FALK GASTRO REVIEW JOURNAL

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Leinenweberstr. 5
79108 Freiburg | Germany

01 2025

Contents

Editorial

Dear colleagues,

In this issue, you can expect some exciting changes, with new content-related focuses. Starting with this issue, Prof. Tobias Böttler, Head of the Gerok Liver Center at the University Medical Center Freiburg, will be serving as co-editor, responsible for the liver and biliary tract sections. He succeeds Prof. Christoph Neumann-Haefelin, who moved to the University Hospital of Cologne as head of the Department of Gastroenterology and Hepatology this September. In addition to offering the usual literature review, experts from our department will critically review selected studies and assess them in terms of their value for everyday practice. In order to better understand the translational therapeutic approaches of tomorrow, selected papers will also be highlighted in a "Translational Science Corner."

As usual, in this editorial we would like to draw your attention to 10 key studies:

Links between ***Helicobacter pylori*** infection and the pathogenesis of **gastric cancer** are well established. However, a large unique population-based study in China has now shown for the first time that **mass screening** for *H. pylori* infection and subsequent eradication indeed **reduces the risk of developing gastric cancer** (Pan et al., page 4). The diagnosis of celiac disease usually requires serology testing and duodenal biopsies. Recently, a subtype of celiac disease has been described in which inflammation is limited to the duodenal bulb **("ultra-short celiac disease").** In the first prospective and multicenter cohort of patients with "ultra-short celiac disease," the disease presentation was comparable to that of individuals with "conventional" celiac disease. This underlines the need for biopsies to be taken from the duodenal bulb as part of the diagnostic workup as recommended by current guidelines (Raju et al., page 3). The benefit **of stress ulcer prophylaxis with proton pump inhibitors** in ventilated patients has not been clearly demonstrated in prospective trials to date. In a large randomized trial with more than 4800 patients receiving invasive ventilatory support, significantly less gastrointestinal bleeding occurred in patients treated with pantoprazole as compared to placebo. However, mortality remained unchanged, as did the rates of ventilator-associated pneumonia or *Clostridioides difficile* infections (Cook et al., page 7).

Immune checkpoint blockade can lead to an excellent response **in colorectal cancer with mismatch repair deficiency**. In the **neoadjuvant setting**, immunotherapy with nivolumab and ipilimumab achieved a remarkable pathologic response (remaining tumor tissue < 10%) in 95% of cases and complete pathologic response rates (no more detectable tumor) in 68% of cases in a phase 2 trial (Chalabi et al., page 19). The **pathogenesis of irritable bowel syndrome** (IBS) is complex. In a large prospective and population-based British cohort study, a **healthy lifestyle** (characterized by non-smoking, optimal sleep habits, physical activity, high-quality diet, and moderate alcohol consumption) was associated with a significantly lower risk of developing IBS (Ho et al., page 18). We would also like to point out the "Translational Science Corner." A recent report based on mouse models demonstrates mechanisms of how **primary sclerosing cholangitis** may be associated with a more **favorable course of chronic inflammatory bowel disease** (Bedke et al., page 40).

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are often incidental findings in older people that result in recurrent follow-up examinations. This raises the question of the optimal age to discontinue screening. Health economic modeling suggests that screening in men may be discontinued between the ages of 76 and 78, regardless of the type of IPMN. For women, this was dependent on the size and type of IPMN (Hamada et al., page 24).

The field of **metabolic dysfunction-associated steatotic liver disease and steatohepatitis (MASLD or MASH)** is very dynamic. With regard to emerging drug therapies, GLP-1 receptor agonists, and more specifically agonists that also bind the GIP (glucose-dependent insulinotropic peptide) or glucagon receptors, appear to be promising novel therapeutic options. In two phase 2 trials, treatment with tirzepatide (Loomba et al., page 30) and survodutide (Sanyal et al., page 30) was superior to placebo therapy in terms of MASH resolution.

The efficacy of **tranexamic acid for gastrointestinal bleeding** remains controversial. In a randomized trial from India in people with liver cirrhosis, the frequency of recurrent bleeding episodes (e.g. endoscopic variceal ligation-induced ulcer bleeding) was reduced by the use of tranexamic acid (Kumar et al., page 35).

We very much hope that these new content-focused additions will appeal to you and make it easier to find the news most relevant to your daily practice. Please feel free to email us at peter.hasselblatt@uniklinik-freiburg.de or tobias.boettler@uniklinik-freiburg.de if you have any suggestions for further improvements!

Best regards,

Peter Hasselblatt and Tobias Böttler
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ESOPHAGUS TO SMALL INTESTINE

Celiac Disease, Gluten Sensitivity and Food Allergy

Gut. 2024;73(7):1124–30

Raju SA, Greenaway EA, Schiepatti A, Arpa G, Vecchione N, Jian CLA, Grobler C, Maregatti M, Green O, Bowker-Howell FJ, Shiha MG, Penny HA, Cross SS, Ciacci C, Rostami K, Ahmadipour S, Moradi A, Rostami-Nejad M, Biagi F, Volta U, Fiorentino M, Lebwohl B, Green PHR, Lewis S, Molina-Infante J, Mata-Romero P, Vaira V, Elli L, Soykan I, Ensari A, Sanders DS

New entity of adult ultra-short coeliac disease: The first international cohort and case-control study

Background: Ultra-short coeliac disease (USCD) is defined as villous atrophy only present in the duodenal bulb (D1) with concurrent positive coeliac serology. The authors present the first, multicentre, international study of patients with USCD.
Methods: Patients with USCD were identified from 10 tertiary hospitals (6 from Europe, 2 from Asia, 1 from North America and 1 from Australasia) and compared with age-matched and sex-matched patients with conventional coeliac disease.
Findings: Patients with USCD (n = 137, median age 27 years, interquartile range [IQR], 21–43 years; 73% female) were younger than those with conventional coeliac disease (27 vs. 38 years, respectively, p < 0.001). Immunoglobulin A-tissue transglutaminase (IgA-tTG) titres at index gastroscopy were lower in patients with USCD versus conventional coeliac disease (1.8 x upper limit of normal [ULN] [IQR, 1.1–5.9] vs. 12.6 x ULN [IQR, 3.3–18.3], p < 0.001). Patients with USCD had the same number of symptoms overall (median 3 [IQR, 2–4] vs. 3 [IQR, 1–4], p = 0.875). Patients with USCD experienced less iron deficiency (41.8% vs. 22.4%, p = 0.006). Both USCD and conventional coeliac disease had the same intraepithelial lymphocytes immunophenotype staining pattern; positive for CD3 and CD8, but not CD4. At follow-up having commenced a gluten-free diet (median of 1181 days, IQR, 440–2160 days) both USCD and the age-matched and sex-matched controls experienced a similar reduction in IgA-tTG titres (0.5 ULN [IQR, 0.2–1.4) vs. 0.7 ULN [IQR, 0.2–2.6], p = 0.312). 95.7% of patients with USCD reported a clinical improvement in their symptoms.

Interpretation: Patients with ultra-short coeliac disease are younger, have a similar symptomatic burden and benefit from a gluten-free diet. This study endorses the recommendation of duodenal bulb sampling as part of the endoscopic coeliac disease diagnostic work-up.

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DOI: 10.1136/gutjnl-2023-330913 ■

EXPERT OPINION

Prof. Dr. Peter Hasselblatt

Ultra-short celiac disease – a new clinical entity?

Ultra-short celiac disease describes a manifestation of celiac disease (CD) in which the inflammation and villous atrophy are confined to the duodenal bulb. This disease presentation was already described several years ago. In this publication, the authors now present data from the first multicenter patient cohort. Patients with ultra-short celiac disease were younger compared to those with conventional disease manifestation, yet their symptom severity was comparable. Serologically, the transglutaminase antibody titers were significantly lower; relevant iron deficiency was rarely observed. All patients responded very well to a gluten-free diet. It remains uncertain whether ultra-short celiac disease is a distinct disease entity or whether it is in fact a transition from potential CD (serological detection of transglutaminase antibodies without symptoms and intestinal inflammation) to conventional CD. After all, a noteworthy proportion of patients had evidence of at least lymphocellular inflammation without villous atrophy in the postbulbar duodenum. Another clinically relevant finding is the fact that almost half of patients had undergone endoscopy before being diagnosed with CD and that their diagnosis was missed because biopsies had not been taken from the duodenal bulb. Current CD guidelines recommend taking 6 biopsies from all sections of the duodenum, including the bulb. Transglutaminase antibody titers were only moderately elevated (< 10-fold) in this patient cohort, underscoring the importance of comprehensive endoscopic examination and biopsy in symptomatic individuals. However, serological testing is still underused in both individuals at risk (e.g., first-degree relatives of CD patients), and in symptomatic patients. This publication thus aims to enhance our awareness of CD diagnostics, ultimately significantly improving patient care. ■

Clin Gastroenterol Hepatol. 2024;22(7):1404–15.e20

Mårild K, Söderling J, Lebwohl B, Green PHR, Törnblom H, Simrén M, Staller K, Olén O, Ludvigsson JF

Association between celiac disease and irritable bowel syndrome: A nationwide cohort study

Background and aims: The aim of this study was to determine the risk of irritable bowel syndrome (IBS) diagnosis in patients with celiac disease compared with general population comparators.

Methods: Using Swedish histopathology and register-based data, the authors identified 27,262 patients with celiac disease diagnosed in 2002–2017 and 132,922 age- and sex-matched general population comparators. Diagnoses of IBS were obtained from nationwide inpatient and non-primary outpatient records. Cox regression estimated hazard ratios (aHRs) for IBS adjusted for education level and Charlson Comorbidity Index. To reduce potential surveillance bias their analyses considered incident IBS diagnosis ≥ 1 year after celiac disease diagnosis. Using conditional logistic regression, secondary analyses were calculated to estimate odds ratios (ORs) for IBS diagnosis ≥ 1 year before celiac disease diagnosis.
Results: During an average of 11.1 years of follow-up, 732 celiac patients (2.7%) were diagnosed with IBS versus 1131 matched general population comparators (0.9%). Overall (≥ 1 year of follow-up), the aHR for IBS was 3.11 (95% confidence interval [CI]: 2.83–3.42), with aHR of 2.00 (95% CI: 1.63–2.45) after ≥ 10 years of follow-up. Compared with siblings (n = 32,010), celiac patients (n = 19,211) had ≥ 2-fold risk of later IBS (aHR = 2.42; 95% CI: 2.08–2.82). Compared with celiac patients with mucosal healing, those with persistent villus atrophy on follow-up biopsy were less likely to be diagnosed with IBS (aHR = 0.66; 95% CI: 0.46–0.95). Celiac disease was also associated with having an earlier IBS diagnosis (OR = 3.62; 95% CI: 3.03–4.34).

Conclusions: In patients with celiac disease, the risk of irritable bowel syndrome is increased long before and after diagnosis. Clinicians should be aware of these long-term associations and their implications on patient management.

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DOI: 10.1016/j.cgh.2024.01.048

Gastritis and Helicobacter Pylori

Nat Med. 2024;30(11):3250–60

Pan KF, Li WQ, Zhang L, Liu WD, Ma JL, Zhang Y, Ulm K, Wang JX, Zhang L, Bajbouj M, Zhang LF, Li M, Vieth M, Quante M, Wang LH, Suchanek S, Mejías-Luque R, Xu HM, Fan XH, Han X, Liu ZC, Zhou T, Guan WX, Schmid RM, Gerhard M, Classen M, You WC

Gastric cancer prevention by community eradication of Helicobacter pylori: A cluster-randomized controlled trial

Gastric cancer is a leading cause of cancer-related deaths in China. Affecting more than 40% of the world's population, Helicobacter pylori is a major risk factor for gastric cancer. While previous clinical trials indicated that eradication of H. pylori could reduce gastric cancer risk, this remains to be shown using a population-based approach. The authors conducted a community-based, cluster-randomized, controlled, superiority intervention trial in Linqu County, China, with individuals who tested positive for H. pylori using a ^{13}C-urea breath test randomly assigned to receiving either (1) a 10-day, quadruple anti-H. pylori treatment (comprising 20 mg of omeprazole, 750 mg of tetracycline, 400 mg of metronidazole and 300 mg of bismuth citrate) or (2) symptom alleviation treatment with a single daily dosage of omeprazole and bismuth citrate. H. pylori-negative individuals did not receive any treatment. The incidence of gastric cancer was examined as the primary outcome. A total of 180,284 eligible participants from 980 villages were enrolled over 11.8 years of follow-up, and a total of 1035 cases of incident gastric cancer were documented. Individuals receiving anti-H. pylori therapy showed a modest reduction in gastric cancer incidence in intention-to-treat analyses (hazard ratio [HR] = 0.86, 95% confidence interval [CI]: 0.74–0.99), with a stronger effect observed for those having successful H. pylori eradication (HR = 0.81, 95% CI: 0.69–0.96) than for those who failed treatment. Moderate adverse effects were reported in 1345 participants during the 10-day treatment. The authors observed no severe intolerable adverse events during either treatment or follow-up.

These findings suggest the potential for Helicobacter pylori mass screening and eradication as a public health policy for gastric cancer prevention.

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DOI: 10.1038/s41591-024-03153-w

Gastroenterology. 2024;167(3):485–92.e3

Wiklund AK, Santoni G, Yan J, Radkiewicz C, Xie S, Birgisson H, Ness-Jensen E, von Euler-Chelpin M, Kauppila JH, Lagergren J

Risk of esophageal adenocarcinoma after Helicobacter pylori eradication treatment in a population-based multinational cohort study

Background and aims: Helicobacter pylori infection is associated with a decreased risk of esophageal adenocarcinoma, and the decreasing prevalence of such infection might contribute to the increasing incidence of this tumor. The authors examined the hypothesis that eradication treatment of H. pylori increases the risk of esophageal adenocarcinoma.
Methods: This population-based multinational cohort, entitled "Nordic Helicobacter Pylori Eradication Project"

(NordHePEP), included all adults (≥ 18 years) receiving H. pylori eradication treatment from 1995–2018 in any of the 5 Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) with follow-up throughout 2019. Data came from national registers. Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) were calculated by dividing the cancer incidence in the exposed cohort by that of the entire Nordic background populations of the corresponding age, sex, calendar period, and country. Analyses were stratified by factors associated with esophageal adenocarcinoma (i.e., education, comorbidity, gastroesophageal reflux, and certain medications).
Results: Among 661,987 participants who contributed 5,495,552 person-years after eradication treatment (median follow-up, 7.8 years; range, 1–24 years), 550 cases of esophageal adenocarcinoma developed. The overall SIR of esophageal adenocarcinoma was not increased (SIR = 0.89; 95% CI: 0.82–0.97). The SIR did not increase over time after eradication treatment, but rather decreased and was 0.73 (95% CI: 0.61–0.86) at 11–24 years after treatment. There were no major differences in the stratified analyses. The overall SIR of esophageal squamous cell carcinoma, calculated for comparison, showed no association (SIR = 0.99; 95% CI: 0.89–1.11).

Conclusions: This absence on an increased risk of esophageal adenocarcinoma after eradication treatment of Helicobacter pylori suggests eradication is safe from a cancer perspective.

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DOI: 10.1053/j.gastro.2024.03.016

Gut. 2024;73(9):1414–20

Gao W, Liu J, Wang X, Li J, Zhang X, Ye H, Li J, Dong X, Liu B, Wang C, Xu Y, Teng G, Tian Y, Dong J, Ge C, Cheng H

Simplified Helicobacter pylori therapy for patients with penicillin allergy: A randomised controlled trial of vonoprazan-tetracycline dual therapy

Background and aims: This study aimed to evaluate the efficacy and safety of vonoprazan and tetracycline (VT) dual therapy as first-line treatment for Helicobacter pylori infection in patients with penicillin allergy.
Methods: In this randomised controlled trial, treatment-naive adults with H. pylori infection and penicillin allergy were randomised 1:1 to receive either open-label VT dual therapy (vonoprazan 20 mg 2 times per day + tetracycline 500 mg 3 times a day) or bismuth quadruple therapy (BQT; lansoprazole 30 mg 2 times per day + colloidal bismuth 150 mg 3 times a day + tetracycline 500 mg 3 times a day + metronidazole 400 mg 3 times a day) for 14 days. The primary outcome was non-inferiority in eradication rates in the VT dual group compared with the BQT group. Secondary outcomes included assessing adverse effects.
Results: 300 patients were randomised. The eradication rates in the VT group and the BQT group were: 92.0% (138/150, 95% confidence interval [CI]: 86.1–95.6%) and 89.3% (134/150, 95% CI: 83.0–93.6%) in intention-to-treat analysis (difference 2.7%; 95% CI: -4.6–10.0%; non-inferiority p = 0.000); 94.5% (138/146, 95% CI: 89.1–97.4%) and 93.1% (134/144, 95% CI: 87.3–96.4%) in modified intention-to-treat analysis (difference 1.5%; 95% CI: -4.9–8.0%; non-inferiority p = 0.001); 95.1% (135/142, 95% CI: 89.7–97.8%) and 97.7% (128/131, 95% CI: 92.9–99.4%) in per-protocol analysis (difference 2.6%; 95% CI: -2.9–8.3%; non-inferiority p = 0.000). The treatment-emergent adverse events (TEAEs) were significantly lower in the VT group (14.0% vs. 48.0%, p = 0.000), with fewer treatment discontinuations due to TEAEs (2.0% vs. 8.7%, p = 0.010).

Conclusions: Vonoprazan and tetracycline dual therapy demonstrated efficacy and safety as a first-line treatment for Helicobacter pylori infection in the penicillin-allergic population, with comparable efficacy and a lower incidence of treatment-emergent adverse events compared with traditional bismuth quadruple therapy.

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DOI: 10.1136/gutjnl-2024-332640

EoE

N Engl J Med. 2024;390(24):2239–51

Chehade M, Dellon ES, Spergel JM, Collins MH, Rothenberg ME, Pesek RD, Hirano I, Liu R, Laws E, Mortensen E, Martincova R, Shabbir A, McCann E, Kamal MA, Kosloski MP, Hamilton JD, Samuely C, Lim WK, Wipperman MF, Farrell A, Patel N, Yancopoulos GD, Glotfelty L, Maloney J

Dupilumab for eosinophilic esophagitis in patients 1–11 years of age

Background: Dupilumab is a human monoclonal antibody that blocks interleukin-4 and interleukin-13 pathways and has shown efficacy in 5 different atopic diseases marked by type-2 inflammation, including eosinophilic esophagitis in adults and adolescents.
Methods: In this phase 3 trial, the authors randomly assigned, in a 2:2:1:1 ratio, patients 1–11 years of age with active eosinophilic esophagitis who had had no response to proton-pump inhibitors to 16 weeks of a higher-exposure or lower-exposure subcutaneous dupilumab regimen or to placebo (2 groups) (Part A). At the end of Part A, eligible patients in each dupilumab group continued the same regimen and those in the placebo groups were assigned to higher-exposure or lower-exposure dupilumab for 36 weeks (Part B). At each level of exposure, dupilumab was administered in 1 of 4 doses tiered according to baseline body weight. The primary end point was histologic remission (peak esophageal intraepithelial eosinophil count, ≤ 6 per high-power field) at week 16. Key secondary end points were tested hierarchically.
Results: In Part A, histologic remission occurred in 25 of the 37 patients (68%) in the higher-exposure group, in 18 of the 31 patients (58%) in the lower-exposure group, and in 1 of the 34 patients (3%) in the placebo

group (difference between the higher-exposure regimen and placebo, 65 percentage points [95% confidence interval {CI}: 48–81; p < 0.001]; difference between the lower-exposure regimen and placebo, 55 percentage points [95% CI: 37–73; p < 0.001]). The higher-exposure dupilumab regimen led to significant improvements in histologic, endoscopic, and transcriptomic measures as compared with placebo. The improvements in histologic, endoscopic, and transcriptomic measures between baseline and week 52 in all the patients were generally similar to the improvements between baseline and week 16 in the patients who received dupilumab in Part A. In Part A, the incidence of coronavirus disease 2019, nausea, injection-site pain, and headache was at least 10 percentage points higher among the patients who received dupilumab (at either dose) than among those who received placebo. Serious adverse events were reported in 3 patients who received dupilumab during Part A and in 6 patients overall during Part B.

Conclusions: Dupilumab resulted in histologic remission in a significantly higher percentage of children with eosinophilic esophagitis than placebo. The higher-exposure dupilumab regimen also led to improvements in measures of key secondary end points as compared with placebo.

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DOI: 10.1056/nejmoa2312282 ■

N Engl J Med. 2024;390(24):2252–63

Rothenberg ME, Dellon ES, Collins MH, Bredenoord AJ, Hirano I, Peterson KA, Brooks L, Caldwell JM, Fjällbrant H, Grindebacke H, Ho CN, Keith M, McCrae C, Sinibaldi D, White WI, Datto CJ; MESSINA Trial Investigators

Eosinophil depletion with benralizumab for eosinophilic esophagitis

Background: Benralizumab is an eosinophil-depleting anti-interleukin-5 receptor α monoclonal antibody. The efficacy and safety of benralizumab in patients with eosinophilic esophagitis are unclear.
Methods: In a phase 3, multicenter, double-blind, randomized, placebo-controlled trial, the authors assigned patients 12–65 years of age with symptomatic and histologically active eosinophilic esophagitis in a 1:1 ratio to receive subcutaneous benralizumab (30 mg) or placebo every 4 weeks. The 2 primary efficacy end points were histologic response (≤ 6 eosinophils per high-power field) and the change from baseline in the score on the Dysphagia Symptom Questionnaire (DSQ; range, 0–84, with higher scores indicating more frequent or severe dysphagia) at week 24.
Results: A total of 211 patients underwent randomization: 104 were assigned to receive benralizumab, and 107 were assigned to receive placebo. At week 24, more patients had a histologic response with benralizumab than with placebo (87.4% vs. 6.5%; difference, 80.8 percentage points; 95% confidence interval [CI]: 72.9–88.8; p < 0.001). However, the change from baseline in the DSQ score did not differ significantly between the 2 groups (difference in least-squares means, 3.0 points; 95% CI: -1.4–7.4; p = 0.18). There was no substantial between-group difference in the change from baseline in the Eosinophilic Esophagitis Endoscopic Reference Score, which reflects endoscopic abnormalities. Adverse events were reported in 64.1% of the patients in the benralizumab group and in 61.7% of those in the placebo group. No patients discontinued the trial because of adverse events.

Conclusions: In this trial involving patients 12–65 years of age with eosinophilic esophagitis, a histologic response (≤ 6 eosinophils per high-power field) occurred in significantly more patients in the benralizumab group than in the placebo group. However, treatment with benralizumab did not result in fewer or less severe dysphagia symptoms than placebo.

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DOI: 10.1056/nejmoa2313318 ■

Am J Gastroenterol. 2024;119(6):1066–73

Lim AHW, Ngoi B, Perkins GB, Wong S, Whitelock G, Hurtado P, Ruszkiewicz A, Le TA, Hissaria P, Nguyen NQ

Outcomes of serum food-specific immunoglobulin G4 to guide elimination diet in patients with eosinophilic esophagitis

Introduction: Eosinophilic esophagitis (EoE) is associated with atopy; however, recent studies have identified an association with food-specific immunoglobulin G4 (FS-IgG4) rather than immunoglobulin E antibodies. This study aimed to evaluate the role of serum FS-IgG4 in guiding an elimination diet and its outcomes.
Methods: Patients with and without EoE were enrolled in a prospective, controlled, single tertiary center trial. Serum FS-IgG4 titers, esophageal eosinophil counts, and dysphagia symptom questionnaire scores were assessed, and participants with elevated FS-IgG4 (cutoff of 10 mgA/L) commenced 6-week targeted elimination diet. Repeat serum FS-IgG4 and endoscopic and histologic examination were performed at 6-week follow-up.
Results: 22 patients with active EoE and 13 controls were recruited. Serum FS-IgG4 to milk, wheat, soy, eggs, and nuts was significantly higher in EoE (p = 0.0002, p = 0.002, p = 0.003, p = 0.012, and p < 0.001, respectively). Elevated serum FS-IgG4 to 1 or more food groups (median 2) was identified in 21 of 22 patients (95.4%) with EoE; 20 of 21 underwent 6-week dietary elimination. Median reductions in Dysphagia Symptom Questionnaire score and Eosinophilic Esophagitis Endoscopic Reference Score after elimination were 8 (p = 0.0007) and 1 (p = 0.002), respectively. Nine patients (45%) had histological remission (< 15 eosinophils per high-power field). Fall in median esophageal eosinophil count was not statistically significant (50 vs. 23; p = 0.068). Serum FS-IgG4 did not decline by 6-week follow-up.

Discussion: Serum food-specific immunoglobulin G4 (FS-IgG4) to milk, wheat, soy, egg, and nuts was present at higher levels in eosinophilic esophagitis (EoE), with targeted elimination resulting in 45% histologic remission rate. Serum FS-IgG4 has potential as

a non-invasive biomarker in EoE. When successful, FS-IgG4-led elimination diet can negate need for medications and be viewed more favorably by patients because of its smaller endoscopic burden compared with empirical elimination diets.

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DOI: 10.14309/ajg.0000000000002678

Conclusions: Among patients undergoing invasive ventilation, pantoprazole resulted in a significantly lower risk of clinically important upper gastrointestinal bleeding than placebo, with no significant effect on mortality.

