FALK GASTRO REVIEW JOURNAL

www.falkfoundation.org

INT

ESOPHAGUS TO SMALL INTESTINE
Page 5–15

COLON TO RECTUM
Page 16–27

PANCREAS
Page 28–30

LIVER AND BILE
Page 32–45

TRANSLATIONAL SCIENCE CORNER
Page 46–47

01

2026

Contents

Editorial	2 – 3
ESOPHAGUS TO SMALL INTESTINE	5 – 15
COLON TO RECTUM	16 – 27
PANCREAS	28 – 30
Symposium 241 Interview with Prof. Britta Siegmund **Lively discussions and open exchange bring the community of IBD researchers together** Oxford (United Kingdom), July 10 – 12, 2025	31
LIVER AND BILE	32 – 45
TRANSLATIONAL SCIENCE CORNER	46 – 47
Congresses 2026	48

Editorial

Dear colleagues,

The indications for **immune checkpoint inhibitor therapy** in **gastrointestinal tumors** continue to expand, enabling markedly improved treatment responses. The MATTERHORN trial demonstrated that, in the **neoadjuvant setting** of **gastric and gastroesophageal junction adenocarcinoma**, the efficacy of standard FLOT chemotherapy (fluorouracil, leucovorin, oxaliplatin, and docetaxel) can be significantly enhanced by the addition of immune therapy with the PD-L1 inhibitor durvalumab. These findings support the establishment of a new standard of care (Janjigian et al., p. 9). Immune therapy has also produced remarkable outcomes in **mismatch repair-deficient (dMMR) tumors**. In a substantial proportion of patients with early-stage dMMR **rectal** cancer and other anatomically accessible tumors typically managed with curative-intent surgery, neoadjuvant PD-1 inhibition allowed for **complete omission of surgery** (Cercek et al., p. 22). However, effective oncologic treatment extends beyond pharmacologic and surgical interventions. A large randomized trial demonstrated that among patients who had completed adjuvant chemotherapy for **colon cancer,** participation in a **structured** 3-year **exercise program** resulted in significantly longer disease-free survival—and potentially overall survival—compared with patients who received health-education materials alone (Courneya et al., p. 22). Another noteworthy scientific advancement in gastrointestinal oncology is the first successful application of **CAR T-cell therapy** for the treatment of **solid tumors**. A randomized phase 2 trial in patients with advanced **gastric cancer** demonstrated, for the first time, that CAR T-cell therapy can confer a survival benefit in solid tumors (Qi et al., p. 7)

The incidence and prevalence of **inflammatory bowel disease** (IBD) are significantly increasing not only in industrialized countries, but also in numerous newly industrialized and emerging regions. A comprehensive analysis of global epidemiological data suggests that the **prevalence of IBD in Europe** may **triple by 2040**, reaching approximately 1.5% of the population. These projections underscore the need for effective strategies for prevention, early detection, and management of IBD (Hracs et al., p. 16). In the pharmacologic management of **Crohn's disease**, IL-23 inhibitors represent a significant therapeutic advance. In the GALAXI studies, treatment with the **IL-23 antibody guselkumab** was not only superior to placebo but also produced significantly improved outcomes after 48 weeks across multiple endpoints compared with ustekinumab (Panaccione et al., p. 14).

To date, the diagnostic utility of laboratory markers such as CA 19-9 for the **early detection of pancreatic cancer** has been limited. Plasma-based metabolic profiling using mass spectrometry may offer improved performance. In the German METAPAC study, two plasma multimetabolite signatures demonstrated significantly better accuracy in ruling out pancreatic ductal adenocarcinoma in patients with diagnostically relevant lesions than CA 19-9 alone (Mahajan et al., p. 28).

There continues to be significant progress in the field of **metabolic dysfunction-associated steatotic liver disease (MASLD)**. In this issue, we focus on several high-impact **therapeutic trials** that advance different treatment approaches toward clinical applicability in different patient populations. In addition to glucagon-like peptide-1 (GLP-1) analogues (Sanyal et al., p. 36), new evidence is presented on the efficacy of fibroblast growth factor 21 (FGF21) analogues (Noureddin et al., p. 36, Noureddin et al., p. 37, Loomba et al., p. 35), and of an antisense inhibitor of diacylglycerol-O-acyltransferase 2 (DGAT2) (Loomba et al., p. 35).

