 patients died in the SMT plus HA group and 46 of 213 in the SMT group. Overall 18-month survival was significantly higher in the SMT plus HA than in the SMT group (Kaplan-Meier estimates 77% vs. 66%; p = 0.028), resulting in a 38% reduction in the mortality hazard ratio (0.62; 95% CI: 0.40–0.95). 46 patients (22%) in the SMT group and 49 (22%) in the SMT plus HA group had grade 3–4 non-liver related adverse events.

**Interpretation:** In this trial, long-term human albumin administration prolongs overall survival and might act as a disease modifying treatment in patients with decompensated cirrhosis.

Prof. Dr. M. Bernardi, Department of Medical and Surgical Sciences, University of Bologna, S. Orsola-Malpighi, University Hospital, via Massarenti, 9, 40138 Bologna, Italy, E-Mail: mauro.bernardi@unibo.it

**J Hepatol. 2018;69(3):697–704**

Otete H, Deleuran T, Fleming KM, Card T, Aithal GP, Jepsen P, West J

**Hip fracture risk in patients with alcoholic cirrhosis: A population-based study using English and Danish data**

**Background and aims:** Cirrhosis, the prevalence of which is increasing, is a risk factor for osteoporosis and fractures. However, little is known of the actual risk of hip fractures in patients with alcoholic cirrhosis. Using linked primary and secondary care data from the English and Danish nationwide registries, the authors quantified the hip fracture risk in 2 national cohorts of patients with alcoholic cirrhosis.

**Methods:** They followed 3706 English and 17,779 Danish patients with a diagnosis of alcoholic cirrhosis and identified matched controls from the general populations. They estimated hazard ratios (HR) of hip fracture for patients versus controls, adjusted for age, sex and comorbidity.

**Results:** The 5-year hip fracture risk was raised both in England (2.9% vs. 0.8% for controls) and Denmark (4.6% vs. 0.9% for controls). With confounder adjustment, patients with cirrhosis had 5-fold (adjusted hazard ratio [aHR] = 5.5; 95% confidence interval [CI]: 4.3–6.9), and 8.5-fold (aHR = 8.5; 95% CI: 7.8–9.3) increased rates of hip fracture, in England and Denmark, respectively. This association between alcoholic cirrhosis and risk of hip fracture showed significant interaction with age (p < 0.001), being stronger in younger age groups (< 45 years, HR = 17.9 and 16.6 for English and Danish patients, respectively) than in patients > 75 years (HR = 2.1 and 2.9, respectively). In patients with alcoholic cir-
rhosis, 30-day mortality following a hip fracture was 11.1% in England and 10.0% in Denmark, giving age-adjusted post-fracture mortality rate ratios of 2.8 (95% CI: 1.9–3.9) and 2.0 (95% CI: 1.5–2.7), respectively.

Conclusions: Patients with alcoholic cirrhosis have a markedly increased risk of hip fracture and post-hip fracture mortality compared with the general population. These findings support the need for more effort towards fracture prevention in this population, to benefit individuals and reduce the societal burden.

Dr. H. Otete, University of Central Lancashire School of Medicine, Harrington Building 242, Fylde Road, Preston PR1 2HE, UK, E-Mail: hotete@uclan.ac.uk

Dose-dependent impact of proton-pump inhibitors on the clinical course of spontaneous bacterial peritonitis

Background and aims: Spontaneous bacterial peritonitis (SBP) is a severe complication in patients with cirrhosis leading to acute kidney injury (AKI), hepatic encephalopathy (HE) and a high mortality. In this study, the authors aimed to investigate the impact of proton-pump inhibitors (PPIs) and the potential relevance of the taken dosage on the incidence and clinical course of SBP.

Methods: Overall, 613 consecutive patients with decompensated cirrhosis were included. All patients were carefully evaluated for PPI intake including the applied dosage and were further followed up for SBP development as well as for the incidence of clinical complications like HE, AKI, and mortality.