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DOI: 10.1056/nejmoa2404245

Upper and Middle Gastrointestinal Bleeding

N Engl J Med. 2024;391(1):9–20

Cook D, Deane A, Lauzier F, Zytaruk N, Guyatt G, Saunders L, Hardie M, Heels-Ansdell D, Alhazzani W, Marshall J, Muscedere J, Myburgh J, English S, Arabi YM, Ostermann M, Knowles S, Hammond N, Byrne KM, Chapman M, Venkatesh B, Young P, Rajbhandari D, Poole A, Al-Fares A, Reis G, Johnson D, Iqbal M, Hall R, Meade M, Hand L, Duan E, Clarke F, Dionne JC, Tsang JLY, Rochwerg B, Karachi T, Lamontagne F, D'Aragon F, St. Arnaud C, Reeve B, Geagea A, Niven D, Vazquez-Grande G, Zarychanski R, Ovakim D, Wood G, Burns KEA, Goffi A, Wilcox ME, Henderson W, Forrest D, Fowler R, Adhikari NKJ, Ball I, Mele T, Binnie A, Trop S, Mehta S, Morgan I, Loubani O, Vanstone M, Fiest K, Charbonney E, Cavayas YA, Archambault P, Rewa OG, Lau V, Kristof AS, Khwaja K, Williamson D, Kanji S, Sy E, Dennis B, Reynolds S, Marquis F, Lellouche F, Rahman A, Hosek P, Barletta JF, Cirrone R, Tutschka M, Xie F, Billot L, Thabane L, Finfer S; REVISE Investigators

Stress ulcer prophylaxis during invasive mechanical ventilation

Background: Whether proton-pump inhibitors are beneficial or harmful for stress ulcer prophylaxis in critically ill patients undergoing invasive ventilation is unclear.
Methods: In this international, randomized trial, the authors assigned critically ill adults who were undergoing invasive ventilation to receive intravenous pantoprazole (at a dose of 40 mg daily) or matching placebo. The primary efficacy outcome was clinically important upper gastrointestinal bleeding in the intensive care unit (ICU) at 90 days, and the primary safety outcome was death from any cause at 90 days. Multiplicity-adjusted secondary outcomes included ventilator-associated pneumonia, Clostridioides difficile infection, and patient-important bleeding.
Results: A total of 4821 patients underwent randomization in 68 ICUs. Clinically important upper gastrointestinal bleeding occurred in 25 of 2385 patients (1.0%) receiving pantoprazole and in 84 of 2377 patients (3.5%) receiving placebo (hazard ratio [HR] = 0.30; 95% confidence interval [CI]: 0.19–0.47; p < 0.001). At 90 days, death was reported in 696 of 2390 patients (29.1%) in the pantoprazole group and in 734 of 2379 patients (30.9%) in the placebo group (HR = 0.94; 95% CI: 0.85–1.04; p = 0.25). Patient-important bleeding was reduced with pantoprazole; all other secondary outcomes were similar in the 2 groups.

Barrett's Esophagus, Esophageal and Gastric Cancer

BMJ. 2024;385:e078876

Qiu MZ, Oh DY, Kato K, Arkenau T, Tabernero J, Correa MC, Zimina AV, Bai Y, Shi J, Lee KW, Wang J, Poddubskaya E, Pan H, Rha SY, Zhang R, Hirano H, Spigel D, Yamaguchi K, Chao Y, Wyrwicz L, Disel U, Cid RP, Fornaro L, Evesque L, Wang H, Xu Y, Li J, Sheng T, Yang S, Li L, Moehler M, Xu RH; RATIONALE-305 Investigators

Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced gastric or gastro-oesophageal junction adenocarcinoma: RATIONALE-305 randomised, double blind, phase 3 trial

Objective: To evaluate the efficacy and safety of tislelizumab added to chemotherapy as first-line (primary) treatment for advanced gastric or gastro-oesophageal junction adenocarcinoma compared with placebo plus chemotherapy.
Design: Randomised, double-blind, placebo-controlled, phase 3 study.
Setting: 146 medical centres across Asia, Europe, and North America, between December 13, 2018, and February 28, 2023.
Participants: 1657 patients aged ≥ 18 years with human epidermal growth factor receptor 2-negative locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma, regardless of programmed death-ligand 1 (PD-L1) expression status, who had not received systemic anticancer therapy for advanced disease.
Interventions: Patients were randomly (1:1) assigned to receive either tislelizumab 200 mg or placebo intravenously every 3 weeks in combination with chemotherapy (investigator's choice of oxaliplatin and capecitabine, or cisplatin and 5-fluorouracil) and stratified by region, PD-L1 expression, presence or absence of peritoneal metastases, and investigator's choice of chemotherapy. Treatment continued until disease progression or unacceptable toxicity.
Main outcome measures: The primary endpoint was overall survival, both in patients with a PD-L1 tumour area positivity (TAP) score of ≥ 5% and in all randomised patients. Safety was assessed in all those who received at least 1 dose of study treatment.
Results: Of 1657 patients screened between December 13, 2018, and February 9, 2021, 660 were ineligible

due to not meeting the eligibility criteria, withdrawal of consent, adverse events, or other reasons. Overall, 997 were randomly assigned to receive tislelizumab plus chemotherapy (n = 501) or placebo plus chemotherapy (n = 496). Tislelizumab plus chemotherapy showed statistically significant improvements in overall survival versus placebo plus chemotherapy in patients with a PD-L1 TAP score of ≥ 5% (median 17.2 months vs. 12.6 months; hazard ratio [HR] = 0.74 [95% confidence interval {CI}: 0.59–0.94]; p = 0.006 [interim analysis]) and in all randomised patients (median 15.0 months vs. 12.9 months; HR = 0.80 [95% CI: 0.70–0.92]; p = 0.001 [final analysis]). Grade 3 or worse treatment-related adverse events were observed in 54% (268/498) of patients in the tislelizumab plus chemotherapy arm versus 50% (246/494) in the placebo plus chemotherapy arm.

Conclusions: Tislelizumab added to chemotherapy as primary treatment for advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma provided superior overall survival with a manageable safety profile versus placebo plus chemotherapy in patients with a programmed death-ligand 1 tumour area positivity score of ≥ 5%, and in all randomised patients.

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DOI: 10.1136/bmj-2023-078876 ■

Lancet. 2024;404(10447):55–66

Kato K, Machida R, Ito Y, Daiko H, Ozawa S, Ogata T, Hara H, Kojima T, Abe T, Bamba T, Watanabe M, Kawakubo H, Shibuya Y, Tsubosa Y, Takegawa N, Kajiwara T, Baba H, Ueno M, Takeuchi H, Nakamura K, Kitagawa Y; JCOG1109 investigators

Doublet chemotherapy, triplet chemotherapy, or doublet chemotherapy combined with radiotherapy as neoadjuvant treatment for locally advanced oesophageal cancer (JCOG1109 NExT): A randomised, controlled, open-label, phase 3 trial

Background: Neoadjuvant therapy is the standard treatment for patients with locally advanced oesophageal squamous cell carcinoma (OSCC). However, the prognosis remains poor and more intensive neoadjuvant treatment might be needed to improve patient outcomes. The authors therefore aimed to compare the efficacy and safety of neoadjuvant doublet chemotherapy, triplet chemotherapy, and doublet chemotherapy plus radiotherapy in patients with previously untreated locally advanced OSCC.
Methods: In this randomised, open-label, phase 3 trial, patients aged 20–75 years with previously untreated locally advanced OSCC and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were recruited from 44 centres across Japan. Patients were randomly assigned (1:1:1) centrally via a web-based system to receive neoadjuvant doublet chemotherapy (2 courses of fluorouracil [800 mg/m^2 per day intravenously on days 1–5] and cisplatin [80 mg/m^2 per day on day 1] separated by an interval of 3 weeks [NeoCF]), triplet chemotherapy (3 courses of fluorouracil [750 mg/m^2 per day on days 1–5], cisplatin [70 mg/m^2 per day on day 1], and docetaxel [70 mg/m^2 per day on day 1] repeated every 3 weeks [NeoCF+D]), or doublet chemotherapy (2 courses of fluorouracil [1000 mg/m^2 per day on days 1–4] and cisplatin [75 mg/m^2 per day on day 1] separated by an interval of 4 weeks plus 41.4 Gy radiotherapy [NeoCF+RT]) followed by oesophagectomy with regional lymph node dissection. Randomisation was stratified by T stage and institution. Participants, investigators, and those assessing outcomes were not masked to group assignment. The primary endpoint was overall survival, analysed by intention to treat. Analysis of safety included all patients who received at least 1 course of chemotherapy, and analysis of surgical complications included those who also underwent surgery.
Findings: A total of 601 patients (529 male individuals and 72 female individuals) were randomly assigned between December 5, 2012, and July 20, 2018, with 199 patients in the NeoCF group, 202 patients in the NeoCF+D group, and 200 patients in the NeoCF+RT group. Compared with the NeoCF group, during a median follow-up period of 50.7 months (interquartile range, 23.8–70.7), the 3-year overall survival rate was significantly higher in the NeoCF+D group (72.1% [95% confidence interval {CI}: 65.4–77.8] vs. 62.6% [95% CI: 55.5–68.9]; hazard ratio [HR] = 0.68, 95% CI: 0.50–0.92; p = 0.006) but not in the NeoCF+RT group (68.3% [95% CI: 61.3–74.3]; HR = 0.84, 95% CI: 0.63–1.12; p = 0.12). Grade 3 or higher febrile neutropenia occurred in 2 (1%) of 193 patients in the NeoCF group, 32 (16%) of 196 patients in the NeoCF+D group, and 9 (5%) of 191 patients in the NeoCF+RT group. Treatment-related adverse events leading to termination of neoadjuvant therapy were more common in the NeoCF+D group (18 [9%] of 202 participants) than in the NeoCF+RT group (12 [6%] of 200 participants) and NeoCF group (8 [4%] of 199 participants). There were 3 (2%) treatment-related deaths during neoadjuvant therapy in the NeoCF group, 4 (2%) deaths in the NeoCF+D group, and 2 (1%) deaths in the NeoCF+RT group. Grade 2 or higher postoperative pneumonia, anastomotic leak, and recurrent laryngeal nerve paralysis were reported in 19 (10%), 19 (10%), and 28 (15%) of 185 patients, respectively, in the NeoCF group; 18 (10%), 16 (9%), and 19 (10%) of 183 patients, respectively, in the NeoCF+D group; and 23 (13%), 23 (13%), and 17 (10%) of 178 patients, respectively, in the NeoCF+RT group. The in-hospital deaths following surgery included 3 deaths in the NeoCF group, 2 deaths in the NeoCF+D group, and 1 death in the NeoCF+RT group.

Interpretation: Neoadjuvant triplet chemotherapy followed by oesophagectomy resulted in a statistically significant overall survival benefit compared with doublet chemotherapy and might be the new standard of care for locally advanced oesophageal squamous cell carcinomas who are in good condition in Japan. Neoadjuvant doublet chemotherapy plus radiotherapy did not show significant improvement of survival compared with doublet chemotherapy.

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DOI: 10.1016/s0140-6736(24)00745-1 ■

Lancet Gastroenterol Hepatol. 2024;9(8):705–17

Kang YK, Terashima M, Kim YW, Boku N, Chung HC, Chen JS, Ji J, Yeh TS, Chen LT, Ryu MH, Kim JG, Omori T, Rha SY, Kim TY, Ryu KW, Sakuramoto S, Nishida Y, Fukushima N, Yamada T, Bai LY, Hirashima Y, Hagihara S, Nakada T, Sasako M

Adjuvant nivolumab plus chemotherapy versus placebo plus chemotherapy for stage III gastric or gastro-oesophageal junction cancer after gastrectomy with D2 or more extensive lymph-node dissection (ATTRACTION-5): A randomised, multicentre, double-blind, placebo-controlled, phase 3 trial

Background: In Asia, adjuvant chemotherapy after gastrectomy with D2 or more extensive lymph-node dissection is standard treatment for people with pathological stage III gastric or gastro-oesophageal junction cancer. The authors aimed to assess the efficacy and safety of adjuvant nivolumab plus chemotherapy versus placebo plus chemotherapy administered in this setting.
Methods: ATTRACTION-5 was a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial conducted at 96 hospitals in Japan, South Korea, Taiwan, and China. Eligible patients were aged between 20 years and 80 years with histologically confirmed pathological stage IIIA–C gastric or gastro-oesophageal junction adenocarcinoma after gastrectomy with D2 or more extensive lymph-node dissection, with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 and available tumour tissue for programmed death-ligand 1 expression analysis. Patients were randomly assigned (1:1) to receive either nivolumab plus chemotherapy or placebo plus chemotherapy via an interactive web-response system with block sizes of 4. Investigational treatment, either nivolumab 360 mg or placebo, was administered intravenously for 30 minutes once every 3 weeks. Adjuvant chemotherapy was administered as either tegafur-gimeracil-oteracil (S-1) at an initial dose of 40 mg/m^2 per dose orally twice per day for 28 consecutive days, followed by 14 days off per cycle, or capecitabine plus oxaliplatin consisting of an initial dose of intravenous oxaliplatin 130 mg/m^2 for 2 hours every 21 days and capecitabine 1000 mg/m^2 per dose orally twice per day for 14 consecutive days, followed by 7 days off treatment. The primary endpoint was relapse-free survival by central assessment. The intention-to-treat population, consisting of all randomly assigned patients, was used for analysis of efficacy endpoints. The safety population, defined as patients who received at least 1 dose of trial drug, was used for analysis of safety endpoints.
Findings: Between February 1, 2017, and August 15, 2019, 755 patients were randomly assigned to receive either adjuvant nivolumab plus chemotherapy (n = 377) or adjuvant placebo plus chemotherapy (n = 378). 267 (71%) of 377 patients in the nivolumab group and 263 (70%) of 378 patients in the placebo group were male; 110 (29%) of 377 patients in the nivolumab group and 115 (31%) of 378 patients in the placebo group were female. 745 patients received assigned treatment (371 in the nivolumab plus chemotherapy group; 374 in the placebo plus chemotherapy group), which was the safety population. Median time from first dose to data cutoff was 49.1 months (interquartile range, 43.1–56.7). 3-year relapse-free survival was 68.4% (95% confidence interval [CI]: 63.0–73.2) in the nivolumab plus chemotherapy group and 65.3% (95% CI: 59.9–70.2) in the placebo plus chemotherapy group; the hazard ratio for relapse-free survival was 0.90 (95.72% CI: 0.69–1.18; p = 0.44). Treatment-related adverse events occurred in 366 (99%) of 371 patients in the nivolumab plus chemotherapy group and 364 (98%) of 374 patients in the placebo plus chemotherapy group. Discontinuation due to adverse events was more frequent in the nivolumab plus chemotherapy group (34 [9%] of 371 patients) than in the placebo plus chemotherapy group (13 [4%] of 374 patients). The most common treatment-related adverse events were decreased appetite, nausea, diarrhoea, neutrophil count decreased, and peripheral sensory neuropathy.

Interpretation: The results of this trial do not support the addition of nivolumab to postoperative adjuvant therapy for patients with untreated, locally advanced, resectable gastric or gastro-oesophageal junction cancer.

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DOI: 10.1016/s2468-1253(24)00156-0 ■

Endoscopy of the Upper GI Tract

Endoscopy. 2024;56(9):641–9

Meinikheim M, Mendel R, Palm C, Probst A, Muzalyova A, Scheppach MW, Nagl S, Schnoy E, Römmele C, Schulz DAH, Schlottmann J, Prinz F, Rauber D, Rückert T, Matsumura T, Fernández-Esparrach G, Parsa N, Byrne MF, Messmann H, Ebigbo A

Influence of artificial intelligence on the diagnostic performance of endoscopists in the assessment of Barrett's esophagus: A tandem randomized and video trial

Background: This study evaluated the effect of an artificial intelligence (AI)-based clinical decision support system on the performance and diagnostic confidence of endoscopists in their assessment of Barrett's esophagus (BE).
Methods: 96 standardized endoscopy videos were assessed by 22 endoscopists with varying degrees of BE experience from 12 centers. Assessment was randomized into 2 video sets: group A (review first without AI and second with AI) and group B (review first with AI and second without AI). Endoscopists were required to evaluate each video for the presence of Barrett's esophagus-related neoplasia (BERN) and then decide on a spot for a targeted biopsy. After the second assessment, they were allowed to change their clinical decision and confidence level.
Results: AI had a stand-alone sensitivity, specificity, and accuracy of 92.2%, 68.9%, and 81.3%, respectively. Without AI, BE experts had an overall sensitivity, specificity, and accuracy of 83.3%, 58.1%, and 71.5%, respectively. With AI, BE non-experts showed a significant improvement in sensitivity and specificity when videos were

assessed a second time with AI (sensitivity 69.8% [95% confidence interval {CI}: 65.2–74.2%] to 78.0% [95% CI: 74.0–82.0%]; specificity 67.3% [95% CI: 62.5–72.2%] to 72.7% [95% CI: 68.2–77.3%]). In addition, the diagnostic confidence of BE non-experts improved significantly with AI.

Conclusion: Barrett's esophagus (BE) non-experts benefitted significantly from additional artificial intelligence (AI). BE experts and non-experts remained significantly below the stand-alone performance of AI, suggesting that there may be other factors influencing endoscopists' decisions to follow or discard AI advice.

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DOI: 10.1055/a-2296-5696

Gastrointest Endosc. 2024;100(2):177–82

Kosirog J, Bouvette C, Pannu J, Gondal J, Madhoun M

Marijuana and endoscopy: The effects of marijuana on sedation

Background and aims: Marijuana usage has increased significantly as it has become more readily available and legal, either recreationally or medicinally, in many states. It has been postulated that marijuana usage increases the amount of sedation required for procedures. However, there are minimal data defining this relationship. The authors aimed to establish the relationship between marijuana usage and the amount of sedation used during endoscopy.
Methods: This was a single-institution prospective study of patients undergoing outpatient endoscopy (both monitored anesthesia care [MAC] and moderate sedation) at the Oklahoma City Veterans Affairs Medical Center. Marijuana usage was assessed by a voluntary de-identified pre-endoscopy survey. Information regarding sedation used, endoscopy outcomes, demographics, comorbidities, medical history, and medications used was extracted from the medical record. A univariate and stratified analysis of alcohol usage was performed. A p value of < 0.05 was considered to be significant.
Results: A total of 976 patients were analyzed; 21.5% of them endorsed marijuana usage (210/976). Marijuana users were found to be younger ($p = 0.0002$), leaner ($p < 0.0001$), and less likely to have diabetes ($p = 0.002$), obstructive sleep apnea ($p = 0.0002$), and hypertension ($p = 0.04$). They were also more likely to smoke ($p < 0.0001$) and vape ($p < 0.0001$). Marijuana usage was associated with a higher requirement of sedation (fentanyl [$p = 0.003$], midazolam [$p = 0.05$], propofol [$p = 0.02$]) and higher use of adjunct sedation (diphenhydramine in moderate sedation [$p = 0.0003$]). Further multivariate analyses were performed to control for possible confounders. Marijuana usage was still deemed to be an independent predictor for high propofol use among MAC cases (odds ratio [OR] = 1.77; 95% confidence interval [CI]: 1.00–3.12). Likewise, marijuana usage was found to be an independent predictor for high midazolam use (OR = 1.57; 95% CI: 1.02–2.42) and high fentanyl use (OR = 1.54; 95% CI: 0.98–2.38) but failed to reach statistical significance in the fentanyl group.
Conclusions: Marijuana use is associated with a significantly higher amount of sedation along with a significantly higher usage of other adjunct sedatives. A patient's marijuana history should be considered when determining the methods of sedation to be used for endoscopy.

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DOI: 10.1016/j.gie.2024.01.013

Crohn's Disease

Lancet Gastroenterol Hepatol. 2024;9(9):793–801

van der Does de Willebois EML, Bellato V, Duijvestein M, van der Bilt JDW, van Dongen K, Spinelli A, D'Haens GR, Mundt MW, Furfaro F, Danese S, Vignali A, Bemelman WA, Buskens CJ; SPICY collaborator group

Effect of mesenteric sparing or extended resection in primary ileocolic resection for Crohn's disease on postoperative endoscopic recurrence (SPICY): An international, randomised controlled trial

Background: Retrospective research suggests that excision of the affected mesentery can improve outcomes after an ileocoecal resection in Crohn's disease. However, prospective data from randomised controlled trials are scarce. The authors aimed to compare rates of postoperative recurrence in patients with Crohn's disease who underwent extended mesenteric resection.
Methods: This international, randomised controlled trial was done in 6 hospitals and tertiary care centres in the Netherlands and Italy. Eligible patients were aged 16 years or older and had Crohn's disease that was previously confirmed by endoscopy in the terminal ileum or ileocolic region (L1 or L3 disease), with an imaging update in the past 3 months (ultrasound, MRI, or CT enterography). Eligible patients were scheduled to undergo primary ileocolic resection with ileocolic anastomosis. Enrolled patients were assigned by use of simple random allocation (1:1) to either extended mesenteric resection (intervention) or conventional mesenteric sparing resection (control). The primary endpoint was endoscopic recurrence 6 months after surgery. Analyses were done in all patients with primary endpoint data, excluding those who had no anastomosis, a postoperative diagnosis other than Crohn's disease, or withdrew consent.
Findings: Between February 19, 2020, and April 24, 2023, the authors assessed 217 patients for eligibility. 78 patients were excluded due to failure to meet the inclusion criteria or refusal to participate. 139 patients were enrolled and randomly assigned to either extended mesenteric resection (n = 71) or mesenteric sparing resection (n = 68). All 139 patients underwent surgery. Six patients were excluded after random assignment due to withdrawal of consent (n = 2), postoperative diagnosis other than Crohn's disease (n = 2) and no anastomosis performed (in case of a stoma; n = 2). Two patients were lost to follow-up, and 2 more patients

deviated from the protocol by undergoing investigations other than endoscopy 6 months after. 133 patients were included in the baseline analysis (67 in the extended resection group and 66 in the sparing resection group) of whom 57 (43%) were male. Baseline characteristics were similar between the groups, and median patient age was 36 years (interquartile range, 25–54). 131 patients were analysed for the primary outcome. There was no difference between groups in the rate of endoscopic recurrence at 6 months after surgery (28 [42%] of 66 patients in the extended mesenteric resection group vs. 28 [43%] of 65 patients in the mesenteric sparing resection group, relative risk = 0.985, 95% confidence interval [CI]: 0.663–1.464; p = 1.0). Five (8%) of 66 patients in the extended mesenteric resection group had anastomotic leakage within the 30 days after surgery, as did 1 (2%) of 65 in the mesenteric sparing group. Postoperative complications of Clavien-Dindo grade IIIa or higher were reported in 7 (11%) patients in the mesenteric resection group and 5 (8%) in the mesenteric sparing group.

Interpretation: Extended mesenteric resection was not superior to conventional resection with regard to endoscopic Crohn's disease recurrence. These data support the guideline-recommended mesenteric sparing approach.

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DOI: 10.1016/s2468-1253(24)00097-9 ■

Aliment Pharmacol Ther. 2024;60(2):224–32

Plotkin L, Buchuk R, Lujan R, Focht G, Greenfeld S, Kariv R, Loewenberg Weisband Y, Lederman N, Matz E, Dotan I, Reifen R, Turner D

Enteral nutrition compared with corticosteroids in children with Crohn's disease: A long-term nationwide study from the epi-IIRN

Background: Both corticosteroids and exclusive enteral nutrition (EEN) have been used as induction therapy in children with Crohn's disease (CD).
Aim: To compare in a nationwide study the long-term outcomes of children with CD receiving either EEN or corticosteroids as induction therapy.
Methods: The authors retrieved data of all children diagnosed with CD (2005–2020) from the Israeli Inflammatory Bowel Disease (IBD) Research Nucleus (epi-IIRN) cohort covering 98% of the Israeli population. The primary outcome was time to complicated disease course (i.e., surgery, steroid dependency, or at least 2 classes of biologics). Patients were matched individually utilising propensity score adjustments.
Results: 410 children treated with EEN and 375 treated with corticosteroids without other treatments (median follow-up, 4.73 [interquartile range, 2.2–7.2] years [1433 patient-years]) were included. For 274 matched children, the probability of a complicated course was higher with corticosteroids than with EEN at 0.5, 3 and 5 years (14% vs. 4%, 42% vs. 27%, and 54% vs. 41%, respectively, p = 0.0066), despite similar use of biologics. Steroid dependency (10% vs. 2%, 15% vs. 3%, and 20% vs. 5%, respectively, p = 0.00018), and hospitalisations (20% vs. 11%, 37% vs. 26%, and 55% vs. 38%, respectively, p = 0.002) were higher with corticosteroids. During follow-up, children receiving corticosteroids as induction treatment were more often further exposed to corticosteroids, and those on EEN were more often further exposed to nutritional treatment (p < 0.001). Induction with EEN had no advantage over corticosteroids regarding survival probability of surgeries, biologic use and growth.

Conclusions: Exclusive enteral nutrition in paediatric Crohn's disease (CD) is associated with lower long-term risks of corticosteroid dependency and hospitalisation than corticosteroids. These results may lend support to favouring nutritional therapy in paediatric CD.