In the area of hepatobiliary tumors, this issue features important advances in both the **early detection** and **systemic treatment of hepatocellular carcinoma (HCC)**. With respect to imaging, recent findings suggest that non-contrast MRI offers advantages over ultrasonography in HCC surveillance (Rhee et al., p. 43), while AI-assisted, contrast-enhanced ultrasound models may improve the differentiation of focal liver lesions (Ding et al., p. 41). Therapeutically, two key topics are addressed: the management of patients with HCC who achieve a complete response to immunotherapy (Scheiner et al., p. 43), and the comparative efficacy of nivolumab plus ipilimumab versus tyrosine kinase inhibitors in HCC treatment (Yau et al., p. 42).

We hope the selected publications give you a helpful overview of current research and clinical trials in the field. May you find these articles both inspiring and informative. We wish you a happy holiday season and all the best in the new year.

Yours sincerely,

Peter Hasselblatt and Tobias Böttler
Department of Internal Medicine II,
University Medical Center Freiburg (Germany)

ESOPHAGUS TO SMALL INTESTINE

Celiac Disease, Gluten Sensitivity and Food Allergy

Clin Gastroenterol Hepatol. 2025;23(7):1143-1151

Lukina P, Andersen IL, Klaasen RA, Warren DJ, Bolstad N, Mjønes P, Rønne E, Iversen R, Sollid LM, Lundin KEA, Ness-Jensen E

The prevalence and rate of undiagnosed celiac disease in an adult general population, the Trøndelag Health Study, Norway

Background and aims: This study aimed to determine the total prevalence of celiac disease (CeD), including undiagnosed cases, in a population-based study of adults screened for CeD.
Methods: The study used the 4th Trøndelag Health Study (HUNT4), conducted in 2017–2019, where 56,042 adult (aged > 20 years) residents of Nord-Trøndelag County, Norway, participated. Serum samples from 54,505 participants were analyzed for anti-transglutaminase 2 IgA and IgG. Seropositive individuals were invited for a clinical assessment, including upper endoscopy with duodenal biopsies. Previously diagnosed and seronegative CeD cases were identified through linkage to hospital records and the Norwegian Patient Registry.
Results: The rate of CeD seropositivity was 2.0% (1,107/54,505). Out of these, 724 individuals attended the clinical assessment. Additionally, the hospital records and registry identified individuals with a known CeD diagnosis, that were seronegative or without serology in HUNT4 or seropositive in HUNT4 but did not participate in the clinical assessment. In total, the study confirmed a new CeD diagnosis after participation in HUNT4 in 470 individuals and a known CeD diagnosis before participation in HUNT4 in 383 individuals. The total biopsy-confirmed prevalence of CeD was 1.5% (853/56,042), and the ratio of new, previously undiagnosed CeD cases (after HUNT4) to known, previously diagnosed CeD cases (before HUNT4) was 1.2:1 (470/383).

Conclusions: The total prevalence of CeD in this population-based study of adults in Norway was high and many individuals were previously undiagnosed. Detection of CeD should be improved, because early diagnosis is crucial for effective management and prevention of complications.

P. Lukina, HUNT Research Centre, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Levanger, Norway, e-mail: polina.lukina@ntnu.no

DOI: 10.1016/j.cgh.2024.06.027

Am J Gastroenterol. 2025;120(7):1636-1644

Zylberberg HM, Lebwohl B, Söderling J, Kochar B, Jylhävä J, Green PHR, Ludvigsson JF

Older adults with celiac disease are at increased risk of frailty: A nationwide cohort study