Results: Cumulative SBP incidence did neither differ between the PPI and the no-PPI group nor between those taking the high (> 40 mg/day) and the low (10–40 mg/day) PPI dose. However, PPI intake was associated with an impaired clinical course of SBP reflected by a higher likelihood for AKI (71% vs. 43%; p = 0.002), severe HE (15% vs. 0%; p = 0.04) and an increased mortality (24% vs. 0%; p = 0.008) within 28 days after SBP diagnosis. In particular, patients with PPI dosages > 40 mg/day had an increased short-term risk for AKI (adjusted hazard ratio [aHR] = 1.86; p = 0.009) and mortality (aHR = 2.05; p = 0.02). In contrast, there was no effect of PPIs on AKI, HE and mortality in patients without SBP irrespective of the applied PPI dosage.

Conclusions: High dosages of proton-pump inhibitors (PPIs) are associated with an adverse outcome in patients with spontaneous bacterial peritonitis. Thus, indication for high-dosage PPI therapy should be evaluated carefully in these patients.

Dr. B. Maasoumy, Klinik für Gastroenterologie, Hepatologie und Endokrinologie, Medizinische Hochschule Hannover, Carl-Neuberg-Str. 1, 30625 Hannover, Germany, E-Mail: maasoumy.benjamin@mh-hannover.de

Liver Int. 2018;38(9):1602–13


Fractional excretion of urea: A simple tool for the differential diagnosis of acute kidney injury in cirrhosis

Current approaches to determine the cause of acute kidney injury (AKI) in patients with cirrhosis are suboptimal. The aim of this study was to determine the utility of fractional excretion of urea (FEUrea) for the differential diagnosis of AKI in patients with cirrhosis. A retrospective analysis was performed in patients (n = 50) with cirrhosis and ascites admitted with AKI. Using adjudicated etiology assessment as the reference standard, receiver-operating curves and optimal cutoff, sensitivity (Sn), and specificity (Sp) for the diagnosis of prerenal azotemia (PRA), type 1 hepatorenal syndrome (HRS), and acute tubular necrosis (ATN) were derived. Validation was performed in an independent cohort (n = 50) and by bootstrap analysis. The causes of AKI (derivation/validation cohorts) were: PRA 21:21, HRS 18:15, and ATN 11:14. Median FEUrea was statistically different across all etiologies of AKI in the derivation cohort (PRA 30.1 vs. HRS 20.2 vs. ATN 43.6; p < 0.001) and validation cohort (PRA 23.1 vs. HRS 13.3 vs. ATN 44.7; p < 0.001). The area underneath the curve (cutoff, Sn/Sp) for FEUrea was 0.96 (33.4, 85/100) for ATN versus non-ATN, 0.87 (28.7, 75/83) for HRS versus non-HRS, and 0.81 (21.6, 90/61) for PRA versus HRS. When applied to the validation cohort, Sn/Sp were maintained for ATN versus non-ATN (93/97), HRS versus non-HRS (100/63), and for PRA versus HRS (67/80). After bootstrapping, Sn/Sp for FEUrea in ATN versus non-ATN, HRS versus non-HRS, and PRA versus HRS was 88/96, 63/97, and 55/87, respectively.

Conclusion: Fractional excretion of urea is a promising tool for the differential diagnosis of acute kidney injury in patients with cirrhosis.

K.R. Patidar, M.D., Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University, 1200 East Broad Street, P.O. Box 98034, Richmond, VA 23298-0341, USA, E-Mail: kavish.patidar@vcuhealth.org

Hepatol. 2018;68(1):224–33

Patidar KR, Kang L, Bajaj JS, Carl D, Sanyal AJ
Low molecular weight heparin does not increase bleeding and mortality after endoscopic variceal band ligation in cirrhotic patients

Background and aims: Anticoagulants are commonly indicated in cirrhotic patients due to high rates of (pro)thrombotic conditions. Low molecular weight heparin (LMWH) is safe in patients with esophageal varices. However, the safety of LMWH is unknown in patients undergoing prophylactic endoscopic variceal ligation (EVL). The aim of this study was to define the 4-week risk of bleeding and death after prophylactic EVL in cirrhotic patients continuously treated with LMWH.

Methods: All EVLs performed at a tertiary Italian Center from 2009 to 2016 were retrospectively reviewed. Patients treated with LMWH were classified as on-LMWH, the remaining as no-LMWH. Endoscopic characteristics at first and index EVL (that preceding an endoscopy either showing a bleeding episode or the absence of further treatable varices) and clinical events within 4 weeks from EVL were recorded.