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DOI: 10.1111/apt.18028 ■

Clin Gastroenterol Hepatol. 2024;22(6):1286–94.e4

Ahuja D, Luo J, Qi Y, Syal G, Boland BS, Chang J, Ma C, Jairath V, Xu R, Singh S

Impact of treatment response on risk of serious infections in patients with Crohn's disease: Secondary analysis of the PYRAMID registry

Background and aims: Traditional risk factors for serious infections with advanced therapies in patients with Crohn's disease (CD) have been assessed at baseline before starting therapy. The authors evaluated the impact of treatment response on the risk of serious infections in adalimumab-treated patients with CD through secondary analysis of the PYRAMID registry.
Methods: They included patients with CD who initiated adalimumab and classified them as treatment responders (achieved steroid-free clinical remission based on patient-reported outcomes) versus non-responders (not in steroid-free clinical remission) at 6 months after treatment initiation (landmark). They compared the risk of serious infections between responders versus non-responders between 6 and 36 months after treatment initiation through stabilized inverse probability of treatment weighting Cox proportional hazards model.
Results: Of 1515 adalimumab-treated patients, 763 (50.4%) were classified as responders at 6 months (37 ± 13 years; 56% female; disease duration, 9.5 ± 8.5 years). Compared with non-responders, responders were less likely to have moderate to severe symptoms (55.6% vs. 33%) or require steroids (45.5% vs. 17.3%) or opiates (6.6% vs. 1.3%) at baseline, without any differences in disease location, perianal disease, and prior CD complications. During follow-up evaluation, using stabilized inverse probability of treatment weighting, responders were 34% less likely to experience serious infections compared with non-responders (hazard ratio = 0.66; 95% confidence interval: 0.46–0.96). Risk of gastrointestinal and extraintestinal infections was lower in responders versus non-responders.

Conclusions: Patients with Crohn's disease (CD) who respond to adalimumab have a lower risk of develop-

ing serious infections compared with non-responders. These findings underscore that initiation of advanced therapy for CD may lower the risk of serious infections through effective disease control and avoidance of corticosteroids.

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DOI: 10.1016/j.cgh.2024.01.003

N Engl J Med. 2024;391(3):213–23

Peyrin-Biroulet L, Chapman JC, Colombel JF, Caprioli F, D'Haens G, Ferrante M, Schreiber S, Atreya R, Danese S, Lindsay JO, Bossuyt P, Siegmund B, Irving PM, Panaccione R, Cao Q, Neimark E, Wallace K, Anschutz T, Kligys K, Duan WR, Pivorunas V, Huang X, Berg S, Shu L, Dubinsky M; SEQUENCE Study Group

Risankizumab versus ustekinumab for moderate-to-severe Crohn's disease

Background: The efficacy and safety of risankizumab as compared with ustekinumab in patients with Crohn's disease are unknown.
Methods: In this phase 3b, multicenter, open-label, randomized, controlled trial with blinded assessment of end points, patients with moderate-to-severe Crohn's disease who had had an inadequate response to anti-tumor necrosis factor therapy or unacceptable side effects with such therapy were randomly assigned to receive risankizumab or ustekinumab at standard doses for 48 weeks. The 2 primary end points, which were tested sequentially, were clinical remission at week 24 (defined as a Crohn's Disease Activity Index score of < 150 [range, 0–600, with higher scores indicating more severe disease activity]), which was analyzed in the first 50% of patients to complete the week-24 visit, with a non-inferiority margin of 10 percentage points; and endoscopic remission at week 48 (defined as a score of ≤ 4, a decrease of ≥ 2 points from baseline, and no subscore > 1 in any individual variable on the Simple Endoscopic Score for Crohn's Disease [range, 0–56, with higher scores indicating more severe disease]), which was analyzed for superiority in 100% of the patients. Safety was assessed in all patients who received at least 1 dose of risankizumab or ustekinumab.
Results: In the full intention-to-treat population for the efficacy analysis, 230 of 255 patients (90.2%) who received risankizumab and 193 of 265 patients (72.8%) who received ustekinumab completed all the assigned treatments. Both primary end points were met; risankizumab was non-inferior to ustekinumab with respect to clinical remission at week 24 (58.6% vs. 39.5%; adjusted difference, 18.4 percentage points; 95% confidence interval [CI]: 6.6–30.3) and superior to ustekinumab with respect to endoscopic remission at week 48 (31.8% vs. 16.2%; adjusted difference, 15.6 percentage points; 95% CI: 8.4–22.9; p < 0.001). The incidence of adverse events appeared to be similar in the 2 groups.

Conclusions: In this head-to-head clinical trial of risankizumab and ustekinumab involving patients with moderate-to-severe Crohn's disease who had had unacceptable side effects with anti-tumor necrosis factor therapy or an inadequate response to such therapy, risankizumab was non-inferior to ustekinumab with respect to clinical remission at week 24 and superior with respect to endoscopic remission at week 48.

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DOI: 10.1056/nejmoa2314585

Aliment Pharmacol Ther. 2024;59(12):1510–20

Vuijk SA, Jongsma MME, Hoeven BM, Cozijnsen MA, van Pieterson M, de Meij TGJ, Norbruis OF, Groeneweg M, Wolters VM, van Wering H, Hummel T, Stapelbroek J, van der Feen C, van Rheenen PF, van Wijk MP, Teklenburg S, Rizopoulos D, Poley MJ, Escher JC, de Ridder L

Randomised clinical trial: First-line infliximab biosimilar is cost-effective compared to conventional treatment in paediatric Crohn's disease

Background: Data on cost-effectiveness of first-line infliximab in paediatric patients with Crohn's disease are limited. Since biologics are increasingly prescribed and accompanied by high costs, this knowledge gap needs to be addressed.
Aim: To investigate the cost-effectiveness of first-line infliximab compared to conventional treatment in children with moderate-to-severe Crohn's disease.
Methods: The authors included patients from the Top-down Infliximab Study in Kids with Crohn's Disease (TISKids) randomised controlled trial. Children with newly diagnosed moderate-to-severe Crohn's disease were treated with azathioprine maintenance and either 5 induction infliximab (biosimilar) infusions or conventional induction treatment (exclusive enteral nutrition or corticosteroids). Direct healthcare consumption and costs were obtained per patient until week 104. This included data on outpatient hospital visits, hospital admissions, drug costs, endoscopies and surgeries. The primary health outcome was the odds ratio of being in clinical remission (weighted Paediatric Crohn's Disease Activity Index < 12.5) during 104 weeks.
Results: 89 patients (44 in the first-line infliximab group and 45 in the conventional treatment group) were included. Mean direct healthcare costs per patient were €36,784 for first-line infliximab treatment and €36,874 for conventional treatment over 2 years (p = 0.981). The odds ratio of first-line infliximab versus conventional treatment to be in clinical remission over 104 weeks was 1.56 (95% confidence interval: 1.03–2.35, p = 0.036).

Conclusions: First-line infliximab treatment resulted in higher odds of being in clinical remission without being more expensive, making it the dominant strategy over conventional treatment in the first 2 years after diagnosis in children with moderate-to-severe Crohn's disease.

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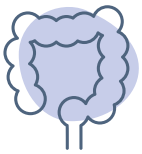
DOI: 10.1111/apt.18000



COLON TO RECTUM

Ulcerative Colitis, Crohn's Colitis

Gastroenterology. 2024;167(2):315–32

Khrom M, Long M, Dube S, Robbins L, Botwin GJ, Yang S, Mengesha E, Li D, Naito T, Bonthala NN, Ha C, Melmed G, Rabizadeh S, Syal G, Vasiliauskas E, Ziring D, Brant SR, Cho J, Duerr RH, Rioux J, Schumm P, Silverberg M, Ananthakrishnan AN, Faubion WA, Jabri B, Lira SA, Newberry RD, Sandler RS, Xavier RJ, Kugathasan S, Hercules D, Targan SR, Sartor RB, Haritunians T, McGovern DPB

Comprehensive association analyses of extraintestinal manifestations in inflammatory bowel disease

Background and aims: Patients with inflammatory bowel disease (IBD) frequently develop extraintestinal manifestations (EIMs) that contribute substantially to morbidity. The authors assembled the largest multicohort data set to date to investigate the clinical, serologic, and genetic factors associated with EIM complications in IBD.
Methods: Data were available in 12,083 unrelated European ancestry IBD cases with presence or absence of EIMs (e.g., ankylosing spondylitis [ankylosing spondylitis and sacroiliitis], primary sclerosing cholangitis [PSC], peripheral arthritis, and skin and ocular manifestations) across 4 cohorts (Cedars-Sinai Medical Center, National Institute for Diabetes and Digestive and Kidney Diseases IBD Genetics Consortium, Sinai Helmsley Alliance for Research Excellence Consortium, and Risk Stratification and Identification of Immunogenetic and Microbial Markers of Rapid Disease Progression in Children with Crohn's Disease cohort). Clinical and serologic parameters were analyzed by means of univariable and multivariable regression analyses using a mixed-effects model. Within-case logistic regression was performed to assess genetic associations.
Results: Most EIMs occurred more commonly in female subjects (overall EIM, p = 9.0E-05; odds ratio [OR] = 1.2; 95% confidence interval [CI]: 1.1–1.4), with Crohn's disease (especially colonic disease location, p = 9.8E-09; OR = 1.7; 95% CI: 1.4–2.0), and in subjects who required surgery (both Crohn's disease and ulcerative colitis, p = 3.6E-19; OR = 1.7; 95% CI: 1.5–1.9). Smoking increased risk of EIMs except for PSC, where there was a "protective" effect. Multiple serologic associations were observed, including with PSC (anti-nuclear cytoplasmic antibody; immunoglobulin G and immunoglobulin A, anti-Saccharomyces cerevisiae antibodies; and anti-flagellin) and any EIM (anti-nuclear cytoplasmic antibody; immunoglobulin G and immunoglobulin A, anti-Saccharomyces cerevisiae antibodies; and anti-Pseudomonas fluorescens-associated sequence). The authors identified genome-wide significant associations within major histocompatibility complex (ankylosing spondylitis and sacroiliitis, p = 1.4E-15; OR = 2.5; 95% CI: 2.0–3.1; PSC, p = 2.7E-10; OR = 2.8; 95% CI: 2.0–3.8; ocular, p = 2E-08; OR = 3.6; 95% CI: 2.3–5.6; and overall EIM, p = 8.4E-09; OR = 2.2; 95% CI: 1.7–2.9) and CPEB4 (skin, p = 2.7E-08; OR = 1.5; 95% CI: 1.3–1.8). Genetic associations implicated tumor necrosis factor, JAK-STAT, and interleukin-6 as potential targets for EIMs. Contrary to previous reports, only 2% of the subjects had multiple EIMs and most co-occurrences were negatively correlated.

Conclusions: The authors have identified demographic, clinical, and genetic associations with extraintestinal manifestations that revealed underlying mechanisms and implicated novel and existing drug targets – important steps toward a more personalized approach to inflammatory bowel disease management.

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DOI: 10.1053/j.gastro.2024.02.026 ■

Aliment Pharmacol Ther. 2024;60(5):604–12

Ferreiro-Iglesias R, Porto Silva S, Marín S, Casanova MJ, Mañosa M, González-Muñoza C, de Francisco R, Caballol B, Arias L, Piqueras M, Zabana Y, Rivero M, Calvet X, Mesonero F, Varela Trastoy P, Busta Nistal R, Gómez Perosanz R, Vega P, Gonzalez-Vivo M, Iborra M, Bermejo F, Madero L, Rodríguez-Lago I, Rodríguez Gonzalez M, Vera I, Ponferrada Díaz Á, Vela M, Torrealba Medina L, Van Domselaar M, Gomollón F, Iglesias E, Gisbert JP, Calafat M, Giordano A, Pérez-Martínez I, Ricart E, Sicilia B, Mena R, Esteve M, Rivas C, Brunet-Mas E, Fernández C, de Jorge Turrión MÁ, Velayos Jiménez B, Quiñones Calvo M, Regueiro Expósito C, Márquez-Mosquera L, Nos P, Granja A, Gutiérrez A, Cabriada JL, Hervías Cruz D, Calvo M, Pérez Pérez J, Rodríguez Díaz Y, Busquets Casal D, Menacho M, Leal C, Lucendo AJ, Royo V, Olivares S, Álvarez Herrero B, Carrillo-Palau M, Gilabert Álvarez P, Manceñido Marcos N, de Jesús Martínez-Pérez T, Muñoz Villafranca MC, Almela P, Argüelles-Arias F, Legido J, Fuentes Coronel AM, Nieto L, Domènech E, Barreiro-de Acosta M; ENEIDA project sponsored by GETECCU

Need for therapeutic escalation in patients with refractory ulcerative proctitis: Results from the PROCU study of the ENEIDA registry

Background: Ulcerative proctitis (UP) can have a milder, less aggressive course than left-sided colitis or extensive colitis. Therefore, immunosuppressants tend to be used less in patients with this condition. Evidence, however, is scarce because these patients are excluded from randomised controlled clinical trials. Aim of the present study was to describe the characteristics of patients with refractory UP and their disease-related complications, and to identify the need for immunosuppressive therapies.
Methods: The authors identified patients with UP from the prospective ENEIDA registry sponsored by the

GETECCU. They evaluated socio-demographic data and complications associated with immunosuppression, and defined immunosuppression as the use of immunomodulators, biologics and/or small molecules. Logistic regression was used to identify factors associated with immunosuppressive therapy.
Results: From a total of 34,716 patients with ulcerative colitis, 6281 (18.1%) were identified with UP; mean age, 53 (standard deviation [SD], 15) years, average disease duration of 12 (SD, 9) years. Immunosuppression was prescribed in 11% of patients, 4.2% needed 1 biologic agent and 1% needed 2 biologic agents; 2% of patients required hospitalisation, and 0.5% underwent panproctocolectomy or subtotal colectomy. The authors identified 0.2% colorectal tumours and 5% extracolonic tumours. Patients with polyarthritis (odds ratio = 3.56, 95% confidence interval: 1.86–6.69; p < 0.001) required immunosuppressants.

Conclusions: Among patients with refractory ulcerative proctitis, 11% required immunosuppressant therapy, and 4.2% required at least 1 biologic agent.

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DOI: 10.1111/apt.18133

Aliment Pharmacol Ther. 2024;60(3):357–68

Strande V, Lund C, Hagen M, Bengtson MB, Cetinkaya RB, Detlie TE, Frigstad SO, Høie O, Medhus AW, Henriksen M, Aass Holten KI, Hovde Ø, Huppertz-Hauss G, Johansen I, Olsen BC, Opheim R, Ricanek P, Torp R, Tønnessen T, Vatn S, Aabrekk TB, Høivik ML, Kristensen VA

Clinical course of ulcerative colitis: Frequent use of biologics and low colectomy rate first year after diagnosis – Results from the IBSEN III inception cohort

Background: The introduction of biologic therapies and the "treat-to-target" treatment strategy may have changed the disease course of ulcerative colitis (UC).
Aims: To describe the early disease course and disease outcome at 1-year follow-up in a population-based inception cohort of adult patients with newly diagnosed UC.
Methods: The Inflammatory Bowel Disease in South-Eastern Norway (IBSEN) III study is a population-based inception cohort study with prospective follow-up. Patients newly diagnosed with inflammatory bowel disease during 2017–2019 were included. Patients ≥ 18 years at diagnosis of UC who attended the 1-year follow-up were investigated. The authors registered clinical, endoscopic and demographic data at diagnosis and 1-year follow-up.
Results: They included 877 patients with UC (median age, 36 years [range, 18–84], 45.8% female). At diagnosis, 39.2% presented with proctitis, 24.7% with left-sided colitis and 36.0% with extensive colitis. At the 1-year follow-up, 13.9% experienced disease progression, and 14.5% had received 1 or more biologic therapies. The colectomy rate was 0.9%. Steroid-free clinical remission was observed in 76.6%, and steroid-free endoscopic remission in 68.7%. Anaemia and initiation of systemic steroid treatment at diagnosis were associated with biologic therapy within the first year after diagnosis.

Conclusion: In this population-based inception cohort, colectomy rate in the first year after diagnosis was low, and a high proportion of patients were in remission at 1-year follow-up. The use of biologic therapy increases, consistent with findings from previous studies.

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DOI: 10.1111/apt.18097

Inflamm Bowel Dis. 2024;30(8):1233–40

Brownson E, Saunders J, Jatkowska A, White B, Gerasimidis K, Seenan JP, Macdonald J

Micronutrient status and prediction of disease outcome in adults with inflammatory bowel disease receiving biologic therapy

Background and aims: Micronutrient deficiencies are common in patients with inflammatory bowel disease (IBD), but whether they relate to disease outcomes remains unknown. This study assessed the micronutrient status of adults with IBD on treatment with biologic therapies and explored predictive relationships with disease outcomes.
Methods: 17 micronutrients were measured in the blood of 216 adults with IBD on biologic therapy. Of these, 127 patients (58%) had Crohn's disease, and the majority (70%) received treatment with infliximab. Patients were followed for 12 months and onset of adverse clinical outcomes (e.g., requirement for treatment with corticosteroids, hospitalization, or surgical intervention) was recorded, and related to micronutrient status.
Results: Among all patients, the most common deficiencies were for vitamin C (n = 35/212 [16.5%]), ferritin (n = 27/189 [14.3%]), folate (n = 24/171 [14.0%]), and zinc (n = 27/210 [12.9%]). During follow-up, 22 (10%) of the 216 patients developed 1 or more adverse clinical outcomes. Patients with Crohn's disease and zinc deficiency were significantly more likely to require surgery (p = 0.002) or treatment with corticosteroids (p < 0.001). In contrast, patients with ulcerative colitis and selenium deficiency were significantly more likely to have a clinical flare of disease (p = 0.001), whereas those with Crohn's disease were not. This relationship with selenium remained significant after adjustment for confounders.

Conclusions: A substantial proportion of adults with inflammatory bowel disease (IBD) present deficiencies for certain micronutrients, with selenium and zinc deficiency predicting adverse disease outcomes. For other micronutrients, deficiencies were less common and should not warrant routine screening. Intervention studies should explore the effect of micronutrient supplementation in modifying disease outcomes in IBD.

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DOI: 10.1093/ibd/izad174

Clin Gastroenterol Hepatol. 2024;22(8):1678–86.e8

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Antibiotic use in the 12 months prior to ileal pouch-anal anastomosis increases the risk for pouchitis

Background and aims: Pouchitis is the most common complication after ileal pouch-anal anastomosis (IPAA) for ulcerative colitis (UC); however, clinical and environmental risk factors for pouchitis remain poorly understood. The authors explored the relationship between specific clinical factors and the incidence of pouchitis.
Methods: They established a population-based cohort of all adult persons in Denmark undergoing proctocolectomy with IPAA for UC from 1996–2020. Cox proportional hazard modeling was used to assess the impact of antibiotic, non-steroidal anti-inflammatory drug (NSAID) exposure, and appendectomy on diagnosis of acute pouchitis in the first 2 years after IPAA surgery.
Results: Among 1616 eligible patients, 46% developed pouchitis in the first 2 years after IPAA. Antibiotic exposure in the 12 months before IPAA was associated with an increased risk of pouchitis (adjusted hazard ratio [aHR] = 1.41; 95% confidence interval [CI]: 1.22–1.64) after adjusting for anti-tumor necrosis factor α use and sex. Compared with persons without any antibiotic prescriptions in the 12 months before IPAA, the risk of pouchitis was increased in those with 1 or 2 courses of antibiotics in that period (aHR = 1.30; 95% CI: 1.11–1.52) and 3 or more courses (aHR = 1.77; 95% CI: 1.41–2.21). NSAID exposure in the 12 months before IPAA and appendectomy were not associated with risk of acute pouchitis (p = 0.201 and p = 0.865, respectively).

Conclusions: In this population-based cohort study it was demonstrated that antibiotic exposure in the 12 months before ileal pouch-anal anastomosis is associated with an increased risk of acute pouchitis. Future prospective studies may isolate specific microbial changes in at-risk patients to drive earlier interventions.

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DOI: 10.1016/j.cgh.2024.03.012

Clin Gastroenterol Hepatol. 2024;22(6):1295–306.e7

Kedia S, Virmani S, Bajaj A, Markandey M, Singh N, Madan D, Kaushal K, Sahu P, Vuyyuru SK, Kante B, Kumar P, Thomas DM, Mundhra SK, Singh MK, Verma M, Sharma R, Das P, Dash NR, Monga N, Awasthi A, Makharia G, Ahuja V

Coconut water induces clinical remission in mild-to-moderate ulcerative colitis: Double-blind placebo-controlled trial

Background and aims: Coconut water (CW) is anti-inflammatory, can manipulate the gut microbiome, and is a rich source of potassium. Gut microbiome modulation improves outcomes in ulcerative colitis (UC), and potassium possesses in vitro anti-inflammatory property. The authors evaluated the effect of CW as an adjunct therapy for patients with mild-to-moderate UC.
Methods: This single-center, double-blind, placebo-controlled trial randomized patients with mild-to-moderate (Simple Clinical Colitis Activity Index [SCCAI]: 3–9) endoscopically active UC (Ulcerative Colitis Endoscopic Index of Severity [UCEIS] > 1) in 1:1 ratio to CW + standard medical therapy (SMT) versus placebo + SMT. 400 milliliter of CW was administered for 8 weeks. Primary outcome measure was clinical remission (SCCAI ≤ 2), and secondary outcome measures were clinical response (SCCAI decline ≥ 3) and adverse events at 8 weeks. Microbiome was analyzed at baseline and 8 weeks.
Results: Of 121 patients screened, 95 were included for modified intention-to-treat analysis (CW, n = 49; placebo, n = 46) (mean age, 37.2 ± 11.2 years; males, 54.1%; disease duration, 48 months [interquartile range {IQR}, 24–90 months]; pancolitis, 26.1%; SCCAI, 5 [IQR, 4–6]; UCEIS, 4 [IQR, 3–5]). Clinical response (57.1% vs. 28.3%; odds ratio [OR] = 3.4; 95% confidence interval [CI]: 1.4–7.9; p = 0.01), remission (53.1% vs. 28.3%; OR = 2.9; 95% CI: 1.2–6.7; p = 0.02), and proportion of patients with fecal calprotectin (FC) < 150 µg/g (30.6% vs. 6.5%; OR = 6.3; 95% CI: 1.7–23.6; p = 0.003) were significantly higher in CW. The relative abundance of bacterial taxa that had a significant or trend towards negative correlation with SCCAI, UCEIS, or FC increased at 8 weeks in CW, and this effect was independent of disease activity and dietary fiber. Adverse events were comparable, and no patient developed hyperkalemia.

Conclusions: Coconut water was more effective than placebo for induction of clinical remission in patients with mild-to-moderate ulcerative colitis.

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DOI: 10.1016/j.cgh.2024.01.013

Inflamm Bowel Dis. 2024;30(7):1055–61

Glickman D, Dalessio S, Raup-Konsavage WM, Vrana KE, Coates MD

The impact of cannabis use on clinical outcomes in inflammatory bowel disease: A population-based longitudinal cohort study

Background: Cannabis use is common in inflammatory bowel disease (IBD). Recent studies demonstrated that use of cannabis may relieve symptoms; however, it is still unclear how safe cannabis and its derivatives are for IBD patients. The authors performed this study to evaluate the impact of cannabis use on several key clinical outcomes in IBD.
Methods: They performed a retrospective study using the TriNetX Diamond Network. Cannabis use and non-cannabis use subcohorts were identified for 3 patient groups: (1) IBD, (2) Crohn's disease (CD), and (3) ulcerative colitis (UC). Baseline differences between subcohorts for each group were controlled by propensity score matching. In each group, relative incidence of emergency department (ED) visits, hospitalization,

corticosteroid use, opioid use, IBD-related surgery, and death between cannabis users and non-cannabis users was compared.
Results: IBD cannabis users demonstrated an increased risk for corticosteroid use (risk ratio [RR] = 1.095; 95% confidence interval [CI]: 1.021–1.174; p = 0.011), ED visits (RR = 2.143; 95% CI: 2.034–2.257; p < 0.001), hospitalizations (RR = 1.925; 95% CI: 1.783–2.079; p < 0.001) and opioid use (RR = 1.35; 95% CI: 1.14–1.6; p < 0.001), but not an increased risk of IBD-related surgery or death. The CD and UC groups exhibited similar outcomes, except only CD demonstrated an increased risk for corticosteroid and opioid use.

Conclusions: Cannabis use in inflammatory bowel disease (IBD) patients is associated with several poor clinical outcomes, including increased risk of corticosteroid and opioid use, emergency department visits and hospitalization, though not IBD-related surgery or death. It is not clear what drives these risks or whether they are directly related to IBD-associated disease activity or other factors. Further prospective studies are warranted to more carefully investigate these relationships.