Introduction: Celiac disease (CeD) is increasingly diagnosed in older adults, though few studies have explored complications in this group. As frailty confers increased risk for adverse events, the authors aimed to explore frailty in older adults with CeD.
Methods: In a nationwide Swedish cohort, the authors identified adults ≥ 60 years with incident CeD between 2004 and 2017 and matched them to population-based controls without CeD by age, sex, county, and calendar-period. Baseline frailty within 3 years before CeD diagnosis or index date was assessed using the Hospital Frailty Risk Score. Among those without baseline frailty, the authors used conditional logistic regression to estimate odds ratios and 95% confidence intervals of future frailty at 5 years comparing CeD with controls. Logistic regression was used to evaluate the association between persistent villous atrophy versus mucosal healing and frailty in patients with CeD.
Results: A total of 4,646 older adults with CeD were matched to 21,944 non-CeD individuals. Baseline frailty was increased in patients with CeD (54.4%) compared with controls (29.7%, $p < 0.001$), which existed across all frailty categories: low-risk (43.4% vs. 23.8%), intermediate-risk (10.3% vs. 5.4%), and high-risk (0.8% vs. 0.6%). Among those without baseline frailty, patients with CeD had a 61% increased risk of overall frailty at 5 years (95% confidence interval: 1.46–1.78). Mucosal healing in CeD individuals on follow-up biopsy did not protect against future frailty.

Discussion: Older adults with CeD were significantly more likely to become frail than matched comparators. This analysis reveals the increased vulnerability that older patients with CeD are likely to experience.

J.F. Ludvigsson, Clinical Epidemiology Division, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, e-mail: jonasludvigsson@yahoo.com

DOI: 10.14309/ajg.0000000000003217

Gastritis and Helicobacter Pylori

Gastroenterology. 2025;169(2):244-250.e1

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 gastric adenocarcinoma after eradication of *Helicobacter pylori*

Background and aims: *Helicobacter pylori* infection of the stomach is the main risk factor for gastric noncardia adenocarcinoma; however, less is known on how eradication of *H. pylori* influences the risk of this tumor

over time, particularly in Western populations. The aim of this study was to delineate how the risk of gastric noncardia adenocarcinoma develops over time after *H. pylori* eradication treatment in a Western population compared with the background population.
Methods: This population-based cohort study included all adults having received *H. pylori* eradication treatment between 1995 and 2019 in any of the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) were calculated by comparing the gastric noncardia adenocarcinoma incidence in the study cohort with the incidence in the background population of the same age, sex, calendar period, and country. Time trends in SIR were assessed using Poisson regression.
Results: Among 659,592 participants having received *H. pylori* eradication treatment, contributing 5,480,873 person-years at risk, 1,311 developed gastric noncardia adenocarcinoma. During up to 24 years of follow-up, the SIR was initially higher than the background population (SIR = 2.27; 95% CI: 2.10–2.44, 1–5 years after treatment), and then gradually decreased over time and approached the level of the background population from 11 years after treatment (SIR = 1.11; 95% CI: 0.98–1.27, 11–24 years after treatment).

Conclusion: This study revealed a decreasing incidence of gastric noncardia adenocarcinoma after *H. pylori* eradication treatment in 5 Western populations. The risk became virtually similar to the background population from 11 years after treatment.

J. Lagergren, Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden,
e-mail: jesper.lagergren@ki.se

DOI: 10.1053/j.gastro.2025.01.239

Gut. 2025;74(9):1410-1418

Yamada H, Abe S, Charvat H, Ando T, Maeda M, Murakami K, Oka S, Maekita T, Sugimoto M, Furuta T, Kaise M, Yamamichi N, Takamaru H, Sasaki A, Oda I, Nanjo S, Suzuki N, Sugiyama T, Kodama M, Mizukami K, Ito M, Kotachi T, Shimazu T, Yamamoto S, Ushijima T

Precision risk stratification of primary gastric cancer after eradication of *H. pylori* by a DNA methylation marker: A multicentre prospective study