Results: 553 EVLs were performed in 265 patients (in 215 as a primary prophylaxis): 169 EVLs in 80 on-LMWH and 384 in 185 no-LMWH. The median age, 63 years, range 34–81) were analyzed. All patients were followed up for a median time of 96 months (range 21–144) through periodically performed clinical/biochemical/ultrasonographic and esophagogastroduodenoscopic examinations.

Results: During the follow-up, 97 individuals (36%) were clinically stable, 104 (38%) developed hepatocellular carcinoma (HCC) and 71 (26%) progressed towards C-P class B/C without developing cancer. 131 patients (48%) died or underwent liver transplantation. Multivariate regression analysis showed that clinical stability was significantly associated with older age (p < 0.001), the absence of diabetes (p = 0.04) and of esophageal varices (p < 0.001), serum albumin > 3.5 g/dl (p = 0.01) and gamma globulin < 1.8 g/dl (p = 0.01). HCC development was significantly associated with younger age (p = 0.01) and serum gamma globulin values ≥ 1.8 g/dl (p < 0.001). C-P score progression was associated with esophageal varices (p < 0.001), lower serum albumin (p = 0.03) and cholesterol (p = 0.01) values, and hypergammaglobulinemia (p = 0.02). Death was associated with younger age (p < 0.001) and hypergammaglobulinemia (p = 0.01). Multivariate Cox regression analysis and Kaplan-Meier’s survival test confirmed that gammaglobulinemia ≥ 1.8 g/dl was a significant predictor of death (p < 0.02, and p < 0.01 respectively).

Conclusions: Hypergammaglobulinemia identifies Child-Pugh class A cirrhotic patients at higher risk of disease progression, development of hepatocellular carcinoma and death.

Dr. I. Cacciola, Division of Clinical and Molecular Hepatology, University Hospital of Messina, Piazza Pugliatti, 1, 98122 Messina, Italy, E-Mail: icacciola@unime.it

Clinical Hepatology, Miscellaneous

Polycystic liver disease: Hepatic venous outflow obstruction lesions of the non-cystic parenchyma have major consequences

In patients with polycystic liver disease (PLD), development of cysts induces hepatic venous outflow obstruction (HVVOO) and parenchymal modifications, challenging the paradigm of a normal non-cystic liver parenchyma. The aims were to reappraise the pathology of the non-cystic parenchyma, by focusing on HVVOO lesions, and to investigate the association with outflow obstruction at imaging and perioperative course after liver resection. This is a retrospective study conducted in 1 tertiary center between 1993 and 2014. PLD patients (n = 125) who underwent resection (n = 90) or transplantation (n = 35) were included.
Conclusion: Apart from a moderately increased risk of preterm birth and small for gestational age, there was no association between liver biopsy during pregnancy and adverse pregnancy outcome; potential excess risks should be weighed against the advantages of having a liver biopsy that may influence clinical management of the patient and indirectly fetal health.

Prof. Dr. J.F. Ludvigsson, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, PO. Box 281, 171 77 Stockholm, Sweden, E-Mail: jonas.ludvigsson@ki.se

HCC


Cabozantinib in patients with advanced and progressing hepatocellular carcinoma

Background: Cabozantinib inhibits tyrosine kinases, including vascular endothelial growth factor receptors 1, 2, and 3, MET, and AXL, which are implicated in the progression of hepatocellular carcinoma (HCC) and the development of resistance to sorafenib, the standard initial treatment for advanced disease. This randomized, double-blind, phase 3 trial evaluated cabozantinib as compared with placebo in previously treated patients with advanced HCC.

Methods: A total of 707 patients were randomly assigned in a 2:1 ratio to receive cabozantinib (60 mg once daily) or matching placebo. Eligible patients had received previous treatment with sorafenib, had disease progression after at least 1 systemic treatment for HCC, and may have received up to 2 previous systemic regimens for advanced HCC. The primary end point was overall survival (OS). Secondary end points were progression-free survival (PFS) and the objective response rate.