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DOI: 10.1093/ibd/izad151

JAMA. 2024;332(11):881–97

Louis E, Schreiber S, Panaccione R, Bossuyt P, Biedermann L, Colombel JF, Parkes G, Peyrin-Biroulet L, D'Haens G, Hisamatsu T, Siegmund B, Wu K, Boland BS, Melmed GY, Armuzzi A, Levine P, Kalabic J, Chen S, Cheng L, Shu L, Duan WR, Pivorunas V, Sanchez Gonzalez Y, D'Cunha R, Neimark E, Wallace K, Atreya R, Ferrante M, Loftus EV, Jr.; INSPIRE and COMMAND Study Group

Risankizumab for ulcerative colitis: Two randomized clinical trials

Importance: The clinical effects of risankizumab (a monoclonal antibody that selectively targets the p19 subunit of interleukin-23) for the treatment of ulcerative colitis are unknown.
Objective: To evaluate the efficacy and safety of risankizumab when administered as an induction and a maintenance therapy for patients with ulcerative colitis.
Design, setting, and participants: Two phase 3 randomized clinical trials were conducted. The induction trial was conducted at 261 clinical centers (in 41 countries) and enrolled 977 patients from November 5, 2020, to August 4, 2022 (final follow-up on May 16, 2023). The maintenance trial was conducted at 238 clinical centers (in 37 countries) and enrolled 754 patients from August 28, 2018, to March 30, 2022 (final follow-up on April 11, 2023). Eligible patients had moderately to severely active ulcerative colitis; a history of intolerance or inadequate response to 1 or more conventional therapies, advanced therapies, or both types of therapies; and no prior exposure to risankizumab.
Interventions: For the induction trial, patients were randomized 2:1 to receive 1200 mg of risankizumab or placebo administered intravenously at weeks 0, 4, and 8. For the maintenance trial, patients with a clinical response (determined using the adapted Mayo score) after intravenous treatment with risankizumab were randomized 1:1:1 to receive subcutaneous treatment with 180 mg or 360 mg of risankizumab or placebo (no longer receiving risankizumab) every 8 weeks for 52 weeks.
Main outcomes and measures: The primary outcome was clinical remission (stool frequency score ≤ 1 and not greater than baseline, rectal bleeding score of 0, and endoscopic subscore ≤ 1 without friability) at week 12 for the induction trial and at week 52 for the maintenance trial.
Results: Among the 975 patients analyzed in the induction trial (aged 42.1 [standard deviation {SD}, 13.8] years; 586/973 [60.1%] were male; and 677 [69.6%] were White), the clinical remission rates at week 12 were 132/650 (20.3%) for 1200 mg of risankizumab and 20/325 (6.2%) for placebo (adjusted between-group difference, 14.0% [95% confidence interval {CI}: 10.0–18.0%], p < 0.001). Among the 548 patients analyzed in the maintenance trial (aged 40.9 [SD, 14.0] years; 313 [57.1%] were male; and 407 [74.3%] were White), the clinical remission rates at week 52 were 72/179 (40.2%) for 180 mg of risankizumab, 70/186 (37.6%) for 360 mg of risankizumab, and 46/183 (25.1%) for placebo (adjusted between-group difference for 180 mg of risankizumab vs. placebo, 16.3% [97.5% CI: 6.1–26.6%], p < 0.001; adjusted between-group difference for 360 mg of risankizumab vs. placebo, 14.2% [97.5% CI: 4.0–24.5%], p = 0.002). No adverse event signals were detected in the treatment groups.

Conclusion and relevance: Compared with placebo, risankizumab improved clinical remission rates in an induction trial and in a maintenance trial for patients with moderately to severely active ulcerative colitis. Further study is needed to identify benefits beyond the 52-week follow-up.

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DOI: 10.1001/jama.2024.12414

J Crohns Colitis. 2024;18(8):1270–82

Peyrin-Biroulet L, Dubinsky MC, Sands BE, Panés J, Schreiber S, Reinisch W, Feagan BG, Danese S, Yarur AJ, D'Haens GR, Goetsch M, Wosik K, Keating M, Lazin K, Wu J, Modesto I, McDonnell A, Bartolome L, Vermeire S

Efficacy and safety of etrasimod in patients with moderately to severely active isolated proctitis: Results from the phase 3 ELEVATE UC clinical programme

Background and aims: Pivotal trials in ulcerative colitis have historically excluded patients with isolated proctitis. Etrasimod is an oral, once-daily, selective sphingosine 1-phosphate$_{1,4,5}$ receptor modulator for the treatment of moderately to severely active ulcerative colitis. This post hoc analysis assessed efficacy and safety of etrasimod 2 mg once daily in patients with isolated proctitis

(centrally read) from the phase 3 ELEVATE UC 52 and ELEVATE UC 12 trials.
Methods: Patients, including those with isolated proctitis (< 10 cm rectal involvement) who met all other inclusion criteria in ELEVATE UC 52 and ELEVATE UC 12, were randomised 2:1 to receive etrasimod or placebo. Primary, secondary and other identified efficacy endpoints and safety were assessed.
Results: The authors analysed data from 64 and 723 patients at week 12 (both trials pooled), and 36 and 397 patients at week 52 (ELEVATE UC 52 only) with isolated proctitis and more extensive colitis (≥ 10 cm rectal involvement), respectively. Patients with isolated proctitis receiving etrasimod demonstrated significant improvements versus placebo, including clinical remission rates at weeks 12 (42.9% vs. 13.6%) and 52 (44.4% vs. 11.1%), endoscopic improvement (52.4% vs. 22.7%) at week 12 and bowel urgency numerical rating scale score at week 12 (all $p < 0.01$). Generally similar trends were observed in patients with more extensive colitis. Safety was consistent across subgroups, with no new findings.

Conclusions: Etrasimod demonstrated significant improvements versus placebo in patients with isolated proctitis, and those with more extensive disease, in most efficacy endpoints at week 12 and 52.

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DOI: 10.1093/ecco-jcc/jjae038

J Crohns Colitis. 2024;18(8):1215–21

Sciberras M, Farrugia Y, Gordon H, Furfaro F, Allocca M, Torres J, Arebi N, Fiorino G, Iacucci M, Verstockt B, Magro F, Katsanos K, Busuttil J, De Giovanni K, Fenech VA, Chetcuti Zammit S, Ellul P

Accuracy of information given by ChatGPT for patients with inflammatory bowel disease in relation to ECCO guidelines

Background: As acceptance of artificial intelligence (AI) platforms increases, more patients will consider these tools as sources of information. The ChatGPT architecture utilizes a neural network to process natural language, thus generating responses based on the context of input text. The accuracy and completeness of ChatGPT3.5 in the context of inflammatory bowel disease (IBD) remains unclear.
Methods: In this prospective study, 38 questions worded by IBD patients were inputted into ChatGPT3.5. The following topics were covered: (1) Crohn's disease (CD), ulcerative colitis (UC), and malignancy; (2) maternal medicine; (3) infection and vaccination; and (4) complementary medicine. Responses given by ChatGPT were assessed for accuracy (1 - completely incorrect to 5 - completely correct) and completeness (3-point Likert scale; range 1 - incomplete to 3 – complete) by 14 expert gastroenterologists, in comparison with relevant European Crohn's and Colitis Organisation (ECCO) guidelines.
Results: In terms of accuracy, most replies (84.2%) had a median score of ≥ 4 (interquartile range [IQR], 2) and a mean score of 3.87 (standard deviation [SD], ± 0.6). For completeness, 34.2% of the replies had a median score of 3 and 55.3% had a median score of between 2 and < 3. Overall, the mean rating was 2.24 (SD, ± 0.4; median, 2; IQR, 1). Though groups 3 and 4 had a higher mean for both accuracy and completeness, there was no significant scoring variation between the 4 question groups (Kruskal-Wallis test $p > 0.05$). However, statistical analysis for the different individual questions revealed a significant difference for both accuracy ($p < 0.001$) and completeness ($p < 0.001$). The questions which rated the highest for both accuracy and completeness were related to smoking, while the lowest rating was related to screening for malignancy and vaccinations especially in the context of immunosuppression and family planning.

Conclusion: This is the first study to demonstrate the capability of an artificial intelligence (AI)-based system to provide accurate and comprehensive answers to real-world patient queries in inflammatory bowel disease. AI systems may serve as a useful adjunct for patients, in addition to standard of care in clinics and validated patient information resources. However, responses in specialist areas may deviate from evidence-based guidance and the replies need to give more firm advice.

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DOI: 10.1093/ecco-jcc/jjae040

IBS, Functional and Motility Disorders

Gastroenterology. 2024;167(2):333–42

Van den Houte K, Colomier E, Routhiaux K, Mariën Z, Schol J, Van den Bergh J, Vanderstappen J, Pauwels N, Joos A, Arts J, Caenepeel P, De Clerck F, Matthys C, Meulemans A, Jones M, Vanuytsel T, Carbone F, Tack J

Efficacy and findings of a blinded randomized reintroduction phase for the low FODMAP diet in irritable bowel syndrome

Background and aims: The efficacy of a low fermentable oligo-, di-, monosaccharides and polyols (FODMAP) diet in irritable bowel syndrome (IBS) is well established. After the elimination period, a reintroduction phase aims to identify triggers. The authors studied the impact of a blinded reintroduction using FODMAP powders to objectively identify triggers and evaluated the effect on symptoms, quality of life, and psychosocial comorbidities.
Methods: Responders to a 6-week low FODMAP diet, defined by a drop in Irritable Bowel Syndrome Symptom Severity Score (IBS-SSS) compared with baseline, entered a 9-week blinded randomized reintroduction phase with 6 FODMAP powders (fructans, fructose, galacto-oligosaccharides, lactose, mannitol, sorbitol) or control (glucose). A rise in IBS-SSS (≥ 50 points) defined a FODMAP trigger. Patients completed daily symptom diaries and questionnaires for quality of life and psychosocial comorbidities.

Results: In 117 recruited patients with IBS, IBS-SSS improved significantly after the elimination period compared with baseline (150 ± 116 vs. 301 ± 97, p < 0.0001, 80% responders). Symptom recurrence was triggered in 85% of the FODMAP powders, by an average of 2.5 ± 2 FODMAPs/patient. The most prevalent triggers were fructans (56%) and mannitol (54%), followed by galacto-oligosaccharides, lactose, fructose, sorbitol, and glucose (respectively 35%, 28%, 27%, 23%, and 26%) with a significant increase in abdominal pain at day 1 for sorbitol/mannitol, day 2 for fructans/galacto-oligosaccharides, and day 3 for lactose.

Conclusion: The authors confirmed the significant benefit of the low fermentable oligo-, di-, monosaccharides and polyols (FODMAP) diet in tertiary-care irritable bowel syndrome. A blinded reintroduction revealed a personalized pattern of symptom recurrence, with fructans and mannitol as the most prevalent, and allows the most objective identification of individual FODMAP triggers.

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DOI: 10.1053/j.gastro.2024.02.008

Gut. 2024;73(6):922–31

Ho FF, Sun H, Zheng H, Wong DCN, Gao YY, Mao C, Cheung YT, Lam CS, Wang MH, Wu IXY, Wu JCY, Chung VCH

Association of healthy lifestyle behaviours with incident irritable bowel syndrome: A large population-based prospective cohort study

Objectives: To evaluate the association between healthy lifestyle behaviours and the incidence of irritable bowel syndrome (IBS).
Design: Population-based prospective cohort study.
Setting: The UK Biobank.
Participants: 64,268 adults aged 37–73 years who had no IBS diagnosis at baseline were enrolled between 2006 and 2010 and followed up to 2022.
Main exposure: The 5 healthy lifestyle behaviours studied were never smoking, optimal sleep, high level of vigorous physical activity, high dietary quality and moderate alcohol intake.
Main outcome measure: The incidence of IBS.
Results: During a mean follow-up of 12.6 years, 961 incident IBS cases (1.5%) were recorded. Among the 64,268 participants (mean age, 55.9 years, 35,342 female [55.0%]), 7604 (11.8%) reported none of the 5 healthy lifestyle behaviours, 20,662 (32.1%) reported 1 behaviour, 21,901 (34.1%) reported 2 behaviours and 14,101 (21.9%) reported 3–5 behaviours at baseline. The multivariable adjusted hazard ratios associated with having 1, 2 and 3–5 behaviours for IBS incidence were 0.79 (95% confidence interval [CI]: 0.65–0.96), 0.64 (95% CI: 0.53–0.78) and 0.58 (95% CI: 0.46–0.72), respectively (p_{trend} < 0.001). Never smoking (0.86, 95% CI: 0.76–0.98, p = 0.02), high level of vigorous physical activity (0.83, 95% CI: 0.73–0.95, p = 0.006) and optimal sleep (0.73, 95% CI: 0.60–0.88, p = 0.001) demonstrated significant independent inverse associations with IBS incidence. No significant interactions were observed between these associations and age, sex, employment status, geographic location, gastrointestinal infection, endometriosis, family history of IBS or lifestyle behaviours.

Conclusions: Adhering to a higher number of healthy lifestyle behaviours is significantly associated with a lower incidence of irritable bowel syndrome (IBS) in the general population. These findings suggest the potential of lifestyle modifications as a primary prevention strategy for IBS.

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DOI: 10.1136/gutjnl-2023-331254

Colorectal Cancer

J Clin Oncol. 2024;42(25):2978–88

Hu H, Zhang J, Li Y, Wang X, Wang Z, Wang H, Kang L, Liu P, Lan P, Wu X, Zhen Y, Pei H, Huang Z, Zhang H, Chen W, Zeng Y, Lai J, Wei H, Huang X, Chen J, Chen J, Tao K, Xu Q, Peng X, Liang J, Cai G, Ding K, Ding Z, Hu M, Zhang W, Tang B, Hong C, Cao J, Huang Z, Cao W, Li F, Wang X, Wang C, Huang Y, Zhao Y, Cai Y, Ling J, Xie X, Wu Z, Shi L, Ling L, Liu H, Wang J, Huang M, Deng Y; OPTICAL study group

Neoadjuvant chemotherapy with oxaliplatin and fluoropyrimidine versus upfront surgery for locally advanced colon cancer: The randomized, phase 3 OPTICAL trial

Purpose: The role of neoadjuvant chemotherapy (NAC) in colon cancer remains unclear. This trial investigated whether 3 months of modified infusional fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or capecitabine and oxaliplatin (CAPOX) as NAC could improve outcomes in patients with locally advanced colon cancer versus upfront surgery.
Patients and methods: OPTICAL was a randomized, phase 3 trial in patients with clinically staged locally advanced colon cancer (T3 with extramural spread into the mesocolic fat ≥ 5 mm or T4). Patients were randomly assigned 1:1 to receive 6 preoperative cycles of mFOLFOX6 or 4 cycles of CAPOX, followed by surgery and adjuvant chemotherapy (NAC group), or immediate surgery and the physician's choice of adjuvant chemotherapy (upfront surgery group). The primary end point was 3-year disease-free survival (DFS) assessed in the modified intention-to-treat (mITT) population.
Results: Between January 2016 and April 2021, of the 752 patients enrolled, 744 patients were included in the mITT analysis (371 in the NAC group; 373 in the upfront surgery group). At a median follow-up of 48.0 months (interquartile range, 46.0–50.1), 3-year DFS rates were 82.1% in the NAC group and 77.5% in the upfront surgery group (stratified hazard ratio [HR] = 0.74 [95% confidence interval {CI}: 0.54–1.03]). The R0 resection was

achieved in 98% of patients who underwent surgery in both groups. Compared with upfront surgery, NAC resulted in a 7% pathologic complete response rate, significantly lower rates of advanced tumor staging (pT3–4: 77% vs. 94%), lymph node metastasis (pN1–2: 31% vs. 46%), and potentially improved overall survival (stratified HR = 0.44 [95% CI: 0.25–0.77]).

Conclusion: Neoadjuvant chemotherapy with modified infusional fluorouracil, leucovorin, and oxaliplatin or capecitabine and oxaliplatin did not show a significant disease-free survival benefit. However, this neoadjuvant approach was safe, resulted in substantial pathologic downstaging, and appears to be a viable therapeutic option for locally advanced colon cancer.

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DOI: 10.1200/jco.23.01889

N Engl J Med. 2024;390(21):1949–58

Chalabi M, Verschoor YL, Tan PB, Balduzzi S, Van Lent AU, Grootscholten C, Dokter S, Büller NV, Grotenhuis BA, Kuhlmann K, Burger JW, Huibregtse IL, Aukema TS, Hendriks ER, Oosterling SJ, Snaebjornsson P, Voest EE, Wessels LF, Beets-Tan RG, Van Leerdam ME, Schumacher TN, van den Berg JG, Beets GL, Haanen JB

Neoadjuvant immunotherapy in locally advanced mismatch repair-deficient colon cancer

Background: Mismatch repair-deficient (dMMR) tumors can be found in 10–15% of patients with non-metastatic colon cancer. In these patients, the efficacy of chemotherapy is limited. The use of neoadjuvant immunotherapy has shown promising results, but data from studies of this approach are limited.
Methods: The authors conducted a phase 2 study in which patients with non-metastatic, locally advanced, previously untreated dMMR colon cancer were treated with neoadjuvant nivolumab plus ipilimumab. The 2 primary end points were safety, defined by timely surgery (i.e., ≤ 2-week delay of planned surgery owing to treatment-related toxic events), and 3-year disease-free survival. Secondary end points included pathological response and results of genomic analyses.
Results: Of 115 enrolled patients, 113 (98%; 97.5% confidence interval [CI]: 93–100) underwent timely surgery; 2 patients had surgery delayed by more than 2 weeks. Grade 3 or 4 immune-related adverse events occurred in 5 patients (4%), and none of the patients discontinued treatment because of adverse events. Among the 111 patients included in the efficacy analysis, a pathological response was observed in 109 (98%; 95% CI: 94–100), including 105 (95%) with a major pathological response (defined as ≤ 10% residual viable tumor) and 75 (68%) with a pathological complete response (0% residual viable tumor). With a median follow-up of 26 months (range, 9–65), no patients have had recurrence of disease.

Conclusions: In patients with locally advanced mismatch repair-deficient colon cancer, neoadjuvant nivolumab plus ipilimumab had an acceptable safety profile and led to a pathological response in a high proportion of patients.

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DOI: 10.1056/nejmoa2400634

EXPERT OPINION

Prof. Dr. Michael Quante

The critical role of MSI status testing in patients receiving neoadjuvant immunotherapy

Immune checkpoint inhibitors have shown significant efficacy in patients with mismatch repair-deficient (dMMR) metastatic colorectal cancers, resulting in improved progression-free survival. dMMR tumors are found in approximately 8–15% of patients with non-metastatic colon cancer. In this subset, chemotherapy has limited efficacy. Even with adjuvant chemotherapy, patients with dMMR tumors, especially those classified as stage T4 or with lymph node involvement, have a high risk of recurrence.
The phase 2 NICHE-2 study, conducted by the Netherlands Cancer Institute, evaluated the safety and efficacy of neoadjuvant immunotherapy in patients with locally advanced dMMR colon cancer. Participants received a single dose of the CTLA4 inhibitor ipilimumab and 2 doses of the PD1 inhibitor nivolumab, followed by surgery within 4 weeks. Of the 115 patients enrolled, 98% (97.5% confidence interval [CI]: 93–100) underwent surgery as planned. In the efficacy analysis of 111 patients, 98% (95% CI: 94–100) showed a pathological response, with 95% achieving a major pathological response and 68% achieving a complete pathological response. No patients discontinued treatment due to adverse events, and no disease recurrence was observed after a median follow-up of 26 months.
While these findings suggest that neoadjuvant nivolumab and ipilimumab may offer a new treatment approach for locally advanced dMMR colon cancer, they do not yet support this approach as the standard of care for all patients with early-stage dMMR colon cancer. Surgical resection alone is curative for most stage II dMMR cases, and adjuvant therapy is primarily recommended for stage III disease. Staging of dMMR colon cancer is challenging due to the frequent presence of enlarged lymph nodes caused by immune infiltration, leading to the possibility of overtreatment. Additionally, while the incidence of grade 3 or 4 adverse events from immune checkpoint blockade in this study was only 4%, 11% of patients developed long-term endocrine dysfunction. A randomized trial comparing neoadjuvant immunotherapy plus surgery with surgery alone or surgery followed by adjuvant immunotherapy in node-positive disease would help clarify the risk-benefit profile. The key takeaway remains the importance of testing for MMR/MSI status in all patients with colon cancer in order to guide appropriate treatment. ■

Colorectal Cancer Screening/ Endoscopy

Lancet Gastroenterol Hepatol. 2024;9(9):802–10

Ortiz O, Daca-Alvarez M, Rivero-Sanchez L, Gimeno-Garcia AZ, Carrillo-Palau M, Alvarez V, Ledo-Rodriguez A, Ricciardiello L, Pierantoni C, Hüneburg R, Nattermann J, Bisschops R, Tejpar S, Huerta A, Riu Pons F, Alvarez-Urturi C, López-Vicente J, Repici A, Hassan C, Cid L, Cavestro GM, Romero-Mascarell C, Gordillo J, Puig I, Herraiz M, Betes M, Herrero J, Jover R, Balaguer F, Pellisé M; TIMELY study group

An artificial intelligence-assisted system versus white light endoscopy alone for adenoma detection in individuals with Lynch syndrome (TIMELY): An international, multicentre, randomised controlled trial

Background: Computer-aided detection (CADe) systems for colonoscopy have been shown to increase small polyp detection during colonoscopy in the general population. People with Lynch syndrome represent an ideal target population for CADe-assisted colonoscopy because adenomas, the primary cancer precursor lesions, are characterised by their small size and higher likelihood of showing advanced histology. The authors aimed to evaluate the performance of CADe-assisted colonoscopy in detecting adenomas in individuals with Lynch syndrome.
Methods: TIMELY was an international, multicentre, parallel, randomised controlled trial done in 11 academic centres and 6 community centres in Belgium, Germany, Italy, and Spain. Individuals aged 18 years or older with pathogenic or likely pathogenic MLH1, MSH2, MSH6, or EPCAM variants were enrolled. Participants were consecutively randomly assigned (1:1) to either CADe-assisted white light endoscopy (WLE) or WLE alone. A centre-stratified randomisation sequence was generated through a computer-generated system with a separate randomisation list for each centre according to block-permuted randomisation (block size 26 patients per centre). Allocation was automatically provided by the online AEG-REDCap database. Participants were masked to the random assignment but endoscopists were not. The primary outcome was the mean number of adenomas per colonoscopy, calculated by dividing the total number of adenomas detected by the total number of colonoscopies and assessed in the intention-to-treat population.
Findings: Between September 13, 2021, and April 6, 2023, 456 participants were screened for eligibility, 430 of whom were randomly assigned to receive CADe-assisted colonoscopy (n = 214) or WLE (n = 216). 256 (60%) participants were female and 174 (40%) were male. In the intention-to-treat analysis, the mean number of adenomas per colonoscopy was 0.64 (standard deviation [SD], 1.57) in the CADe group and 0.64 (SD, 1.17) in the WLE group (adjusted rate ratio = 1.03 [95% confidence interval: 0.72–1.47]; p = 0.87). No adverse events were reported during the trial.

Interpretation: In this multicentre international trial, computer-aided detection did not improve the detection of adenomas in individuals with Lynch syndrome. High-quality procedures and thorough inspection and exposure of the colonic mucosa remain the cornerstone in surveillance of Lynch syndrome.

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DOI: 10.1016/s2468-1253(24)00187-0

Gastroenterology. 2024;167(2):378–91

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Comparative effectiveness and cost-effectiveness of colorectal cancer screening with blood-based biomarkers (liquid biopsy) vs. fecal tests or colonoscopy

Background and aims: Colorectal cancer (CRC) screening is highly effective but underused. Blood-based biomarkers (liquid biopsy) could improve screening participation.
Methods: Using the established Markov model, screening every 3 years with a blood-based test that meets minimum Centers for Medicare & Medicaid Services' thresholds (CMS_{min}) (CRC sensitivity 74%, specificity 90%) was compared with established alternatives. Test attributes were varied in sensitivity analyses.
Results: CMS_{min} reduced CRC incidence by 40% and CRC mortality by 52% versus no screening. These reductions were less profound than the 68–79% and 73–81%, respectively, achieved with multi-target stool DNA every 3 years, annual fecal immunochemical testing (FIT), or colonoscopy every 10 years. Assuming the same cost as multi-target stool DNA, CMS_{min} cost $28,500/quality-adjusted life-year gained versus no screening, but FIT, colonoscopy, and multi-target stool DNA were less costly and more effective. CMS_{min} would match FIT's clinical outcomes if it achieved 1.4–1.8-fold FIT's participation rate. Advanced precancerous lesion (APL) sensitivity was a key determinant of a test's effectiveness. A paradigm-changing blood-based test (sensitivity > 90% for CRC and 80% for APL; 90% specificity; cost ≤ $120–$140) would be cost-effective versus FIT at comparable participation.

Conclusions: Minimum Centers for Medicare & Medicaid Services' thresholds (CMS_{min}) could contribute to colorectal cancer (CRC) control by achieving screening in those who will not use established methods. Substituting blood-based testing for established effective CRC screening methods will require higher CRC and advanced precancerous lesion (APL) sensitivities that deliver programmatic benefits matching those of fecal immunochemical testing. High APL sensitivity, which can result in CRC prevention, should be a top priority for screening test developers. APL detection should not be penalized by a definition of test specificity that focuses on CRC only.

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DOI: 10.1053/j.gastro.2024.03.011

EXPERT OPINION

PD Dr. Armin Küllmer

Liquid biopsy for colon cancer screening – balancing hype and hope

Numerous studies have impressively demonstrated the importance of colorectal cancer screening and its associated prognostic value. Despite this substantial body of evidence, uptake of colorectal cancer screening remains insufficient, particularly with regard to colonoscopy. The implementation of blood testing as a screening tool may increase individuals' willingness to undergo screening, reduce healthcare costs, and ultimately also mitigate the risks associated with colonoscopy, albeit rare. This study therefore examined the potential introduction of a hypothetical blood test as a screening method that could satisfy the minimum requirements for approval of the FDA, which would lead to coverage by the U.S. Centers for Medicare & Medicaid Services for health insurers. Using sophisticated health economic models, various health-policy scenarios were explored and evaluated to determine whether introducing this new screening test would be beneficial. The results clearly indicate that the blood-based test does not match the efficacy of existing alternatives, as they are both more effective and more cost-efficient. Although improved participation in screening due to the blood-based test could partially compensate for its lower effectiveness, this effect is limited. Conversely the evaluation revealed that a significantly improved test capable of detecting both precancerous and cancerous lesions (which, under current assessment protocols, might be paradoxically classified as "false positives") could yield outcomes comparable to those of the DNA stool test. While the publication highlights the significant potential of blood-based tests ("liquid biopsy"), it also emphasizes that considerable progress is needed before an alternative suitable for routine use and competitive with existing methods can be developed. In addition, the therapeutic benefit of polypectomy as part of the detection process in colonoscopy was not factored into this analysis. The premature introduction of less effective testing methods risks leading patients to choose these options for the sake of convenience, thereby forgoing more reliable and established methods such as colonoscopy screening. Such a shift could ultimately undermine efforts to improve preventive care. ■

Gut. 2024;73(8):1313–20

Mao X, Cheung KS, Tan JT, Mak LY, Lee CH, Chiang CL, Cheng HM, Hui RWH, Yuen MF, Leung WK, Seto WK

Optimal glycaemic control and the reduced risk of colorectal adenoma and cancer in patients with diabetes: A population-based cohort study

Objective: Whether varying degrees of glycaemic control impact colonic neoplasm risk in patients with diabetes mellitus (DM) remains uncertain.

Design: Patients with newly diagnosed DM were retrieved from 2005 to 2013. Optimal glycaemic control at baseline was defined as mean haemoglobin A1c (HbA1c) < 7%. Outcomes of interest included colorectal cancer (CRC) and colonic adenoma development. The authors used propensity score matching with competing risk models to estimate subdistribution hazard ratios (SHRs). They further analysed the combined effect of baseline and postbaseline glycaemic control based on time-weighted mean HbA1c during follow-up.
Results: Of 88,468 propensity score-matched patients with DM (mean [standard deviation] age, 61.5 [± 11.7] years; male, 47,127 [53.3%]), 1229 (1.4%) patients developed CRC during a median follow-up of 7.2 (interquartile range, 5.5–9.4) years. Optimal glycaemic control was associated with lower CRC risk (SHR = 0.72; 95% confidence interval [CI]: 0.65–0.81). The beneficial effect was limited to left-sided colon (SHR = 0.71; 95% CI: 0.59–0.85) and rectum (SHR = 0.71; 95% CI: 0.57–0.89), but not right-sided colon (SHR = 0.86; 95% CI: 0.67–1.10). Setting suboptimal glycaemic control at baseline/postbaseline as a reference, a decreased CRC risk was found in optimal control at postbaseline (SHR = 0.79), baseline (SHR = 0.71) and both time periods (SHR = 0.61). Similar associations were demonstrated using glycaemic control as a time-varying covariate (HR = 0.75). A stepwise greater risk of CRC was found (p_{trend} < 0.001) with increasing HbA1c (SHRs = 1.34, 1.30, 1.44, 1.58 for HbA1c 7.0% to < 7.5%, 7.5% to < 8.0%, 8.0% to < 8.5% and ≥ 8.5%, respectively). Optimal glycaemic control was associated with a lower risk of any, non-advanced and advanced colonic adenoma (SHRs = 0.73–0.87).

Conclusion: Glycaemic control in patients with diabetes mellitus was independently associated with the risk of colonic adenoma and colorectal cancer development with a biological gradient.

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DOI: 10.1136/gutjnl-2023-331701 ■

Am J Gastroenterol. 2024;119(6):1154–7

Yao R, Gala KS, Ghusn W, Abboud DM, Wallace FK, Vargas EJ

Effect of glucagon-like peptide-1 receptor agonists on bowel preparation for colonoscopy

Introduction: Inadequate bowel preparation can result in decreased diagnostic accuracy and therapeutic safety of colonoscopy for colon cancer screening. The Boston Bowel Preparation Scale (BBPS) has been used to assess the quality of bowel preparation. Glucagon-like peptide-1 receptor agonists (GLP-1RA) are commonly used medications for diabetes mellitus and obesity that are known to delay gastrointestinal motility. The authors hypothesized that the use of GLP-1RA would be associated with decreased quality of bowel preparation.
Methods: They performed a retrospective cohort study of patients who underwent screening or surveillance colonoscopy at a large academic medical center between December 2021 and December 2022. Patients

taking any GLP-1RA for diabetes or obesity during colonoscopy were included and were defined as cases, and patients who were prescribed GLP-1RA at one point but not within 3 months of colonoscopy were defined as controls. Patients on any promotility or antimotility agents and those without BBPS recorded on their procedure report were excluded. Independent t test assessed statistical differences in the case and control groups to compare the quality of bowel preparation for continuous variables, and the $\chi 2$ test was used for categorical variables. Multivariate linear regression including diabetes as a covariate was also performed for continuous variables, and multivariate logistic regression was performed for categorical variables.
Results: A total of 446 patients were included in the study, comprising 265 (59%) cases and 181 (41%) controls. There were no statistically significant differences between groups at baseline except for the diagnosis of diabetes (p = 0.001) with a higher proportion of patients with diabetes in the cases. The mean BBPS was significantly higher in controls (7.0 ± 1.9 vs. 7.5 ± 2.4, p = 0.046) when controlling for diabetes. The percentage of patients with a total BBPS score of < 5 was significantly higher in cases (15.5% vs. 6.6%, p = 0.01). The proportion of patients who required a repeat colonoscopy due to poor bowel preparation was also significantly higher in cases (18.9% vs. 11.1%, p = 0.041).

Discussion: The use of glucagon-like peptide-1 receptor agonists was associated with a statistically significantly lower quality of bowel preparation, with additional clinical significance given a notable difference in the need for a repeat colonoscopy. It will be essential to understand the cumulative effect of medications that may delay gastric emptying on the quality of bowel preparation to better understand the appropriate measures and counseling that need to be taken before undergoing outpatient colonoscopies.

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DOI: 10.14309/ajg.0000000000002564 ■

Gastroenterology. 2024;167(4):764–77

Steinbrück I, Ebigbo A, Kuellmer A, Schmidt A, Kouladouros K, Brand M, Koenen T, Rempel V, Wannhoff A, Faiss S, Pech O, Möschler O, Dumoulin FL, Kirstein MM, von Hahn T, Allescher HD, Gölder SK, Götz M, Hollerbach S, Lewerenz B, Meining A, Messmann H, Rösch T, Allgaier HP

Cold versus hot snare endoscopic resection of large non-pedunculated colorectal polyps: Randomized controlled German CHRONICLE trial

Background and aims: Endoscopic mucosal resection (EMR) is standard therapy for non-pedunculated colorectal polyps ≥ 20 mm. It has been suggested recently that polyp resection without current (cold resection) may be superior to the standard technique using cutting/coagulation current (hot resection) by reducing adverse events (AEs), but evidence from a randomized trial is missing.
Methods: In this randomized controlled multicentric trial involving 19 centers, non-pedunculated colorectal polyps ≥ 20 mm were randomly assigned to cold or hot EMR. The primary outcome was major AE (e.g., perforation or postendoscopic bleeding). Among secondary outcomes, major AE subcategories, postpolypectomy syndrome, and residual adenoma were most relevant.
Results: Between 2021 and 2023, there were 396 polyps in 363 patients (48.2% were female) enrolled for the intention-to-treat analysis. Major AEs occurred in 1.0% of the cold group and in 7.9% of the hot group (p = 0.001; odds ratio [OR] = 0.12; 95% confidence interval [CI]: 0.03–0.54). Rates for perforation and postendoscopic bleeding were significantly lower in the cold group, with 0% versus 3.9% (p = 0.007) and 1.0% versus 4.4% (p = 0.040). Postpolypectomy syndrome occurred with similar frequency (3.1% vs 4.4%; p = 0.490). After cold resection, residual adenoma was found more frequently, with 23.7% versus 13.8% (p = 0.020; OR = 1.94; 95% CI: 1.12–3.38). In multivariable analysis, lesion diameter of ≥ 4 cm was an independent predictor both for major AEs (OR = 3.37) and residual adenoma (OR = 2.47) and high-grade dysplasia/cancer for residual adenoma (OR = 2.92).

Conclusions: Cold resection of large, non-pedunculated colorectal polyps appears to be considerably safer than hot endoscopic mucosal resection; however, at the cost of a higher residual adenoma rate. Further studies have to confirm to what extent polyp size and histology can determine an individualized approach.

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DOI: 10.1053/j.gastro.2024.05.013 ■

Small Bowel Syndrome

Aliment Pharmacol Ther. 2024;60(6):727–36

Timmer AS, de Vries F, Gans SL, Zwanenburg PR, Bemelman WA, Dijkgraaf MGW, Dijkstra G, van der Heide F, Haveman JW, Serlie MJ, Boermeester MA

Clinical trial: The effectiveness of long-acting somatostatin analogue for output reduction of high-output intestinal fistula or small bowel enterostomy. A randomised controlled trial

Background: High-output intestinal fistulas and small bowel enterostomies are associated with morbidity and mortality. Current standard treatment for output reduction consists of fluid and dietary restrictions and medical therapy. There is conflicting evidence regarding the use of somatostatin analogues for output reduction.
Aim: The aim of this study is to investigate whether lanreotide, added to current standard treatment, further reduces intestinal output in patients with high-output fistulas and enterostomies.
Methods: This was an open-label, multicentre, randomised controlled trial. Adult patients with a high-output intes-

tinal fistula (> 500 ml/24 h) or small bowel enterostomy (> 1500 ml/24 h) more than 4 weeks postsurgery and receiving standard medical treatment (dietary and fluid restriction, proton-pump inhibitors, loperamide and codeine) for at least 2 weeks were eligible for inclusion. The authors randomised patients 1:1 between continuing standard treatment (control), and subcutaneous lanreotide 120 mg every 4 weeks with standard treatment. The primary outcome was the number of responders, with response defined as an output reduction of ≥ 25%, 8 weeks after randomisation. The proportional change in output was also investigated.

Results: 40 patients were randomised; 17 had a fistula and 23 a small bowel enterostomy. There were 9/20 responders in the intervention group and 2/20 in the control group (p = 0.013). The proportional output reduction was -26% (interquartile range [IQR], -4 to -38) in the intervention group, compared to an increase of 4% (IQR, 20 to -13) in the control group (p = 0.004).

Conclusions: In patients with a high-output fistula or small bowel enterostomy, addition of lanreotide to current standard treatment can provide a clinically relevant output reduction.

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DOI: 10.1111/apt.18166

PANCREAS

Pancreatic Tumors

Gut. 2024;73(6):955–65

Hamada T, Oyama H, Igarashi A, Kawaguchi Y, Lee M, Matsui H, Michihata N, Nakai Y, Fushimi K, Yasunaga H, Fujishiro M

Optimal age to discontinue long-term surveillance of intraductal papillary mucinous neoplasms: Comparative cost-effectiveness of surveillance by age

Objective: Current guidelines recommend long-term image-based surveillance for patients with low-risk intraductal papillary mucinous neoplasms (IPMNs). This simulation study aimed to examine the comparative cost-effectiveness of continued versus discontinued surveillance at different ages and define the optimal age to stop surveillance.
Design: The authors constructed a Markov model with a lifetime horizon to simulate the clinical course of patients with IPMNs receiving imaging-based surveillance. They calculated incremental cost-effectiveness ratios (ICERs) for continued versus discontinued surveillance at different ages to stop surveillance, stratified by sex and IPMN types (branch-duct vs. mixed-type). The authors determined the optimal age to stop surveillance as the lowest age at which the ICER exceeded the willingness-to-pay threshold of US$100,000 per quality-adjusted life year. To estimate model parameters, they used a clinical cohort of 3000 patients with IPMNs and a national database including 40,166 patients with pancreatic cancer receiving pancreatectomy as well as published data.
Results: In male patients, the optimal age to stop surveillance was 76–78 years irrespective of the IPMN types, compared with 70, 73, 81, and 84 years for female patients with branch-duct IPMNs < 20 mm, = 20–29 mm, ≥ 30 mm and mixed-type IPMNs, respectively. The suggested ages became younger according to an increasing level of comorbidities. In cases with high comorbidity burden, the ICERs were above the willingness-to-pay threshold irrespective of sex and the size of branch-duct IPMNs.

Conclusions: The cost-effectiveness of long-term intraductal papillary mucinous neoplasm (IPMN) surveillance depended on sex, IPMN types, and comorbidity levels, suggesting the potential to personalise patient management from the health economic perspective.

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DOI: 10.1136/gutjnl-2023-330329 ■

United European Gastroenterol J. 2024;12(6):726–36

Selin D, Maret-Ouda J, Oskarsson V, Lindblad M, Arnelo U, Holmberg M, Yang B, Sema K, Nilsson M, Sadr-Azodi O

Exploring the association between acute pancreatitis and biliary tract cancer: A large-scale population-based matched cohort study

Background: Biliary tract cancer (BTC) often goes undetected until its advanced stages, resulting in a poor prognosis. Given the anatomical closeness of the gallbladder and bile ducts to the pancreas, the inflammatory processes triggered by acute pancreatitis might increase the risk of BTC.
Objective: To assess the association between acute pancreatitis and the risk of BTC.
Methods: Using the Swedish Pancreatitis Cohort (SwePan), the authors compared the BTC risk in patients with a first-time episode of acute pancreatitis during 1990–2018 to a 1:10 matched pancreatitis-free control group. Multivariable Cox regression models, stratified by follow-up duration, were used to calculate hazard ratios (HRs), adjusting for socioeconomic factors, alcohol use, and comorbidities.
Results: BTC developed in 0.94% of 85,027 acute pancreatitis patients and in 0.23% of 814,993 controls. The BTC risk notably increased within 3 months of hospital discharge (HR = 82.63; 95% confidence interval [CI]: 63.07–108.26) and remained elevated beyond 10 years of follow-up (HR = 1.82; 95% CI: 1.35–2.47). However, the long-term risk of BTC subtypes did not increase with anatomical proximity to the pancreas, with a null association for gallbladder and extrahepatic tumors. Importantly, patients with acute pancreatitis had a higher occurrence of early-stage BTC within 2 years of hospital discharge than controls (13.0% vs. 3.6%; $p < 0.01$).

Conclusion: This nationwide study found an elevated biliary tract cancer (BTC) risk in acute pancreatitis patients; however, the risk estimates for BTC subtypes were inconsistent, thereby questioning the causality of the association. Importantly, the amplified detection of early-stage BTC within 2 years after a diagnosis of acute pancreatitis underscores the necessity for proactive BTC surveillance in these patients.

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DOI: 10.1002/ueg2.12567 ■

Gut. 2024;73(8):1336–42

Crippa S, Marchegiani G, Belfiori G, Rancoita PVM, Pollini T, Burelli A, Apadula L, Scarale MG, Socci D, Biancotto M, Vanella G, Arcidiacono PG, Capurso G, Salvia R, Falconi M

Impact of age, comorbidities and relevant changes on surveillance strategy of intraductal papillary mucinous neoplasms: A competing risk analysis

Objective: Cost-effectiveness of surveillance for branch-duct intraductal papillary mucinous neoplasms

(BD-IPMNs) is debated. The authors combined different categories of risks of IPMN progression and of IPMN-unrelated mortality to improve surveillance strategies.
Design: Retrospective analysis of 926 presumed BD-IPMNs lacking worrisome features/high-risk stigmata under surveillance. Charlson Comorbidity Index (CACI) defined the severity of comorbidities. IPMN-relevant changes included development of worrisome features/high-risk stigmata, pancreatectomy or death for IPMN or pancreatic cancer. Pancreatic malignancy-unrelated death was recorded. Cumulative incidence of IPMN-relevant changes were estimated using the competing risk approach.
Results: 5-year cumulative incidence of relevant changes was 17.83% and 1.6% developed pancreatic malignancy. 5-year cumulative incidences for IPMN-relevant changes were 13.73%, 19.93% and 25.04% in low-risk, intermediate-risk and high-risk groups, respectively. Age ≥ 75 years (hazard ratio [HR] = 4.15) and CACI > 3 (HR = 3.61) were independent predictors of pancreatic malignancy-unrelated death. 5-year cumulative incidence for death for other causes was 15.93% for age ≥ 75+CACI > 3 group, and 1.49% for age < 75+CACI ≤ 3. 5-year cumulative incidence of IPMN-relevant changes were 13.94% in patients with age < 75+CACI ≤ 3 compared with 29.60% in those with age ≥ 75+CACI > 3. In this group 5-year rate of malignancy-free patients was 95.56% with a 5-year survival of 79.51%.

Conclusion: Although it is not uncommon, the occurrence of changes considered by current guidelines as relevant during surveillance of low-risk branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs), malignancy rate is low and survival is significantly affected by competing patients' age and comorbidities. IPMN surveillance strategy should be tailored based on these features and modulated over time.

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DOI: 10.1136/gutjnl-2023-329961

Lancet. 2024;403(10446):2807–17

Singh S, Halperin D, Myrehaug S, Herrmann K, Pavel M, Kunz PL, Chasen B, Tafuto S, Lastoria S, Capdevila J, García-Burillo A, Oh DY, Yoo C, Halfdanarson TR, Falk S, Folitar I, Zhang Y, Aimone P, de Herder WW, Ferone D; NETTER-2 Trial Investigators

[^{177}Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2–3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): An open-label, randomised, phase 3 study

Background: There are currently no standard first-line treatment options for patients with higher grade 2–3, well-differentiated, advanced, gastroenteropancreatic neuroendocrine tumours. The present study aimed to investigate the efficacy and safety of first-line [^{177}Lu]Lu-DOTA-TATE (^{177}Lu-Dotatate) treatment.
Methods: NETTER-2 was an open-label, randomised, parallel-group, superiority, phase 3 trial. The authors enrolled patients (aged ≥ 15 years) with newly diagnosed higher grade 2 (Ki67 ≥ 10% and ≤ 20%) and grade 3 (Ki67 > 20% and ≤ 55%), somatostatin receptor-positive (in all target lesions), advanced gastroenteropancreatic neuroendocrine tumours from 45 centres across 9 countries in North America, Europe, and Asia. They used interactive response technologies to randomly assign (2:1) patients to receive 4 cycles (cycle interval was 8 weeks ± 1 week) of intravenous ^{177}Lu-Dotatate plus intramuscular octreotide 30 mg long-acting repeatable (LAR), then octreotide 30 mg LAR every 4 weeks (^{177}Lu-Dotatate group) or high-dose octreotide 60 mg LAR every 4 weeks (control group), stratified by neuroendocrine tumour grade (2 vs. 3) and origin (pancreas vs. other). Tumour assessments were done at baseline, week 16, and week 24, and then every 12 weeks until disease progression or death. The primary endpoint was progression-free survival by blinded, independent, central radiology assessment. The authors did the primary analysis at 101 progression-free survival events as the final progression-free survival analysis.
Findings: Between January 22, 2020, and October 13, 2022, they screened 261 patients, 35 (13%) of whom were excluded. They randomly assigned 226 (87%) patients (121 [54%] male and 105 [46%] female) to the ^{177}Lu-Dotatate group (n = 151 [67%]) and to the control group (n = 75 [33%]). Median progression-free survival was 8.5 months (95% confidence interval [CI]: 7.7–13.8) in the control group and 22.8 months (95% CI: 19.4–not estimated) in the ^{177}Lu-Dotatate group (stratified hazard ratio = 0.276 [0.182–0.418]; p < 0.0001). During the treatment period, adverse events (of any grade) occurred in 136 (93%) of 147 treated patients in the ^{177}Lu-Dotatate group and 69 (95%) of 73 treated patients in the control group. There were no study drug-related deaths during the treatment period.

Interpretation: First-line ^{177}Lu-Dotatate plus octreotide LAR significantly extended median progression-free survival (by 14 months) in patients with grade 2 or 3 advanced gastroenteropancreatic neuroendocrine tumours. ^{177}Lu-Dotatate should be considered a new standard of care in first-line therapy in this population.

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DOI: 10.1016/s0140-6736(24)00701-3

Acute/Chronic Pancreatitis

Endoscopy. 2024;56(9):676–83

de Jong DM, Stassen PMC, Schoots IG, Verdonk RC, Bruno MJ, Voermans RP, de Jonge PJF

Impact of long-term transmural plastic stents on recurrence after endoscopic treatment of walled-off pancreatic necrosis

Background: Endoscopic transmural drainage (ETD) using double-pigtail stents (DPSs) is a well-established treatment for walled-off pancreatic necrosis (WON).

This study aimed to compare outcomes in patients undergoing ETD with DPSs left indwelling versus those where stents were removed or migrated.
Methods: This retrospective multicenter cohort study included patients with WON who underwent ETD using DPSs between July 2001 and December 2019. The primary outcome was recurrence of a pancreatic fluid collection (PFC). Secondary outcomes were long-term complications and recurrence-associated factors. Competing risk regression analysis considered DPS removal or migration as time-varying covariates.
Results: Among 320 patients (median age, 58 years; 36% women), DPSs were removed in 153 (47.8%), migrated spontaneously in 27 (8.4%), and remained indwelling in 140 (43.8%). PFC recurrence was observed in 57 patients (17.8%): after removal (n = 39; 25.5%); after migration (n = 4; 14.8%); in patients with indwelling DPSs (n = 14; 10.0%). In 25 patients (7.8%), drainage of recurrent PFC was indicated. Risk factors for recurrence were DPS removal or migration (hazard ratio [HR] = 3.45, 95% confidence interval [CI]: 1.37–8.70) and presence of a disconnected pancreatic duct (HR = 5.08, 95% CI: 1.84–14.0).

Conclusions: Among patients who undergo endoscopic transmural drainage of walled-off pancreatic necrosis, leaving double-pigtail stents (DPSs) in situ seems to lower the risk of recurrent fluid collections, without any long-term DPS-related complications. These results suggest that DPSs should not be routinely removed and can be safely left indwelling indefinitely.

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DOI: 10.1055/a-2307-7123

LIVER AND BILE

Viral Hepatitis

N Engl J Med. 2024;391(2):133–43

Asselah T, Chulanov V, Lampertico P, Wedemeyer H, Streinu-Cercel A, Pântea V, Lazar S, Placinta G, Gherlan GS, Bogomolov P, Stepanova T, Morozov V, Syutkin V, Sagalova O, Manuilov D, Mercier RC, Ye L, Da BL, Chee G, Lau AH, Osinusi A, Bourliere M, Ratziu V, Pol S, Hilleret MN, Zoulim F

Bulevirtide combined with pegylated interferon for chronic hepatitis D

Background: In a phase 3 trial, bulevirtide monotherapy led to a virologic response in patients with chronic hepatitis D. Pegylated interferon (peginterferon) α-2a is recommended by guidelines as an off-label treatment for this disease. The role of combination therapy with bulevirtide and peginterferon α-2a, particularly with regard to finite treatment, is unclear.
Methods: In this phase 2b, open-label trial, the authors randomly assigned patients to receive peginterferon α-2a alone (180 µg per week) for 48 weeks; bulevirtide at a daily dose of 2 mg or 10 mg plus peginterferon α-2a (180 µg per week) for 48 weeks, followed by the same daily dose of bulevirtide for 48 weeks; or bulevirtide at a daily dose of 10 mg alone for 96 weeks. All the patients were followed for 48 weeks after the end of treatment. The primary end point was an undetectable level of hepatitis D virus (HDV) RNA at 24 weeks after the end of treatment. The primary comparison was between the 10-mg bulevirtide plus peginterferon α-2a group and the 10-mg bulevirtide monotherapy group.
Results: A total of 24 patients received peginterferon α-2a alone, 50 received 2 mg and 50 received 10 mg of bulevirtide plus peginterferon α-2a, and 50 received 10 mg of bulevirtide monotherapy. At 24 weeks after the end of treatment, HDV RNA was undetectable in 17% of the patients in the peginterferon α-2a group, in 32% of those in the 2-mg bulevirtide plus peginterferon α-2a group, in 46% of those in the 10-mg bulevirtide plus peginterferon α-2a group, and in 12% of those in the 10-mg bulevirtide group. For the primary comparison, the between-group difference was 34 percentage points (95% confidence interval: 15–50; $p < 0.001$). At 48 weeks after the end of treatment, HDV RNA was undetectable in 25% of the patients in the peginterferon α-2a group, in 26% of those in the 2-mg bulevirtide plus peginterferon α-2a group, in 46% of those in the 10-mg bulevirtide plus peginterferon α-2a group, and in 12% of those in the 10-mg bulevirtide group. The most frequent adverse events were leukopenia, neutropenia, and thrombocytopenia. The majority of adverse events were of grade 1 or 2 in severity.
Conclusions: The combination of 10 mg bulevirtide plus pegylated interferon α-2a was superior to bulevirtide monotherapy with regard to an undetectable hepatitis D virus RNA level at 24 weeks after the end of treatment.

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DOI: 10.1056/nejmoa2314134

EXPERT OPINION

Prof. Dr. Tobias Böttler

Combination therapy for chronic hepatitis D virus infection?