Results: At the second planned interim analysis, the trial showed significantly longer OS with cabozantinib than with placebo. Median OS was 10.2 months with cabozantinib and 8.0 months with placebo (hazard ratio [HR] for death = 0.76; 95% confidence interval [CI]: 0.63–0.92; p = 0.005). Median PFS was 5.2 months with cabozantinib and 1.9 months with placebo (HR for disease progression or death = 0.44; 95% CI: 0.36–0.52; p < 0.001), and the objective response rates were 4% and < 1%, respectively (p = 0.009). Grade 3 or 4 adverse events occurred in 68% of patients in the cabozantinib group and in 36% in the placebo group. The most common high-grade events were palmar-plantar erythrodysesthesia (17% with cabozantinib vs. 0% with placebo), hypertension (16% vs. 2%), increased aspartate aminotransferase level (12% vs. 7%), fatigue (10% vs. 4%), and diarrhea (10% vs. 2%).

Conclusions: Among patients with previously treated advanced hepatocellular carcinoma, treatment with cabozantinib resulted in longer overall survival and progression-free survival than placebo. The rate of high-grade adverse events was lower with cabozantinib than with placebo.
in the cabozantinib group was approximately twice that observed in the placebo group.

G.K. Abou-Alfa, M.D., Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA, E-Mail: abou-alg@mskcc.org

Liver Transplantation

Gastroenterology. 2018;155(2):422–30.e1


Outcomes of early liver transplantation for patients with severe alcoholic hepatitis

Background and aims: The American Consortium of Early Liver Transplantation for Alcoholic Hepatitis comprises 12 centers from 8 United Network for Organ Sharing regions studying early liver transplantation (LT) (without mandated period of sobriety) for patients with severe alcoholic hepatitis (AH). The authors analyzed the outcomes of these patients.

Methods: They performed a retrospective study of consecutive patients with a diagnosis of severe AH and no prior diagnosis of liver disease or episodes of AH, who underwent LT before 6 months of abstinence from 2006 through 2017 at 12 centers. Data on baseline characteristics, psychosocial profiles, level of alcohol consumption before LT, disease course and treatment, and outcomes of LT were collected. The interval of alcohol abstinence was defined as the time between last drink and the date of LT. The primary outcomes were survival and alcohol use after LT, defined as slip or sustained.

Results: Among 147 patients with AH who received liver transplants, the median duration of abstinence before LT was 55 days; 54% received corticosteroids for AH and the patients had a median Lille score of 0.82 and a median Sodium Model for End-stage Liver Disease score of 39. Cumulative patient survival percentages after LT were 94% at 1 year (95% confidence interval [CI]: 89–97%) and 84% at 3 years (95% CI: 75–90%). Following hospital discharge after LT, 72% were abstinent, 18% had slips, and 11% had sustained alcohol use. The cumulative incidence of any alcohol use was 25% at 1 year (95% CI: 18–34%) and 34% at 3 years (95% CI: 25–44%) after LT. The cumulative incidence of sustained alcohol use was 10% at 1 year (95% CI: 6–18%) and 17% at 3 years (95% CI: 10–27%) after LT. In multivariable analysis, only younger age was associated with alcohol following LT (p = 0.01). Sustained alcohol use after LT was associated with increased risk of death (hazard ratio = 4.59; p = 0.01).

Conclusions: In a retrospective analysis of 147 patients who underwent early liver transplantation (LT; before 6 months of abstinence) for severe alcoholic hepatitis (AH), it was found that most patients survive for 1 year (94%) and 3 years (84%), similar to patients receiving liver transplants for other indications. Sustained alcohol use after LT was infrequent but associated with increased mortality. These findings support the selective use of LT as a treatment for severe AH. Prospective studies are needed to optimize selection criteria, management of patients after LT, and long-term outcomes.

Z. Li, M.D., Johns Hopkins University School of Medicine, 912 Ross Building, 720 Rutland Avenue, Baltimore, MD 21205, USA, E-Mail: zhipingli@jhmi.edu

or

N.A. Terrault, M.D., Liver Disease and Liver Transplant, University of California San Francisco, 513 Parnassus Avenue, Suite 3007, San Francisco, CA 94143, USA, E-Mail: norah.terrault@ucsf.edu
IBD: From Diagnosis to Therapy

July 5–6, 2019
St. Petersburg, Russia

Congress Venue
Park Inn by Radisson Pribaltiyskaya
14 Korablestroiteley street
199226 St. Petersburg
Russia

Scientific Organization
H. Herfarth, Chapel Hill (USA)
I. Khalif, Moscow (Russia)
W. Reinisch, Vienna (Austria)
Y. Shelygin, Moscow (Russia)
International Gastroenterological Congresses 2019