The treatment of chronic hepatitis D virus (HDV) infection, which tends to progress more rapidly than other hepatitis virus infections, remains challenging. Current therapies, including nucleoside and nucleotide analogues, demonstrate limited efficacy. However, treatment with pegylated interferon α has proven effective in reducing viral loads, achieving undetectable levels in some patients. Despite these effects, viral relapse is common and can occur even years post-therapy. Therapy with the recently approved entry inhibitor bulevirtide has become a clinical standard in many countries. Despite this significant progress, key aspects such as the optimal duration of therapy, potential combination therapy partners, and the most effective dosing regimen (with the currently approved dose being 2 mg/day) remain uncertain. This study primarily addresses the latter two aspects. The combination of pegylated interferon-α with bulevirtide resulted in significantly better virological and biochemical response rates at the end of therapy compared to either monotherapy alone. A detailed analysis of response rates both at the end of therapy and 48 weeks post-therapy suggests that the benefit of pegylated interferon α primarily lies in enhancing response rates during therapy rather than in reducing virological relapse rates among patients who initially responded to therapy. In fact, all bulevirtide groups experienced a comparable decline rate within the first 48 weeks post-treatment, although the combination therapy arms began from significantly higher response levels. However, due to the substantial adverse effect profile of pegylated interferon α, combination therapy is a viable option only for certain patients with chronic hepatitis D. Regarding dose, combination therapy showed higher response rates in the 10 mg/day group, although the study lacked sufficient power to directly compare this with the 2 mg/day group. Interestingly, similar findings regarding virological response were observed in a study on bulevirtide monotherapy (DOI: 10.1016/j.jhep.2024.05.001). In conclusion, the current study suggests that combination therapy with pegylated interferon α and bulevirtide at a dose of 10 mg/day is a promising option. However, the optimal duration of therapy is still undetermined and warrants further investigation. Additionally, other agents are currently in preclinical and clinical development, making it an exciting field to watch as these new therapeutic options evolve. ■

Lancet Gastroenterol Hepatol. 2024;9(8):718–33

Janssen HLA, Lim YS, Lampertico P, Heo J, Chen CY, Fournier C, Tsang TYO, Bae H, Chen CH, Coffin CS, Ahn SH, Trinh H, Flaherty JF, Abramov F, Zhao Y, Liu Y, Lau A, German P, Chuang WL, Agarwal K, Gane E

Switching to tenofovir alafenamide in patients with virologically suppressed chronic hepatitis B and renal or hepatic impairment: Final week 96 results from an open-label, multicentre, phase 2 study

Background: Phase 3 studies in patients with chronic hepatitis B have shown tenofovir alafenamide to have non-inferior efficacy to tenofovir disoproxil fumarate, with improved renal and bone safety. This study was conducted to evaluate the safety and efficacy of switching to tenofovir alafenamide in participants with chronic hepatitis B and renal or hepatic impairment.
Methods: This open-label, multicentre, phase 2 study was done in 8 countries or territories at 30 sites. The authors recruited adults (≥ 18 years) with chronic hepatitis B who were virally suppressed on nucleos(t)ide analogues and had renal impairment (part A: moderate or severe in cohort 1 [estimated glomerular filtration rate by the Cockcroft-Gault formula {$eGFR_{CG}$} 15–59 ml/min] or end-stage renal disease [$eGFR_{CG}$ < 15 ml/min] on haemodialysis in cohort 2) or hepatic impairment including decompensation (part B: Child-Turcotte-Pugh score 7–12). Participants switched to 25 mg of tenofovir alafenamide given orally once daily for 96 weeks. The primary end point was the proportion of participants with viral suppression (HBV DNA < 20 IU/ml) at week 24 by missing-equals-failure analysis. Efficacy (full analysis set) and safety (safety analysis set) analyses included all enrolled participants who received at least 1 dose of the study drug. Week 96 safety was assessed, including renal and bone parameters.
Findings: 124 participants (93 in part A [78 in cohort 1 and 15 in cohort 2] and 31 in part B) were enrolled between August 11, 2017, and October 17, 2018, and included in the full and safety analysis sets. 106 participants (85%) completed the study. There were 69 men (74%) and 24 women (26%) in part A and 21 men (68%) and 10 women (32%) in part B. At week 24, 91 (97.8%, 95% confidence interval [CI]: 92.4–99.7) of 93 individuals in part A (76 [97.4%, 95% CI: 91.0–99.7] of 78 in cohort 1 and 15 [100.0%, 95% CI: 78.2–100.0] of 15 in cohort 2) and 31 (100.0%, 95% CI: 88.8–100.0) in part B had HBV DNA of less than 20 IU/ml. By week 96, the most common adverse event was upper respiratory tract infection, which occurred in 14 participants (15%) in part A and in 6 participants (19%) in part B. Serious adverse events occurred in 20 part A participants (22%) and in 10 part B participants (32%); none were related to treatment. No treatment-related deaths occurred. At week 96, median change in estimated glomerular filtration rate (Cockcroft-Gault method) was 1.0 ml/min (interquartile range [IQR], -2.8–4.5) in cohort 1 and -2.4 ml/min (IQR, -11.4–10.7) in part B. Mean changes in spine and hip bone mineral density were 1.02% (standard deviation [SD], 4.44) and 0.20% (SD, 3.25) in part A and -0.25% (SD, 3.91) and 0.28% (SD, 3.25) in part B.

Interpretation: Tenofovir alafenamide might offer continued antiviral efficacy and a favourable safety profile for patients with renal or hepatic impairment and chronic hepatitis B switching from tenofovir disoproxil fumarate or other antivirals.

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DOI: 10.1016/s2468-1253(24)00096-7 ■

J Hepatol. 2024;81(3):404–14

Agarwal K, Buti M, van Bömmel F, Lampertico P, Janczewska E, Bourliere M, Vanwolleghem T, Lenz O, Verbinnen T, Kakuda TN, Mayer C, Jezorwski J, Muenz D, Beumont M, Kalmeijer R, Biermer M, Lonjon-Domanec I

JNJ-73763989 and bersacapavir treatment in nucleos(t)ide analogue-suppressed patients with chronic hepatitis B: REEF-2

Background and aims: Functional cure for chronic hepatitis B (CHB) requires finite treatment. Two agents under investigation with the goal of achieving functional cure are the small-interfering RNA JNJ-73763989 (JNJ-3989) and the capsid assembly modulator JNJ-56136379 (JNJ-6379; bersacapavir).
Methods: REEF-2, a phase 2b, double-blind, placebo-controlled, randomized study, enrolled 130 nucleos(t)ide analogue (NA)-suppressed hepatitis B e-antigen (HBeAg)-negative patients with CHB who received JNJ-3989 (200 mg subcutaneously every 4 weeks) + JNJ-6379 (250 mg oral daily) + NA (oral daily; active arm) or placebos for JNJ-3989 and JNJ-6379 + active NA (control arm) for 48 weeks followed by 48 weeks off-treatment follow-up.
Results: At follow-up week 24, no patients achieved the primary endpoint of functional cure (off-treatment hepatitis B surface antigen [HBsAg] seroclearance). No patients achieved functional cure at follow-up week 48. There was a pronounced on-treatment reduction in mean HBsAg from baseline at week 48 in the active arm versus no decline in the control arm (1.89 vs. 0.06 log_{10} IU/ml; p = 0.001). At follow-up week 48, reductions from baseline were > 1 log_{10} IU/ml in 81.5% versus 12.5% of patients in the active and control arms, respectively, and 38/81 (46.9%) patients in the active arm achieved HBsAg < 100 IU/ml versus 6/40 (15.0%) patients in the control arm. Off-treatment hepatitis B virus DNA relapse and alanine aminotransferase increases were less frequent in the active arm, with 7/77 (9.1%) and 11/41 (26.8%) patients in the active and control arms, respectively, restarting NAs during follow-up.

Conclusions: Finite 48-week treatment with JNJ-3989 + JNJ-6379 + nucleos(t)ide analogue resulted in fewer and less severe post-treatment hepatitis B virus (HBV) DNA increases and alanine aminotransferase flares, and a higher proportion of patients with off-treatment HBV DNA suppression, with or without hepatitis B surface antigen suppression, but did not result in functional cure.

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DOI: 10.1016/j.jhep.2024.03.046 ■

Steatotic Liver Disease incl. MASLD*

* MASH/MASLD: formerly non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD). The new international terms “MASH” (metabolic dysfunction-associated steatohepatitis) and “MASLD” (metabolic dysfunction-associated steatotic liver disease) were introduced by the multi-society Delphi panel in June 2023.

Gastroenterology. 2024;167(2):357–67.e9

van Kleef LA, Francque SM, Prieto-Ortiz JE, Sonneveld MJ, Sanchez-Luque CB, Prieto-Ortiz RG, Kwanten WJ, Vonghia L, Verrijken A, De Block C, Gadi Z, Janssen HLA, de Knegt RJ, Brouwer WP

Metabolic dysfunction-associated fibrosis 5 (MAF-5) score predicts liver fibrosis risk and outcome in the general population with metabolic dysfunction

Background and aims: There is an unmet need for non-invasive tests to improve case-finding and aid primary care professionals in referring patients at high risk of liver disease.
Methods: A metabolic dysfunction-associated fibrosis (MAF-5) score was developed and externally validated in a total of 21,797 individuals with metabolic dysfunction in population-based (National Health and Nutrition Examination Survey 2017–2020, National Health and Nutrition Examination Survey III, and Rotterdam Study) and hospital-based (from Antwerp and Bogota) cohorts. Fibrosis was defined as liver stiffness ≥ 8.0 kPa. Diagnostic accuracy was compared with Fibrosis-4 index (FIB-4), non-alcoholic fatty liver disease fibrosis score (NFS), LiverRisk score and steatosis-associated fibrosis estimator (SAFE). MAF-5 was externally validated with liver stiffness measurement ≥ 8.0 kPa, with shear-wave elastography ≥ 7.5 kPa, and biopsy-proven steatotic liver disease according to Metavir and Nonalcoholic Steatohepatitis Clinical Research Network scores, and was tested for prognostic performance (all-cause mortality).
Results: The MAF-5 score comprised waist circumference, body mass index (calculated as kg/m^2), diabetes, aspartate aminotransferase, and platelets. With this score, 60.9% was predicted at low, 14.1% at intermediate, and 24.9% at high risk of fibrosis. The observed prevalence was 3.3%, 7.9%, and 28.1%, respectively. The area under the receiver operating curve of MAF-5 (0.81) was significantly higher than FIB-4 (0.61), and outperformed the FIB-4 among young people (negative predictive value [NPV], 99%; area under the curve [AUC], 0.86 vs. NPV, 94%; AUC, 0.51) and older adults (NPV, 94%; AUC, 0.75 vs. NPV, 88%; AUC, 0.55). MAF-5 showed excellent performance to detect liver stiffness measurement ≥ 12 kPa (AUC, 0.86 training; AUC, 0.85 validation) and good performance in detecting liver stiffness and biopsy-proven liver fibrosis among the external validation cohorts. MAF-5 score > 1 was associated with increased risk of all-cause mortality in (un)adjusted models (adjusted hazard ratio = 1.59; 95% confidence interval: 1.47–1.73).

Conclusions: The metabolic dysfunction-associated fibrosis 5 score is a validated, age-independent, inexpensive referral tool to identify individuals at high risk of liver fibrosis and all-cause mortality in primary care populations, using simple variables.

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DOI: 10.1053/j.gastro.2024.03.017

Hepatology. 2024;79(6):1381–92

Wang A, Blackford AL, Behling C, Wilson LA, Newton KP, Xanthakos SA, Fishbein MH, Vos MB, Mouzaki M, Molleston JP, Jain AK, Hertel P, Harlow Adams K, Schwimmer JB; NASH CRN

Development of Fibro-PeN, a clinical prediction model for moderate-to-severe fibrosis in children with non-alcoholic fatty liver disease

Background and aims: Liver fibrosis is common in children with non-alcoholic fatty liver disease (NAFLD) and is an important determinant of outcomes. High-performing non-invasive models to assess fibrosis in children are needed. The objectives of this study were to evaluate the performance of existing pediatric and adult fibrosis prediction models and to develop a clinical prediction rule for identifying moderate-to-severe fibrosis in children with NAFLD.
Approach and results: The authors enrolled children with biopsy-proven NAFLD in the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) within 90 days of liver biopsy, and staged liver fibrosis in consensus using the NASH CRN scoring system. They evaluated existing pediatric and adult models for fibrosis and developed a new pediatric model using the least absolute shrinkage and selection operator with linear and spline terms for discriminating moderate-to-severe fibrosis from none or mild fibrosis. The model was internally validated with 10-fold cross-validation. 1055 children were evaluated with NAFLD, of whom 26% had moderate-to-severe fibrosis. Existing models performed poorly in classifying fibrosis in children, with area under the receiver operating curves (AUCs) ranging from 0.57 to 0.64. In contrast, the new model, fibrosis in pediatric NAFLD was derived from 14 common clinical variables and had an AUC of 0.79 (95% confidence interval: 0.77–0.81) with 72% sensitivity and 76% specificity for identifying moderate-to-severe fibrosis.

Conclusion: Existing fibrosis prediction models have limited clinical utility in children with non-alcoholic fatty liver disease (NAFLD). Fibrosis in pediatric NAFLD offers improved performance characteristics for risk stratification by identifying moderate-to-severe fibrosis in children with NAFLD.

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DOI: 10.1097/hep.0000000000000644

Gastroenterology. 2024;166(6):1156–65.e4

Wong RJ, Yang Z, Cheung R, Singal AK, Do A, Ahmed A, Yeoh A

Impact of longitudinal alcohol use patterns on long-term risk of cirrhosis among US veterans with steatotic liver disease

Background and aims: Conflicting data exist on the impact of alcohol use on risk of liver disease progression in patients with steatotic liver disease (SLD). The authors aimed to evaluate the effect of longitudinal alcohol use on risk of cirrhosis among veterans with SLD.
Methods: US veterans with SLD were identified from January 2010 through December 2022. Alcohol use was assessed using documented Alcohol Use Disorders Identification Test-Concise (AUDIT-C) scores and categorized as no alcohol (AUDIT-C = 0), low-risk alcohol use (AUDIT-C 1–2 for women and 1–3 for men), and high-risk alcohol (AUDIT-C ≥ 3 for women and ≥ 4 for men). Incidence of cirrhosis was evaluated with competing risks Nelson-Aalen methods. Adjusted multivariable regression models evaluated risks of cirrhosis associated with baseline alcohol use and changes in alcohol use during follow-up.
Results: There were 1,156,189 veterans with SLD identified (54.2% no alcohol, 34.6% low-risk alcohol, and 11.2% high-risk alcohol). Veterans with SLD and high-risk alcohol have a 43% higher incidence of cirrhosis compared with patients reporting no alcohol use. Compared with patients with baseline high-risk alcohol who reported no change in alcohol use, those who decreased their alcohol use during follow-up experienced a 39% reduction in long-term risk of cirrhosis (hazard ratio = 0.61; 95% confidence interval: 0.45–0.83; p < 0.01).

Conclusions: One in 9 veterans with steatotic liver disease (SLD) report concurrent high-risk alcohol use, which is associated with a 43% greater risk of cirrhosis compared with no alcohol use. However, reducing alcohol use lowers risk of cirrhosis, emphasizing the importance of timely alcohol use assessment and early interventions to address high-risk alcohol use in SLD.

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DOI: 10.1053/j.gastro.2024.02.032

N Engl J Med. 2024;391(4):311–9

Sanyal AJ, Bedossa P, Fraessdorf M, Neff GW, Lawitz E, Bugianesi E, Anstee QM, Hussain SA, Newsome PN, Ratziu V, Hosseini-Tabatabaei A, Schattenberg JM, Noureddin M, Alkhouri N, Younes R; 1404-0043 Trial Investigators

A phase 2 randomized trial of survodutide in MASH and fibrosis

Background: Dual agonism of glucagon receptor and glucagon-like peptide-1 (GLP-1) receptor may be more effective than GLP-1 receptor agonism alone for treating metabolic dysfunction-associated steatohepatitis (MASH). The efficacy and safety of survodutide (a dual agonist of glucagon receptor and GLP-1 receptor) in persons with MASH and liver fibrosis are unclear.
Methods: In this 48-week, phase 2 trial, the authors randomly assigned adults with biopsy-confirmed MASH and fibrosis stage F1 through F3 in a 1:1:1:1 ratio to receive once-weekly subcutaneous injections of survodutide at a dose of 2.4 mg, 4.8 mg, or 6.0 mg or placebo. The trial had 2 phases: a 24-week rapid-dose-escalation phase, followed by a 24-week maintenance phase. The primary end point was histologic improvement (reduction) in MASH with no worsening of fibrosis. Secondary end points included a decrease in liver fat content by at least 30% and biopsy-assessed improvement (reduction) in fibrosis by at least 1 stage.
Results: A total of 293 randomly assigned participants received at least 1 dose of survodutide or placebo. Improvement in MASH with no worsening of fibrosis occurred in 47% of the participants in the survodutide 2.4-mg group, 62% of those in the 4.8-mg group, and 43% of those in the 6.0-mg group, as compared with 14% of those in the placebo group (p < 0.001 for the quadratic dose-response curve as best-fitting model). A decrease in liver fat content by at least 30% occurred in 63% of the participants in the survodutide 2.4-mg group, 67% of those in the 4.8-mg group, 57% of those in the 6.0-mg group, and 14% of those in the placebo group; improvement in fibrosis by at least 1 stage occurred in 34%, 36%, 34%, and 22%, respectively. Adverse events that were more frequent with survodutide than with placebo included nausea (66% vs. 23%), diarrhea (49% vs. 23%), and vomiting (41% vs. 4%); serious adverse events occurred in 8% with survodutide and 7% with placebo.

Conclusions: Survodutide was superior to placebo with respect to improvement in metabolic dysfunction-associated steatohepatitis without worsening of fibrosis, warranting further investigation in phase 3 trials.

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DOI: 10.1056/nejmoa2401755

N Engl J Med. 2024;391(4):299–310

Loomba R, Hartman ML, Lawitz EJ, Vuppalanchi R, Boursier J, Bugianesi E, Yoneda M, Behling C, Cummings OW, Tang Y, Brouwers B, Robins DA, Nikooie A, Bunck MC, Haupt A, Sanyal AJ; SYNERGY-NASH Investigators

Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease associated with liver-related complications and death. The efficacy and safety of tirzepatide, an agonist of the glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors, in patients with MASH and moderate or severe fibrosis is unclear.
Methods: The authors conducted a phase 2, dose-finding, multicenter, double-blind, randomized, placebo-controlled trial involving participants with biopsy-confirmed MASH and stage F2 or F3 (moderate or severe) fibrosis. Participants were randomly assigned to receive once-

weekly subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 52 weeks. The primary end point was resolution of MASH without worsening of fibrosis at 52 weeks. A key secondary end point was an improvement (decrease) of at least 1 fibrosis stage without worsening of MASH.

Results: Among 190 participants who had undergone randomization, 157 had liver-biopsy results at week 52 that could be evaluated, with missing values imputed under the assumption that they would follow the pattern of results in the placebo group. The percentage of participants who met the criteria for resolution of MASH without worsening of fibrosis was 10% in the placebo group, 44% in the 5-mg tirzepatide group (difference vs. placebo, 34 percentage points; 95% confidence interval [CI]: 17–50), 56% in the 10-mg tirzepatide group (difference, 46 percentage points; 95% CI: 29–62), and 62% in the 15-mg tirzepatide group (difference, 53 percentage points; 95% CI: 37–69) ($p < 0.001$ for all 3 comparisons). The percentage of participants who had an improvement of at least 1 fibrosis stage without worsening of MASH was 30% in the placebo group, 55% in the 5-mg tirzepatide group (difference vs. placebo, 25 percentage points; 95% CI: 5–46), 51% in the 10-mg tirzepatide group (difference, 22 percentage points; 95% CI: 1–42), and 51% in the 15-mg tirzepatide group (difference, 21 percentage points; 95% CI: 1–42). The most common adverse events in the tirzepatide groups were gastrointestinal events, and most were mild or moderate in severity.

Conclusions: In this phase 2 trial involving participants with metabolic dysfunction-associated steatohepatitis (MASH) and moderate or severe fibrosis, treatment with tirzepatide for 52 weeks was more effective than placebo with respect to resolution of MASH without worsening of fibrosis. Larger and longer trials are needed to further assess the efficacy and safety of tirzepatide for the treatment of MASH.

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DOI: 10.1056/nejmoa2401943

EXPERT OPINION

Dr. Dr. Natascha Röhlen

GLP-1 receptor agonists as a therapeutic approach for MASH treatment

Metabolic dysfunction-associated steatohepatitis (MASH) is one of the leading causes of liver fibrosis and cirrhosis in western countries. In March 2024, resmetirom, a liver-selective thyroid hormone receptor beta (TRH-β) agonist, became the first drug approved for the treatment of patients with MASH and moderate to advanced fibrosis in the United States. Approval by the European Medicines Agency is still pending, but is expected by early 2025. In addition to resmetirom, incretins in particular have been tested for the treatment of MASH in recent years.

Incretins have already been well-established in the treatment of obesity and type 2 diabetes. By mimicking the effects of the endogenous hormones glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), or glucagon, incretins lead to weight loss and increased insulin sensitivity. While Newsome et al. already described protective effects of the GLP-1 receptor analogue semaglutide on histologically detectable inflammation and hepatocyte ballooning in 2021, current clinical studies are primarily investigating the effects of GLP-1/GIP and GLP-1/glucagon receptor agonists, which are associated with particularly effective weight loss.

In their phase 2 study, Loomba et al. investigated the effects of the GLP-1/GIP agonist tirzepatide in 190 MASH patients with moderate (F2) or severe fibrosis (F3). In the same issue of the New England Journal of Medicine, Sanyal et al. published a paper investigating the efficacy of the GLP-1/glucagon receptor agonist survodutide in 293 MASH patients with stage F1–F3 fibrosis. Both tirzepatide and survodutide were injected subcutaneously once a week with a dose-escalation phase of 1–6 months. Both studies showed a significant reduction in histological MASH activity without worsening of fibrosis after 52 or 48 weeks of therapy with tirzepatide or survodutide compared to the placebo group. In both studies, the verum group further showed a decrease in transaminases and a reduction in the liver fat content, as measured by magnetic resonance imaging. Treatment with a GLP-1 receptor agonist further tended to be associated with a higher percentage of patients with histologically detectable fibrosis regression (tirzepatide: +21%, survodutide: +14% compared to the placebo group). Both studies observed a higher incidence of gastrointestinal adverse events such as nausea and diarrhea under the respective therapy. However, serious adverse events did not occur more frequently than with placebo in either study.

While differences in the study design (different end points, differences in the degree of fibrosis, the patient cohort and the statistical analyses) do not allow a comparison of the efficacy of the 2 substances, both studies indicate a potential role for GLP-1 receptor agonists in the treatment of obese MASH patients. However, it remains unclear whether the observed effects on histological MASH activity are directly mediated by tirzepatide or survodutide, or whether they primarily reflect indirect effects of weight loss. In both studies, there was an average weight loss of 10–16% over the approximately 1-year therapy with a GLP-1 receptor agonist. With regard to fibrosis, the study durations of 48–52 weeks were most likely too short and the sample size too small to assess the long-term antifibrotic efficacy of GLP-1 receptor agonists. If the potential therapeutic effect is mainly mediated by weight loss, the maximum fibrosis regression can be expected after a treatment duration of > 1 year, according to published data from bariatric studies.

Patients with MASH cirrhosis were excluded from both studies. However, Loomba et al. published a phase 2 study in 2023 that indicated that the GLP-1 agonist semaglutide was safe for the treatment of compensated MASH cirrhosis. The already planned phase 3 studies with cirrhosis patients, as well as long-term data, are urgently needed not only to validate the short-term effect on MASH inflammation and fibrosis but also to assess the effect of GLP-1 receptor agonists on clinical end points such as decompensation events and the incidence of hepatocellular carcinoma (HCC). ■

Hepatology. 2024;80(1):173–85

Ratziu V, Francque S, Behling CA, Cejvanovic V, Cortez-Pinto H, Iyer JS, Krarup N, Le Q, Sejling AS, Tiniakos D, Harrison SA

Artificial intelligence scoring of liver biopsies in a phase 2 trial of semaglutide in non-alcoholic steatohepatitis

Background and aims: Artificial intelligence (AI)-powered digital pathology offers the potential to quantify histological findings in a reproducible way. This analysis compares the evaluation of histological features of non-alcoholic steatohepatitis (NASH) between pathologists and a machine-learning (ML) pathology model.
Approach and results: This post hoc analysis included data from a subset of patients (n = 251) with biopsy-confirmed NASH and fibrosis stage F1–F3 from a 72-week randomized placebo-controlled trial of once-daily subcutaneous semaglutide 0.1 mg, 0.2 mg, or 0.4 mg. Biopsies at baseline and week 72 were read by 2 pathologists. Digitized biopsy slides were evaluated by PathAI's NASH ML models to quantify changes in fibrosis, steatosis, inflammation, and hepatocyte ballooning using categorical assessments and continuous scores. Pathologist- and ML-derived categorical assessments detected a significantly greater percentage of patients achieving the primary endpoint of NASH resolution without worsening of fibrosis with semaglutide 0.4 mg versus placebo (pathologist 58.5% vs. 22.0%, p < 0.0001; ML 36.9% vs. 11.9%, p = 0.0015). Both methods detected a higher but non-significant percentage of patients on semaglutide 0.4 mg versus placebo achieving the secondary endpoint of liver fibrosis improvement without NASH worsening. ML continuous scores detected significant treatment-induced responses in histological features, including a quantitative reduction in fibrosis with semaglutide 0.4 mg versus placebo (p = 0.0099) that could not be detected using pathologist or ML categorical assessment.

Conclusions: Machine learning (ML) categorical assessments reproduced pathologists' results of histological improvement with semaglutide for steatosis and disease activity. ML-based continuous scores demonstrated an antifibrotic effect not measured by conventional histopathology.

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DOI: 10.1097/hep.0000000000000723 ■

Gut. 2024;73(8):1343–9

Loomba R, Amangurbanova M, Bettencourt R, Madamba E, Siddiqi H, Richards L, Behling C, Sirlin CB, Gottwald MD, Feng S, Margalit M, Huang DQ

MASH Resolution Index: Development and validation of a non-invasive score to detect histological resolution of MASH

Background: Dynamic changes in non-invasive tests, such as changes in alanine aminotransferase (ALT) and magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF), may help to detect metabolic dysfunction-associated steatohepatitis (MASH) resolution, but a combination of non-invasive tests may be more accurate than either alone. The authors developed a novel non-invasive score, the MASH Resolution Index, to detect the histological resolution of MASH.
Methods: This study included a derivation cohort of 95 well-characterised adult participants (67% female) with biopsy-confirmed MASH who underwent contemporaneous laboratory testing, MRI-PDFF and liver biopsy at 2 time points. The primary objective was to develop a non-invasive score to detect MASH resolution with no worsening of fibrosis. The most predictive logistic regression model was selected based on the highest area under the receiver operating curve (AUC), and the lowest Akaike information criterion and Bayesian information criterion. The model was then externally validated in a distinct cohort of 163 participants with MASH from a clinical trial.
Results: The median (interquartile range [IQR]) age and body mass index were 55 (IQR, 45–62) years and 32.0 (IQR, 30–37) kg/m^2, respectively, in the derivation cohort. The most accurate model (MASH Resolution Index) included MRI-PDFF, ALT and aspartate aminotransferase (AST). The index had an AUC of 0.81 (95% confidence interval [CI]: 0.69–0.93) for detecting MASH resolution in the derivation cohort. The score calibrated well and performed robustly in a distinct external validation cohort (AUC, 0.83; 95% CI: 0.76–0.91), and outperformed changes in ALT and MRI-PDFF.

Conclusion: The Metabolic Dysfunction-Associated Steatohepatitis (MASH) Resolution Index may be a useful score to non-invasively identify MASH resolution.

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DOI: 10.1136/gutjnl-2023-331401 ■

AIH/PBC/PSC

JHEP Rep. 2024;6(7):101088

Stoelinga AEC, Biewenga M, Drenth JPH, Verhelst X, van der Meer AJP, de Boer YS, Bouma G, de Vries ES, Verdonk RC, van der Berg AP, Brouwer JT, Vanwolleghem T, Lammers W, Beuers U, Sarasqueta AF, Verheij J, Roskams T, Crobach S, Tushuizen ME, van Hoek B; Dutch Autoimmune Hepatitis Study Group

Diagnostic criteria and long-term outcomes in AIH-PBC variant syndrome under combination therapy

Background and aims: Autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) can co-exist in AIH-PBC, requiring combined treatment with immuno-

suppression and ursodeoxycholic acid (UDCA). The Paris criteria are commonly used to identify these patients; however, the optimal diagnostic criteria are unknown. The authors aimed to evaluate the use and clinical relevance of both Paris and Zhang criteria.
Methods: 83 patients with a clinical suspicion of AIH-PBC who were treated with combination therapy were included. Histology was re-evaluated. Characteristics and long-term outcomes were retrospectively compared to patients with AIH and PBC.
Results: 17 patients (24%) treated with combination therapy fulfilled the Paris criteria. 52 patients (70%) fulfilled the Zhang criteria. Patients who met Paris and Zhang criteria more often had inflammation and fibrosis on histology compared to patients only meeting the Zhang criteria. 10-year liver transplant (LT)-free survival was 87.3% (95% confidence interval [CI]: 78.9–95.7%) in patients with AIH-PBC. This did not differ in patients in or outside the Paris or Zhang criteria (p = 0.46 and p = 0.40, respectively) or from AIH (p = 0.086). LT-free survival was significantly lower in patients with PBC and severe hepatic inflammation – not receiving immunosuppression – compared to those with AIH-PBC (65%; 95% CI: 52.2–77.8% vs. 87%; 95% CI: 83.2–90.8%; hazard ratio = 0.52; p = 0.043).

Conclusions: In this study, patients with autoimmune hepatitis and primary biliary cholangitis (AIH-PBC) outside Paris or Zhang criteria were frequently labeled as having AIH-PBC and were successfully treated with combination therapy with similar outcomes. Liver transplant-free survival was worse in patients with PBC and hepatic inflammation than in those treated as having AIH-PBC. More patients may benefit from combination therapy.

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DOI: 10.1016/j.jhepr.2024.101088

J Hepatol. 2024;81(2):227–37

Plagiannakos CG, Hirschfield GM, Lytvyak E, Roberts SB, Ismail M, Gulamhusein AF, Selzner N, Qumosani KM, Worobetz L, Hercun J, Vincent C, Flemming JA, Swain MG, Cheung A, Chen T, Grbic D, Peltekain K, Mason AL, Montano-Loza AJ, Hansen BE; Canadian Network for Autoimmune Liver Disease (CaNAL)

Treatment response and clinical event-free survival in autoimmune hepatitis: A Canadian multicentre cohort study

Background and aims: Treatment outcomes for people living with autoimmune hepatitis (AIH) are limited by a lack of specific therapies, as well as limited well-validated prognostic tools and clinical trial endpoints. The authors sought to identify predictors of outcome for people living with AIH.
Methods: They evaluated the clinical course of people with AIH across 11 Canadian centres. Biochemical changes were analysed using linear mixed-effect and logistic regression. Clinical outcome was dynamically modelled using time-varying Cox proportional hazard modelling and landmark analysis.
Results: In 691 patients (median age, 49 years, 75.4% female), with a median follow-up of 6 years (25th–75th percentile, 2.5–11), 118 clinical events occurred. Alanine aminotransferase (ALT) normalisation occurred in 63.8% of the cohort by 12 months. Older age at diagnosis (odds ratio [OR] = 1.19, 95% confidence interval [CI]: 1.06–1.35) and female sex (OR = 1.94, 95% CI: 1.18–3.19) were associated with ALT normalisation at 6 months, whilst baseline cirrhosis status was associated with reduced chance of normalisation at 12 months (OR = 0.52, 95% CI: 0.33–0.82). Baseline total bilirubin, aminotransferases, and immunoglobulin G (IgG) values, as well as initial prednisone dose, did not predict average ALT reduction. At baseline, older age (hazard ratio [HR] = 1.25, 95% CI: 1.12–1.40), cirrhosis at diagnosis (HR = 3.67, 95% CI: 2.48–5.43), and elevated baseline total bilirubin (HR = 1.36, 95% CI: 1.17–1.58) increased the risk of clinical events. Prolonged elevations in ALT (HR = 1.07, 95% CI: 1.00–1.13) and aspartate aminotransferase (AST; HR = 1.13, 95% CI: 1.06–1.21), but not IgG (HR = 1.01, 95% CI: 0.95–1.07), were associated with higher risk of clinical events. Higher ALT at 6 months was associated with worse clinical event-free survival.

Conclusion: In people living with autoimmune hepatitis, sustained elevated aminotransferase values, but not immunoglobulin G, are associated with poorer long-term outcomes. Biochemical response and long-term survival are not associated with starting prednisone dose.

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DOI: 10.1016/j.jhep.2024.03.021

Hepatology. 2024;80(3):527–35

Lundberg Båve A, von Seth E, Ingre M, Nordenvall C, Bergquist A

Autoimmune diseases in primary sclerosing cholangitis and their first-degree relatives

Background and aims: Primary sclerosing cholangitis (PSC) is linked to inflammatory bowel disease (IBD). However, there is limited overlap between IBD and PSC risk genes, but a stronger association between PSC and other autoimmune conditions. The authors aimed to assess the coexistence and familial association of autoimmune disorders in PSC, and the influence of autoimmune comorbidity on severe outcomes.
Approach and results: In a matched cohort study, 1378 individuals with PSC and 13,549 general population comparators and their first-degree relatives were evaluated. National registries provided data on diagnoses and outcomes (liver transplantation, hepatobiliary cancer, and liver-related death). The odds ratio (OR) of autoimmune disease was estimated by logistic regression. The Fine and Gray competing risk regression estimated hazard ratios (HRs) for severe outcomes. The prevalence of non-IBD, non-autoimmune hepatitis, and autoimmune disease was 18% in PSC and 11% in comparators (OR = 1.77, 95% confidence interval [CI]: 1.53–2.05). Highest odds were seen for celiac disease (OR = 4.36, 95% CI: 2.44–7.49), sarcoidosis (OR = 2.74, 95% CI:

1.29–5.33), diabetes type 1 (OR = 2.91, 95% CI: 2.05–4.05), and autoimmune skin disease (OR = 2.15, 95% CI: 1.52–2.96). First-degree relatives of individuals with PSC had higher odds of developing IBD, autoimmune hepatitis, and any autoimmune disease than relatives of the comparators (OR = 3.25, 95% CI: 2.68–3.91; OR = 5.94, 95% CI: 2.82–12.02; OR = 1.34, 95% CI: 1.19–1.50). Autoimmune comorbidity in PSC was not associated with poorer outcomes (HR = 0.96, 95% CI: 0.71–1.28).

Conclusions: Individuals with primary sclerosing cholangitis and their first-degree relatives had higher odds of autoimmune disease compared to matched comparators. This finding provides validation for prior genetic discoveries at a phenotypic level. Autoimmune comorbidity did not impact severe outcomes.

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DOI: 10.1097/hep.0000000000000823

Hepatology. 2024;80(1):27–37

Kremer AE, Mayo MJ, Hirschfield GM, Levy C, Bowlus CL, Jones DE, Johnson JD, McWherter CA, Choi YJ

Seladelpar treatment reduces IL-31 and pruritus in patients with primary biliary cholangitis

Background and aims: Pruritus is a debilitating symptom for many people living with primary biliary cholangitis (PBC). In studies with seladelpar, a selective peroxisome proliferator-activated receptor-δ agonist, patients with PBC experienced significant improvement in pruritus and reduction of serum bile acids. Interleukin-31 (IL-31) is a cytokine known to mediate pruritus, and blocking IL-31 signaling provides relief in pruritic skin diseases. This study examined the connection between seladelpar's antipruritic effects and IL-31 and bile acid levels in patients with PBC.
Approach and results: IL-31 levels were quantified in serum samples from the ENHANCE study of patients with PBC receiving daily oral doses of placebo (n = 55), seladelpar 5 mg (n = 53) or 10 mg (n = 53) for 3 months, and for healthy volunteers (n = 55). IL-31 levels were compared with pruritus using a numerical rating scale (NRS, 0–10) and with bile acid levels. Baseline IL-31 levels closely correlated with pruritus NRS ($r = 0.54$, $p < 0.0001$), and total ($r = 0.54$, $p < 0.0001$) and conjugated bile acids (up to 0.64, $p < 0.0001$). Decreases in IL-31 were observed with seladelpar 5 mg (-30%, $p = 0.0003$) and 10 mg (-52%, $p < 0.0001$) versus placebo (+31%). Patients with clinically meaningful improvement in pruritus (NRS ≥ 2 decrease) demonstrated greater dose-dependent reductions in IL-31 compared to those without pruritus improvement (NRS < 2 decrease). Strong correlations were observed for the changes between levels of IL-31 and total bile acids ($r = 0.63$, $p < 0.0001$) in the seladelpar 10 mg group.

Conclusions: Seladelpar decreased serum interleukin-31 (IL-31) and bile acids in patients with primary biliary cholangitis. The reductions of IL-31 and bile acids correlated closely with each other and pruritus improvement, suggesting a mechanism to explain seladelpar's antipruritic effects.

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DOI: 10.1097/hep.0000000000000728

Liver Cirrhosis

J Hepatol. 2024;81(3):441–50

Ma AT, Solé C, Juanola A, Escudé L, Napoleone L, Avitabile E, Pérez-Guasch M, Carol M, Pompili E, Gratacós-Ginés J, Soria A, Rubio AB, Cervera M, Moreta MJ, Morales-Ruiz M, Solà E, Poch E, Fabrellas N, Graupera I, Pose E, Ginès P

Prospective validation of the EASL management algorithm for acute kidney injury in cirrhosis

Background and aims: The management of acute kidney injury (AKI) in cirrhosis is challenging. The European Association for the Study of the Liver (EASL) guidelines proposed an algorithm for the management of AKI, but this has never been validated. The authors aimed to prospectively evaluate this algorithm in clinical practice.
Methods: They performed a prospective cohort study in consecutive hospitalized patients with cirrhosis and AKI. The EASL management algorithm includes identification/treatment of precipitating factors, 2-day albumin infusion in patients with AKI ≥ stage 1B, and treatment with terlipressin in patients with hepatorenal syndrome (HRS-AKI). The primary outcome was treatment response, which included both full and partial response. Secondary outcomes were survival and adverse events associated with terlipressin therapy.
Results: A total of 202 AKI episodes in 139 patients were included. Overall treatment response was 80%, while renal replacement therapy was required in only 8%. Response to albumin infusion was achieved in one-third of episodes. Of patients not responding to albumin, most (74%) did not meet the diagnostic criteria of HRS-AKI, with acute tubular necrosis (ATN) being the most common phenotype. The response rate in patients not meeting the criteria for HRS-AKI was 70%. Only 30 patients met the diagnostic criteria for HRS-AKI, and their response rate to terlipressin was 61%. Median time from AKI diagnosis to terlipressin initiation was only 2.5 days. While urinary neutrophil gelatinase-associated lipocalin (uNGAL) could differentiate ATN from other phenotypes (area under the receiver operating characteristics [AUROC], 0.78), it did not predict response to therapy in HRS-AKI. 90-day transplant-free survival was negatively associated with Model for End-stage Liver Disease (MELD)-Na, ATN and HRS-AKI as well as uNGAL. Three patients treated with terlipressin developed pulmonary edema.

Conclusions: The application of the European Association for the Study of the Liver (EASL) acute kidney injury algorithm is associated with very good response rates and does not significantly delay initiation of terlipressin therapy.

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DOI: 10.1016/j.jhep.2024.03.006

Clin Gastroenterol Hepatol. 2024;22(6):1255–64.e18

Yen FS, Hou MC, Wei JCC, Shih YH, Hsu CY, Hsu CC, Hwu CM

Glucagon-like peptide-1 receptor agonist use in patients with liver cirrhosis and type 2 diabetes

Background and aims: Liver cirrhosis is often associated with type 2 diabetes (T2D), but research on treatment of T2D in cirrhotic patients is scarce. The authors investigated the long-term outcomes of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in patients with T2D and cirrhosis.
Methods: Using propensity score matching, they selected 467 matched pairs of GLP-1RA users and non-users from the National Health Insurance Research Database of Taiwan from January 1, 2008, to December 31, 2019. Multivariable-adjusted Cox proportional hazards models were used to compare the outcomes between GLP-1RA users and non-users.
Results: The mean follow-up time was 3.28 and 3.06 years for GLP-1RA users and non-users, respectively. The rates of death were 27.46 and 55.90 per 1000 person-years for GLP-1RA users and non-users, respectively. The multivariable-adjusted models showed that GLP-1RA users had lower risks of mortality (adjusted hazard ratio [aHR] = 0.47; 95% confidence interval [CI]: 0.32–0.69), cardiovascular events (aHR = 0.6; 95% CI: 0.41–0.87), decompensated cirrhosis (aHR = 0.7; 95% CI: 0.49–0.99), hepatic encephalopathy (aHR = 0.59; 95% CI: 0.36–0.97), and liver failure (aHR = 0.54; 95% CI: 0.34–0.85) than non-users. A longer cumulative duration of GLP-1RA use had a lower risk of these outcomes than GLP-1RA non-use.

Conclusions: This population-based cohort study showed that glucagon-like peptide-1 receptor agonist users exhibited a significantly lower risk of death, cardiovascular events, decompensated cirrhosis, hepatic encephalopathy, and liver failure in patients with type 2 diabetes and compensated liver cirrhosis. Additional studies are needed to confirm these results.

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DOI: 10.1016/j.cgh.2023.06.004

Hepatology. 2024;80(2):376–88

Kumar M, Venishetty S, Jindal A, Bihari C, Maiwall R, Vijayaraghavan R, Saggere Muralikrishna S, Arora V, Kumar G, Sarin SK

Tranexamic acid in upper gastrointestinal bleed in patients with cirrhosis: A randomized controlled trial

Background and aims: Patients with Child-Turcotte-Pugh class B and C cirrhosis with upper gastrointestinal bleeding (UGIB) have systemic as well as localized (in the mucosa of the esophagus and stomach) fibrinolysis. The aim of this study was to evaluate the efficacy and safety of tranexamic acid in the treatment of acute UGIB in patients with cirrhosis.
Approach and results: A total of 600 patients with advanced liver cirrhosis (Child-Turcotte-Pugh class B or C) presenting with UGIB were randomly allocated to either the tranexamic acid (n = 300) or the placebo group (n = 300). The primary outcome measure was the proportion of patients developing 5-day treatment failure. Failure to control bleeding by day 5 was seen in 19/300 (6.3%) patients in the tranexamic acid group and 40/300 (13.3%) patients in the placebo group (p = 0.006). Esophageal endoscopic variceal ligation (EVL) site as a source of failure to control bleeding by day 5 among patients undergoing first-time esophageal EVL (excluding patients with a previous post-EVL ulcer as a source of bleed) was seen in 11/222 (4.9%) patients in the tranexamic acid group and 27/225 (12.0%) patients in the placebo group (p = 0.005). However, 5-day and 6-week mortality was similar in the tranexamic acid and placebo groups.

Conclusions: Tranexamic acid significantly reduces the failure to control bleeding by day 5 and failure to prevent rebleeding after day 5 to 6 weeks in patients with advanced liver cirrhosis (Child-Turcotte-Pugh class B or C) presenting with upper gastrointestinal bleeding, by preventing bleeding from the endoscopic variceal ligation site.

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DOI: 10.1097/hep.0000000000000817

EXPERT OPINION

PD Dr. Michael Schultheiß

Should tranexamic acid be included in the therapeutic algorithm for variceal bleeding?

Patients with liver cirrhosis frequently experience gastrointestinal bleeding. Although the summary of product characteristics (SMPC) for tranexamic acid injectable solution lists „gastrointestinal bleeding“ as a potential indication, there is limited data on its use in patients with liver cirrhosis. The recent study by Kumar

et al. addresses this gap by evaluating tranexamic acid in patients with upper gastrointestinal bleeding and Child-Pugh class B and C liver cirrhosis, providing significant insights into its potential clinical utility.
The study outcomes, while encouraging, align with existing expectations. In the tranexamic acid group, higher and statistically significant bleeding control was achieved by day 5 (6.3% vs. 13.3%; p = 0.006) and after day 5 (12% vs. 21.3%; p = 0.002). One study focus was on variceal bleeding, which was the cause of bleeding in > 85% in both groups. Patients experiencing rebleeding from esophageal endoscopic variceal ligation (EVL) sites also benefited from the use of tranexamic acid by day 5 (4.9% vs. 12%; p = 0.005) and after day 5 (8.5% vs. 16.4%; p = 0.007). However, no statistically significant survival benefit was achieved with tranexamic acid over a follow-up period of up to 6 weeks.
Despite the clinical relevance of these findings, the study has several obvious weaknesses. The fact that liver cirrhosis disproportionately affects men in India as well, where the study was conducted, is understandable; however, the nearly 9:1 male-to-female ratio is astonishing. In addition, very few of the patients in either group underwent preemptive transjugular intrahepatic portosystemic shunt (TIPS; 1.6% and 1.3%) – despite Baveno guidelines recommending TIPS for variceal bleeding in this particular patient cohort. It would be interesting to evaluate the risk of TIPS occlusions due to thrombosis in the context of tranexamic acid use. It is also notable that while portal vein thrombosis (PVT) was an exclusion criterion, a significant percentage of patients with hepatocellular carcinoma (HCC) and malignant PVT were included (7% and 9%, respectively).
Prokinetics, antibiotics, and vasoactive drugs are essential medications for treating patients with liver cirrhosis and variceal bleeding. Further studies are required to determine whether tranexamic acid should be considered a similarly essential therapeutic in this setting. ■

HCC

J Hepatol. 2024;81(2):258–64

Chan SL, Ryoo BY, Mo F, Chan LL, Cheon J, Li L, Wong KH, Yim N, Kim H, Yoo C

Multicentre phase 2 trial of cabozantinib in patients with hepatocellular carcinoma after immune checkpoint inhibitor treatment

Background and aims: Prospective data on treatment after immune checkpoint inhibitor (ICI) therapy in hepatocellular carcinoma (HCC) are lacking. The authors conducted a phase 2 multicentre study on cabozantinib after ICI treatment in HCC.
Methods: This is an investigator-initiated, single-arm, clinical trial involving academic centres in Hong Kong and Korea. Key eligibility criteria included diagnosis of HCC, refractoriness to prior ICI-based treatment, and Child-Pugh A liver function. A maximum of 2 prior lines of therapy were allowed. All patients were commenced on cabozantinib at 60 mg/day. The primary endpoint was progression-free survival (PFS).
Results: 47 patients were recruited from October 2020 to May 2022; 27 and 20 patients had received 1 and 2 prior therapies, respectively. Median follow-up was 11.2 months. The median PFS was 4.1 months (95% confidence interval [CI]: 3.3–5.3). The median overall survival (OS) was 9.9 months (95% CI: 7.3–14.4), and the 1-year OS rate was 45.3%. Partial response and stable disease occurred in 3 (6.4%) and 36 (76.6%) patients, respectively. When used as a second-line treatment (n = 27), cabozantinib was associated with a median PFS and OS of 4.3 (95% CI: 3.3–6.7) and 14.3 (95% CI: 8.9–not reached) months, respectively. The corresponding median PFS and OS were 4.3 (95% CI: 3.3–11.0) and 14.3 (95% CI: 9.0–not reached) months, respectively, for those receiving ICI-based regimens with proven benefits (n = 17). The most common grade-3–4 treatment-related adverse event was thrombocytopenia (6.4%). The median dose of cabozantinib was 40 mg/day. The number of prior therapies was an independent prognosticator (1 vs. 2; hazard ratio = 0.37; p = 0.03).

Conclusions: Cabozantinib demonstrated efficacy in patients who had received prior immune checkpoint inhibitor (ICI) regimens; survival data for second-line cabozantinib following first-line ICI regimens provide a reference for future clinical trial design. The number of prior lines of treatment may be considered a stratification factor in randomised studies.

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DOI: 10.1016/j.jhep.2024.03.033 ■

J Hepatol. 2024;81(2):278–88

Lamarque C, Segaux L, Bachellier P, Buchard B, Chermak F, Conti F, Decaens T, Dharancy S, Di Martino V, Dumortier J, Francoz-Caudron C, Gugenheim J, Hardwigsen J, Muscari F, Radenne S, Salamé E, Uguen T, Ursic-Bedoya J, Antoine C, Deshayes A, Jacquelinet C, Natella PA, Leroy V, Cherqui D, Oubaya N, Duvoux C

Evaluation of a delayed liver transplantation strategy for patients with HCC receiving bridging therapy: The DELTA-HCC study

Background and aims: To maximize utility and prevent premature liver transplantation (LT), a delayed LT strategy (DS) was adopted in France in 2015 in patients listed for any single hepatocellular carcinoma (HCC) treated with resection or thermal ablation during the waiting phase. The DS involves postponing LT until recurrence. The purpose of this study was to evaluate the DS to make sure that it did not hamper pre- and post-LT outcomes.
Methods: Patients listed for HCC in France between 2015 and 2018 were studied. After data extraction from the national LT database, 2025 patients were identified and classified according to 6 groups: single tumor entering DS, single tumor not entering DS, multiple tumors,

no curative treatment, untreatable HCC or T1 tumors. Kaplan-Meier estimates of the 18-month risk of dropout for death, too sick to be transplanted or tumor progression before LT, 5-year post-LT HCC recurrence and post-LT survival rates were compared.
Results: Median waiting-time in the DS group was 910 days. Pre-LT dropout probability was significantly lower in the DS group compared to other groups (13% vs. 19%, p = 0.0043) and significantly higher in the T1 group (25.4%, p = 0.05). Post-LT HCC recurrence rate in the multiple nodules group was significantly higher (19.6%, p = 0.019), while 5-year post-LT survival did not differ among groups and was 74% in the DS group (p = 0.22).

Conclusion: The DELTA-HCC study shows that a delayed liver transplantation (LT) strategy does not negatively impact either pre- nor post-LT patient outcomes, and has the potential to allow for redistribution of organs to patients in more urgent need of LT. It can reasonably be proposed and pursued. The unexpectedly high risk of dropout in T1 patients seems related to the Model for End-stage Liver Disease (MELD)-based offering rules underserving this subgroup.