January 14–15, 2019, Paris, France
12th Paris Hepatology Conference (PHC)
International Conference on the Management of Liver Diseases
Telephone: +33 5 34452645
E-Mail: regist-phc@europa-organisation.com
Website: https://www.phc.info

January 16–18, 2019, Düsseldorf, Germany
Liver Cell Isolation and Characterisation
EASL Basic School of Hepatology
Telephone: +41 22 8070360
Telefax: +41 22 3280724
E-Mail: easloffice@easloffice.eu
Website: http://www.easleu

January 31 – February 2, 2019, Florence, Italy
ESPGHAN Monothematic Conference Hepatology: Infections of the Liver at Paediatric Age
Telephone: +41 22 5934732 or
Telephone: +41 22 5934733
E-Mail: office@espghan.org
Website: http://www.espghan.org

February 14–16, 2019, Lisbon, Portugal
HCC Summit 2019
Telephone: +41 22 8070360
Telefax: +41 22 3280724
E-Mail: hccsummit@easloffice.eu
Website: http://www.easleu/hcc2019

February 21–22, 2019, Heidelberg, Germany
Workshop
From Viral Hepatitis to Chronic Inflammation and Liver Cancer
Telephone: +49 6221 56-4569
Telefax: +49 6221 56-4570
E-Mail: ralf_bartenschlager@med.uni-heidelberg.de
Website: http://www.falk-foundation-symposia.org

February 22–23, 2019, Heidelberg, Germany
35th Annual Meeting of the German Association for the Study of the Liver (GASL)
Telephone: +49 6221 56-4569
Telefax: +49 6221 56-4570
E-Mail: ralf_bartenschlager@med.uni-heidelberg.de
Website: http://www.gasl.de

March 6–9, 2019, Copenhagen, Denmark
14th Congress of ECCO – European Crohn’s and Colitis Organisation
Inflammatory Bowel Diseases 2019
Telephone: +43 1 7102242-0
Telefax: +43 1 7102242-001
E-Mail: ecco@ecco-ibd.eu
Website: https://www.ecco-ibd.eu

March 6–9, 2019, Kuala Lumpur, Malaysia
17th Congress of Asia Pacific Federation of Coloproctology
Telephone: +6032 302 9898
E-Mail: secretariat@apfcp2019.com
Website: http://www.apfcp2019.com

March 21–24, 2019, Havana, Cuba
International Organization for the Study of Inflammatory Bowel Disease – IOIBD 2019 Meeting
Telephone: +31 35 5426745
Telefax: +31 35 5430468
Mobile: +31 624 565 410
E-Mail: ioibd@mkproducties.nl
Website: http://www.mkproducties.nl
Website: http://www.ioibd.org

March 29–30, 2019, Oxford, Great Britain
Symposium 214
Inflammatory Bowel Disease; From Pathophysiology to Personalized Medicine
Telephone: +49 9133 85-3500
Telefax: +49 9133 85-35209
E-Mail: markus.neurath@uk-erlangen.de
Website: http://falk-foundation-symposia.org

April 4–6, 2019, Prague, Czech Republic
ESGE Days 2019
Telephone: +49 89 9077936-16
Telefax: +49 89 9077936-20
E-Mail: secretariat@esgedays.org
Website: http://www.esgedays.org

April 10–14, Vienna, Austria
The International Liver Congress™ 2019
Annual Meeting of the European Association for the Study of the Liver (EASL)
Telephone: +41 22 8070360
Telefax: +41 22 3280724
E-Mail: ilc.information@easloffice.eu
Website: https://ilc-congress.eu

Imprint

Publisher: Falk Foundation e.V.
Leinenweberstr. 5
D-79108 Freiburg i. Br. (Germany)
Telephone: +49 761 1514-0, Telefax: +49 761 1514-321
E-Mail: literaturservice@falkfoundation.de
www.falkfoundation.org

Published: quarterly

Editors: PD Dr. Peter Hasselblatt, Head of the Freiburg Outpatient Clinic for Ileal Diseases, and PD Dr. Christoph Neumann-Haefelin, Head of the Freiburg Liver Center, Medical University Clinic of Freiburg, D-79106 Freiburg i. Br. (Germany)