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DOI: 10.1016/j.jhep.2024.03.019

Liver Transplantation

Clin Gastroenterol Hepatol. 2024;22(8):1646–56.e2

Musto JA, Palmer G, Nemer M, Schell T, Waclawik G, Glover Q, Lucey MR, Osman F, Rice JP

Early liver transplant for alcohol-associated liver disease has excellent survival but higher rates of harmful alcohol use

Background and aims: Early liver transplantation (LT) for alcohol-associated liver disease (ALD) has increased worldwide. Short-term outcomes have been favorable, but data on longer-term outcomes are lacking.
Methods: Single-center retrospective study of primary LT recipients between 2010 and 2020, with follow-up through July 1, 2022. Survival analysis was performed using log rank, Cox models, and Kaplan-Meier method. Cox models were created to identify variables associated with mortality; logistic regression to identify variables associated with post-LT alcohol use.
Results: Of 708 patients who underwent LT, 110 (15.5%) had ALD and abstinence < 6 months prior to LT (early LT, ELT), 234 (33.1%) had ALD and alcohol abstinence > 6 months (standard LT, SLT), and 364 (51.4%) had non-ALD diagnoses. Median follow-up was 4.6 years (interquartile range, 2.6–7.3 years). ELT recipients were younger (p = 0.001) with median abstinence pre-LT of 61.5 days. On adjusted Cox model, post-LT survival was similar in ELT and SLT (hazard ratio [HR] = 1.31; p = 0.30) and superior to non-ALD (HR = 1.68; p = 0.04). Alcohol use (40.9% vs. 21.8%; p < 0.001) and harmful alcohol use (31.2% vs. 16.0%; p = 0.002) were more common in ELT recipients. Harmful alcohol use was associated with post-LT mortality on univariate (HR = 1.69; p = 0.03), but not multivariable regression (HR = 1.54; p = 0.10). Recurrence of decompensated ALD trended toward more common in ELT (9.1% vs. 4.4%; p = 0.09). Greater than 6 months pre-LT abstinence was associated with a decreased risk of harmful alcohol use (odds ratio [OR] = 0.42; p = 0.001), but not in a multivariable model (OR = 0.71; p = 0.33).

Conclusions: Patients who undergo early liver transplantation (LT) for alcohol-associated liver disease have similar or better survival than other diagnoses in the first 10 years after LT despite a higher incidence of post-LT alcohol use.

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DOI: 10.1016/j.cgh.2024.04.025

Hepatology. 2024;80(1):136–51

Dongelmans E, Erler N, Adam R, Nadalin S, Karam V, Yilmaz S, Kelly C, Pirenne J, Acarli K, Allison M, Hakeem A, Dhakshinamoorthy V, Fedaruk D, Rummo O, Kilic M, Nordin A, Fischer L, Parente A, Mirza D, Bennet W, Tokat Y, Faitot F, Antonelli BB, Berlakovich G, Patch D, Berrevoet F, Ribnikar M, Gerster T, Savier E, Gruttadauria S, Ericzon BG, Valdivieso A, Cuervas-Mons V, Perez Saborido B, Croner RS, De Carlis L, Magini G, Rossi R, Popescu I, Razvan L, Schneeberger S, Blokzijl H, Llado L, Gomez Bravo MA, Duvoux C, Mezjlík V, Oniscu GC, Pearson K, Dayangac M, Lucidi V, Detry O, Rotellar F, den Hoed C, Polak WG, Darwish Murad S; European Liver and Intestine Transplant Association (ELITA)

Recent outcomes of liver transplantation for Budd-Chiari syndrome: A study of the European Liver Transplant Registry (ELTR) and affiliated centers

Background and aims: Management of Budd-Chiari syndrome (BCS) has improved over the last decades. The main aim was to evaluate the contemporary post-liver transplant (post-LT) outcomes in Europe.
Approach and results: Data from all patients who underwent transplantation from 1976 to 2020 was obtained from the European Liver Transplant Registry (ELTR). Patients < 16 years, with secondary BCS or hepatocellular carcinoma (HCC) were excluded. Patient survival (PS) and graft survival (GS) before and after 2000 were compared. Multivariate Cox regression analysis identified predictors of PS and GS after 2000. Supplemental data was requested from all ELTR-affiliated centers and received from 44. In all, 808 patients underwent transplantation between 2000 and 2020. One-, 5- and 10-year PS was 84%, 77%, and 68%, and GS was 79%, 70%, and 62%, respectively. Both significantly improved compared to outcomes before 2000 (p < 0.001). Median follow-up was 50 months and retransplantation rate was 12%. Recipient age (adjusted hazard ratio [aHR] = 1.04, 95% confidence interval [CI]: 1.02–1.06) and Model for End-stage Liver Disease (MELD) score (aHR = 1.04, 95% CI: 1.01–1.06), especially above 30, were associated with worse PS, while male sex had better outcomes

(aHR = 0.63, 95% CI: 0.41–0.96). Donor age was associated with worse PS (aHR = 1.01, 95% CI: 1.00–1.03) and GS (aHR = 1.02, 95% CI: 1.01–1.03). In 353 patients (44%) with supplemental data, 33% had myeloproliferative neoplasm, 20% underwent placement of a transjugular intrahepatic portosystemic shunt (TIPS) pre-LT, and 85% used anticoagulation post-LT. Post-LT anticoagulation was associated with improved PS (aHR = 0.29, 95% CI: 0.16–0.54) and GS (aHR = 0.48, 95% CI: 0.29–0.81). Hepatic artery thrombosis and portal vein thrombosis occurred in 9% and 7%, while recurrent BCS was rare (3%).

Conclusions: Liver transplantation for Budd-Chiari syndrome results in excellent patient and graft survival. Older recipient or donor age and higher Model for End-stage Liver Disease (MELD) score are associated with poorer outcomes, while long-term anticoagulation improves both patient and graft outcomes.

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DOI: 10.1097/hep.0000000000000778

Bile Ducts

Gastroenterology. 2024;166(6):1145–55

Ridtitid W, Karuehardsuwan J, Faknak N, Piyachaturawat P, Vongwattanakit P, Kulpatcharapong S, Angsuwatcharakon P, Mekaroonkamol P, Kongkam P, Rerknimitr R

Endoscopic gallbladder stenting to prevent recurrent cholecystitis in deferred cholecystectomy: A randomized trial

Background and aims: Endoscopic transpapillary gallbladder stenting (ETGS) has been proposed as one of the adjunctive treatments, apart from antibiotics, before surgery in patients with acute cholecystitis whose cholecystectomy could not be performed or was deferred. Currently, there are no comparative data on the outcomes of ETGS in those who receive and do not receive ETGS. The authors aimed to compare the rates of recurrent cholecystitis at 3 and 6 months in these 2 groups.
Methods: Between 2020 and 2023, eligible acute calculous cholecystitis patients with a high probability of common bile duct stone, who were surgical candidates but could not have an early cholecystectomy during COVID-19 surgical lockdown, were randomized into groups A (received ETGS) and B (did not receive ETGS). A definitive cholecystectomy was performed at 3 months or later in both groups.
Results: A total of 120 eligible patients were randomized into group A (n = 60) and group B (n = 60). In group A, technical and clinical success rates were 90% (54/60) and 100% (54/54), respectively. Based on intention-to-treat analysis, group A had a significantly lower rate of recurrence than group B at 3 months (0% [0/60] vs. 18.3% [11/60]; p = 0.001). At 3–6 months, group A showed a non-significantly lower rate of recurrent cholecystitis compared to group B (0% [0/32] vs. 10% [3/30]; p = 0.11).

Conclusions: Endoscopic transpapillary gallbladder stenting (ETGS) could prevent recurrent cholecystitis in acute cholecystitis patients with common bile duct stone whose cholecystectomy was deferred for 3 months. In those who did not receive ETGS, the majority of recurrences occurred within 3 months.

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DOI: 10.1053/j.gastro.2024.02.007

Hepatology. 2024;79(6):1324–36

Huang YH, Loftfield E, Argirion I, Adami HO, Albanes D, Chan AT, Fedirko V, Fraser GE, Freedman ND, Giles GG, Hartge P, Katzke V, Knutsen SF, Lacey J, Jr., Liao LM, Luo J, Milne RL, O'Brien KM, Peters U, Poynter JN, Purdue MP, Robien K, Sandin S, Sandler DP, Setiawan VW, Kang JH, Simon TG, Sinha R, VoPham T, Weinstein SJ, White E, Zhang X, Zhu B, McGlynn KA, Campbell PT, Lee MH, Koshiol J

Association of tea and coffee consumption and biliary tract cancer risk: The Biliary Tract Cancers Pooling Project

Background and aims: Tea and coffee are widely consumed beverages worldwide. The authors evaluated their association with biliary tract cancer (BTC) incidence.
Approach and results: They pooled data from 15 studies in the Biliary Tract Cancers Pooling Project to evaluate associations between tea and coffee consumption and BTC development. Participants were categorized as non-drinkers (0 cup/day), moderate drinkers (> 0 and < 3 cups/day), and heavy drinkers (≥ 3 cups/day). Multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox models. During 29,911,744 person-years of follow-up, 851 gallbladder cancer (GBC), 588 intrahepatic bile duct cancer (IHBDC), 753 extrahepatic bile duct cancer (EHBDC), and 458 ampulla of Vater cancer (AVC) cases were diagnosed. Individuals who drank tea showed a statistically significantly lower incidence rate of GBC relative to tea non-drinkers (HR = 0.77; 95% CI: 0.64–0.91), and IHBDC had an inverse association (HR = 0.81; 95% CI: 0.66–1.00). However, no associations were observed for EHBDC or AVC. In contrast, coffee consumption was positively associated with GBC, with a higher incidence rate for individuals consuming more coffee ($HR_{< 3\ cups/day}$ = 1.29, 95% CI: 1.01–1.66; $HR_{\geq 3\ cups/day}$ = 1.49, 95% CI: 1.11–1.99, p_{trend} = 0.01) relative to coffee non-drinkers. However, there was no association between coffee consumption and GBC when restricted to coffee drinkers. There was little evidence of associations between coffee consumption and other BTCs.

Conclusions: Tea consumption was associated with a lower incidence of gallbladder cancer (GBC) and possibly intrahepatic bile duct cancer. Further research is warranted to replicate the observed positive association between coffee and GBC.

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DOI: 10.1097/hep.0000000000000748

General Hepatology

Hepatology. 2024;79(6):1401–11

Engström A, Wintzell V, Melbye M, Svanström H, Eliasson B, Gudbjörnsdottir S, Hveem K, Jonasson C, Hviid A, Ueda P, Pasternak B

Association of glucagon-like peptide-1 receptor agonists with serious liver events among patients with type 2 diabetes: A Scandinavian cohort study

Background and aims: Clinical trials suggest that glucagon-like peptide-1 receptor agonists (GLP-1RA) may have beneficial effects on non-alcoholic fatty liver disease (NAFLD), but the impact on hard hepatic end points is unknown. The authors assessed the association between the use of GLP-1RA and the risk of serious liver events in routine clinical practice.
Approach and results: Cohort study using data from nationwide registers in Sweden, Denmark, and Norway, 2007–2020, including 91,479 initiators of GLP-1RA and 244,004 initiators of the active comparator, dipeptidyl peptidase-4 (DPP4) inhibitors, without a history of chronic liver disease other than NAFLD/non-alcoholic steatohepatitis (NASH). The primary outcome was serious liver events: a composite of incident compensated and decompensated cirrhosis and hepatocellular carcinoma (HCC). Secondary outcomes were the individual components of the primary outcome. Cox regression was used to estimate hazard ratios (HRs), using propensity score weighting to control for confounding. Users of GLP-1RA had 608 serious liver events (adjusted incidence rate = 16.9 events per 10,000 person-years), compared with 1770 events among users of DPP4 inhibitors (19.2 events per 10,000 person-years). The adjusted HR was 0.85 (95% confidence interval [CI]: 0.75–0.97), and the rate difference was -2.1 (-4.4–0.1) events per 10,000 person-years. In secondary outcome analyses, the adjusted HR was 0.85 (95% CI: 0.75–0.97) for compensated and decompensated cirrhosis and 1.05 (95% CI: 0.80–1.39) for HCC.

Conclusions: The use of glucagon-like peptide-1 receptor agonists was associated with a significantly reduced risk of serious liver events, driven by a reduction of compensated and decompensated cirrhosis.

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DOI: 10.1097/hep.0000000000000712

TRANSLATIONAL SCIENCE CORNER

IBD

Gut. 2024;73(8):1292–301

Bedke T, Stumme F, Tomczak M, Steglich B, Jia R, Bohmann S, Wittek A, Kempski J, Göke E, Böttcher M, Reher D, Franke A, Lennartz M, Clauditz T, Sauter G, Fründt T, Weidemann S, Tiegs G, Schramm C, Gagliani N, Pelczar P, Huber S

Protective function of sclerosing cholangitis on IBD

Objective: There is a strong clinical association between inflammatory bowel disease (IBD) and primary sclerosing cholangitis (PSC), a chronic disease of the liver characterised by biliary inflammation that leads to strictures and fibrosis. Approximately 60–80% of people with PSC will also develop IBD (PSC-IBD). One hypothesis explaining this association would be that PSC drives IBD. Therefore, the authors' aim was to test this hypothesis and to decipher the underlying mechanism.
Design: Colitis severity was analysed in experimental mouse models of colitis and sclerosing cholangitis, and people with IBD and PSC-IBD. Foxp3⁺ regulatory T (Treg)-cell infiltration was assessed by quantitative polymerase chain reaction (qPCR) and flow cytometry. Microbiota profiling was carried out from faecal samples of people with IBD, PSC-IBD and mouse models recapitulating these diseases. Faecal microbiota samples collected from people with IBD and PSC-IBD were transplanted into germ-free mice followed by colitis induction.
Results: The authors show that sclerosing cholangitis attenuated IBD in mouse models. Mechanistically, sclerosing cholangitis causes an altered intestinal microbiota composition, which promotes Foxp3⁺ Treg-cell expansion, and thereby protects against IBD. Accordingly, sclerosing cholangitis promotes IBD in the absence of Foxp3⁺ Treg cells. Furthermore, people with PSC-IBD have an increased Foxp3⁺ expression in the colon and an overall milder IBD severity. Finally, by transplanting faecal microbiota into gnotobiotic mice, it was shown that the intestinal microbiota of people with PSC protects against colitis.

Conclusion: This study shows that primary sclerosing cholangitis attenuates inflammatory bowel disease and provides a comprehensive insight into the mechanisms involved in this effect.

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DOI: 10.1136/gutjnl-2023-330856

EXPERT OPINION

Dr. Lena Sophie Mayer

Protective function of sclerosing cholangitis on IBD

The reciprocal relationship between the intestine and liver has been the focus of research for several years. In terms of anatomy, the "gut-liver axis" is represented by the portal vein and the biliary system, while functionally, it is represented by the microbiome and circulating metabolites. The clinical association between chronic inflammatory bowel disease (IBD) and primary sclerosing cholangitis (PSC) is just one of many examples highlighting a connection between the gut and the liver. Approximately 60–80% of patients with PSC develop IBD, while only about 5% of patients with IBD develop PSC. PSC induces changes in the intestinal microbiome, and these changes modulate the mucosal immune system.
Earlier studies have described the association between PSC-IBD and attenuated inflammation and changes in the microbiome compared to IBD without concomitant PSC. Bedke et al. confirmed this observation using various mouse models. A fecal microbiome transfer from patients with IBD and PSC-IBD to germ-free mice also showed attenuated inflammation in the presence of the PSC-IBD microbiota. An enrichment of *Lachnospiraceae* was found both in the mouse model and in human microbiome samples in patients with PSC-IBD. Limitations of such analyses include the heterogeneity of patient cohorts, different sampling sites, and differences in the sample type (stool, biopsy). However, this study shows an enrichment of *Lachnospiraceae* in both biopsies and stool samples from patients with PSC-IBD. The correlation of inflammatory activity with the microbiota at the family level is also of limited significance, as different species have distinct metabolic properties, and thus can have either proinflammatory or anti-inflammatory effects.
The microbiome and intestinal immune system constantly interact. While dysbiosis can lead to an excessive immune response and cause intestinal damage, a favorable composition of the microbiota contributes to immune homeostasis. The differentiation and expansion of regulatory T cells (Treg), which play a central role in limiting intestinal inflammation, are also largely influenced by the microbiome. Indeed, the authors found an enrichment of mucosal Foxp3⁺ Treg in the PSC-IBD mouse model and an increased expression of Foxp3 mRNA was detected in the mucosa of PSC-IBD patients. In a lymphocytopenic mouse model where Treg were absent, inflammation of PSC-IBD was more severe, proving that the attenuation of inflammation mechanistically depends on Treg. However, functional differences of Treg regarding their suppressive capacity in PSC-IBD versus IBD alone were not explored. Moreover it remains unclear whether Treg expansion occurs directly in the mucosa or in the cholestatic liver. In addition, it is yet to be determined whether other cholestatic liver diseases or treatment with ursodeoxycholic acid (UDCA) influence the development of IBD.
PSC increases the risk of various malignancies. In patients with PSC-IBD, the risk of developing colon cancer is significantly higher compared to patients with IBD alone,

warranting annual screening colonoscopies. The fact that the PSC-associated microbiome modulates inflammation raises the question of whether modifications to the microbiome might also reduce cancer risk. However, this was not investigated in the present study.
In summary, this study suggests that PSC may positively influence the outcome of IBD by modulating the microbiome and promoting the expansion of regulatory T cells. However, more detailed microbiome analyses and functional immunological assessments are still needed. Moreover, the influence of cholestasis and its treatment on mucosal inflammation remain unexplored. In addition, the impact of the PSC-associated microbiome on the occurrence of IBD-related complications needs to be further investigated. At present, this study does not lead to any direct recommendations for clinical practice. Microbiome or immunological analyses do not yet provide a basis for specific therapeutic interventions and thus should not be routinely performed. However, fecal microbiome transfer as a potential treatment option for IBD patients with and without concomitant PSC is already under clinical investigation. Thus studies such as this one are particularly important for improving patient care. ■

Liver

Nature. 2024;631(8022):867–75

Bosch M, Kallin N, Donakonda S, Zhang JD, Wintersteller H, Hegenbarth S, Heim K, Ramirez C, Fürst A, Lattouf EI, Feuerherd M, Chattopadhyay S, Kumpesa N, Griesser V, Hoflack JC, Siebourg-Polster J, Mogler C, Swadling L, Pallett LJ, Meiser P, Manske K, de Almeida GP, Kosinska AD, Sandu I, Schneider A, Steinbacher V, Teng Y, Schnabel J, Theis F, Gehring AJ, Boonstra A, Janssen HLA, Vandenbosch M, Cuypers E, Öllinger R, Engleitner T, Rad R, Steiger K, Oxenius A, Lo WL, Klepsch V, Baier G, Holzmann B, Maini MK, Heeren R, Murray PJ, Thimme R, Herrmann C, Protzer U, Böttcher JP, Zehn D, Wohlleber D, Lauer GM, Hofmann M, Luangsay S, Knolle PA

A liver immune rheostat regulates CD8 T cell immunity in chronic HBV infection

Chronic hepatitis B virus (HBV) infection affects 300 million patients worldwide, in whom virus-specific CD8 T cells by still ill-defined mechanisms lose their function and cannot eliminate HBV-infected hepatocytes. Here the authors demonstrate that a liver immune rheostat renders virus-specific CD8 T cells refractory to activation and leads to their loss of effector functions. In preclinical models of persistent infection with hepatotropic viruses such as HBV, dysfunctional virus-specific CXCR6$^+$ CD8 T cells accumulated in the liver and, as a characteristic hallmark, showed enhanced transcriptional activity of cAMP-responsive element modulator (CREM) distinct from T cell exhaustion. In patients with chronic hepatitis B, circulating and intrahepatic HBV-specific CXCR6$^+$ CD8 T cells with enhanced CREM expression and transcriptional activity were detected at a frequency of 12–22% of HBV-specific CD8 T cells. Knocking out the inhibitory CREM/ICER isoform in T cells, however, failed to rescue T cell immunity. This indicates that CREM activity was a consequence, rather than the cause, of loss in T cell function, further supported by the observation of enhanced phosphorylation of protein kinase A (PKA) which is upstream of CREM. Indeed, the authors found that enhanced cAMP-PKA-signalling from increased T cell adenylyl cyclase activity augmented CREM activity and curbed T cell activation and effector function in persistent hepatic infection. Mechanistically, CD8 T cells recognizing their antigen on hepatocytes established close and extensive contact with liver sinusoidal endothelial cells, thereby enhancing adenylyl cyclase-cAMP-PKA signalling in T cells. In these hepatic CD8 T cells, which recognize their antigen on hepatocytes, phosphorylation of key signalling kinases of the T cell receptor signalling pathway was impaired, which rendered them refractory to activation. Thus, close contact with liver sinusoidal endothelial cells curbs the activation and effector function of HBV-specific CD8 T cells that target hepatocytes expressing viral antigens by means of the adenylyl cyclase-cAMP-PKA axis in an immune rheostat-like fashion.

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DOI: 10.1038/s41586-024-07630-7 ■

EXPERT OPINION

Prof. Dr. Dr. Bertram Bengsch

T cells amp'd down: Identification of a novel mechanism of intrahepatic immune regulation

The mechanisms by which hepatitis B virus (HBV) infection evades immune control through the T-cell response in chronic HBV (cHBV) infection are as yet unclear. Until recently, it has been assumed that this immune evasion is mediated primarily via the induction of T cell exhaustion, where virus-specific CD8 T cells are driven into a state of relative dysfunction, rendering them unable to clear viral infection due to an imbalance of immunological overstimulation and inhibitory signals. Here, Bosch et al. identify a distinct liver-specific immunoregulatory mechanism in a murine model of Ad-HBV infection. A subset of CXCR6$^+$ HBV-specific CD8 T cells was regulated via the cAMP-protein kinase A (PKA) pathway activating the transcription factor CREM and lacked significant antiviral effector function. Unlike T-cell exhaustion associated with high transcriptional activity of Tox and strong T-cell receptor stimulation, these cells exhibited elevated phosphatase activity, which inhibited proximal TCR signaling without prominent Tox activity. Further analyses indicated that this regulatory pathway could be triggered through close interactions between HBV-specific CD8 T cells and liver sinusoidal endothelial cells (LSECs). Known for their immunological gatekeeping role in the liver, LSECs can reside next to virus-infected hepatocytes. The data suggests that LSEC cells contribute to attenuating the virus-specific CD8 T-cell response via an intrahepatic mechanism that effectively muffles TCR signaling. This

has important implications for our understanding and targeting of T-cell responses against hepatic antigens. While this study indicates that LSECs can coregulate HBV-specific CD8 T cells due to their spatial proximity when engaging HBV-infected hepatocytes, several aspects warrant further investigation. First, the precise triggers for this mechanism are still unclear, such as whether it necessitates simultaneous T-cell recognition of viral antigens presented by infected hepatocytes or specific hepatocyte-LSEC crosstalk. Second, further research is needed to understand the mediators involved in T-cell suppression. Third, questions remain about the durability of this regulatory effect and whether these CREM-signature T cells could be reprogrammed; the expression of co-stimulatory receptors suggests a potential for reactivation via agents such as 4-1BB agonists (DOI: 10.1016/j.cell.2024.05.038). Finally, it is uncertain what proportion of T-cell dysfunction in cHBV patients this mechanism accounts for. Recent single-cell RNA-Seq analysis of HBV-specific CD8 T cells identified heterogeneity, including T cells with signs of classic T-cell exhaustion, T cells with evidence of TGF-beta dependent effector attenuation, as well as a share of cells marked by CREM signatures (DOI: 10.1038/s41590-024-01928-4). Bosch et al. observe peak CREM activity in active hepatitis, suggesting that its role might be linked to a higher degree of liver inflammation. Overall this suggests that multiple mechanisms contribute to T-cell dysfunction in cHBV infection. ■

Nature. 2024;630(8015):166–73

Gribben C, Galanakis V, Calderwood A, Williams EC, Chazarra-Gil R, Larraz M, Frau C, Puengel T, Guillot A, Rouhani FJ, Mahbubani K, Godfrey E, Davies SE, Athanasiadis E, Saeb-Parsy K, Tacke F, Allison M, Mohorianu I, Vallier L

Acquisition of epithelial plasticity in human chronic liver disease

For many adult human organs, tissue regeneration during chronic disease remains a controversial subject. Regenerative processes are easily observed in animal models, and their underlying mechanisms are becoming well characterized, but technical challenges and ethical aspects are limiting the validation of these results in humans. The authors decided to address this difficulty with respect to the liver. This organ displays the remarkable ability to regenerate after acute injury, although liver regeneration in the context of recurring injury remains to be fully demonstrated. Here they performed single-nucleus RNA sequencing (snRNA-seq) on 47 liver biopsies from patients with different stages of metabolic dysfunction-associated steatotic liver disease to establish a cellular map of the liver during disease progression. Then they combined these single-cell-level data with advanced 3D imaging to reveal profound changes in the liver architecture. Hepatocytes lose their zonation and considerable reorganization of the biliary tree takes place. More importantly, this study uncovers transdifferentiation events that occur between hepatocytes and cholangiocytes without the presence of adult stem cells or developmental progenitor activation. Detailed analyses and functional validations using cholangiocyte organoids confirm the importance of the PI3K-AKT-mTOR pathway in this process, thereby connecting this acquisition of plasticity to insulin signalling. Together, these data indicate that chronic injury creates an environment that induces cellular plasticity in human organs, and understanding the underlying mechanisms of this process could open new therapeutic avenues in the management of chronic diseases.

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DOI: 10.1038/s41586-024-07465-2 ■

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EASL SLD Summit 2025
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EASL Liver Cancer Summit 2025
E-Mail: easlsummit@easloffice.eu
http://www.easl.eu
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February 27 – March 1, 2025, Heidelberg, Germany
44th Annual Meeting of the German Pancreatic Club (DPC)
E-Mail: kbornschein@eventlab.org
https://dpc-congress.com/

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E-Mail: info@neurogastro.de
https://www.neurogastro.de

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Joint CDDW™-CLM Conference 2025
E-Mail: casl@hepatology.ca
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Imprint

Publisher

Falk Foundation e. V.
Leinenweberstr. 5
79108 Freiburg | Germany
www.falkfoundation.org
media@falkfoundation.org
Director: Dr. Martin Falk
Official Register: Freiburg 1147

Published: quarterly

Editors:
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