Background: Precision cancer risk stratification for gastric cancer is urgently needed for the growing number of healthy people after *Helicobacter pylori* eradication. The epimutation burden in non-malignant tissues has been associated with cancer risk in multiple cross-sectional studies.
Objective: To confirm the clinical usefulness of a DNA methylation marker for epimutation burden, and to identify a cut-off methylation level for a super-high-risk population.
Design: Healthy people after *H. pylori* eradication with open-type atrophy were prospectively recruited. DNA methylation levels of a marker gene, *RIMS1*, were measured in biopsy specimens from gastric antrum and body. The primary endpoint was the incidence rate of gastric cancer in quartiles of the methylation levels.
Results: 1,624 participants had at least one endoscopic follow-up with a median follow-up of 4.05 years, and a primary gastric cancer developed in 27 participants. The highest quartile of *RIMS1* methylation levels had a higher incidence rate (972.8 per 100,000 person-years) than the lowest quartile (127.1). Cox regression analysis revealed a univariate HR of 7.7 (95% confidence interval [CI]: 1.8–33.7) and an age- and sex-adjusted HR of 5.7 (95% CI: 1.3–25.5). As a secondary objective, a cut-off methylation level of 25.7% (95% CI: 1.7–7.7) was obtained to identify a population with a super-high risk based on the number needed to screen of 1,000.

Conclusion: A DNA methylation marker can risk-stratify healthy people after *H. pylori* eradication even though all of them have clinically high risk. Individuals with super-high risk will need more frequent gastric cancer screening than currently recommended.

T. Ushijima, Department of Epigenomics, Institute for Advanced Life Sciences, Hoshi University, Tokyo, Japan,
e-mail: tushijima142@hoshi.ac.jp

DOI: 10.1136/gutjnl-2025-335039

Gut. 2025;74(10):1561-1570

Schulz C, Liou JM, Alboraie M, Bornschein J, Campos Nunez C, Coelho LG, Quach DT, Fallone CA, Chen YC, Gerhard M, Gisbert JP, Jung HY, Katelaris PH, Kim JG, Lu H, Macke L, Mahachai V, Moss SF, Remes Troche JM, Riquelme A, Romano M, Setshedi M, Smith S, Suerbaum S, Tshibangu-Kabamba E, Vilaichone RK, Yadegar A, Yamaoka Y, Mégraud F, El-Omar EM, Sugano K, Malfertheiner P

Helicobacter pylori antibiotic resistance: A global challenge in search of solutions

Background: *Helicobacter pylori* resistance to antibiotics commonly used in eradication regimens is increasing dramatically in many locations; new strategies are needed to manage this infectious disease.
Objective: This study's aim was to collect and update information on antibiotic resistance (AR) rates in *H. pylori* as well as current strategies for *H. pylori* management, including public health issues, from a global perspective.
Design: An international survey was conducted in 31 countries on 6 continents to address key issues concerning the management of *H. pylori*-related AR. Individual aspects included the prevalence of AR for specific antibiotics, antibiotic susceptibility testing (AST) in different healthcare systems, availability of drugs, reimbursement issues and strategies for *H. pylori* AR surveillance.
Results: Resistance to the most effective antibiotics used in *H. pylori* eradication regimens is increasing globally, with clarithromycin and levofloxacin resistance exceeding 15% in 24/31 and 18/31 countries, respectively. Amoxicillin remains an exception, with resistance rates under 2% in 14/31 countries; though African countries have reported amoxicillin resistance rates of over 90%. Bismuth-based treatment regimens are the most effective and are recommended as first-line treatment in several countries. However, more than 1 billion inhabitants worldwide have no access to bismuth-based regimens. PCR-based tests for AR are used in 16/26 countries but

are reimbursed in only 4, while next generation sequencing-based tests are available, but not reimbursed, in 3 countries. In 22/26 countries only culture-based methods are available (reimbursed in 9/26 countries). AR surveillance programmes have only been established in 4/26 countries. Therefore, in most countries, empirical therapy with the most effective local regimen available locally is practiced.

Conclusion: The dramatic global rise in *H. pylori* antibiotic resistance requires an urgent revision of current management strategies. Possible solutions include AST-based selection of effective treatment regimens, identification of novel combinations of existing drugs and exploration of novel drugs.

C. Schulz, Medical Department 2, LMU Munich, Munich, Germany, e-mail: chr.schulz@med.uni-muenchen.de

DOI: 10.1136/gutjnl-2025-335523

EoE

Lancet Gastroenterol Hepatol. 2025;10(7):622-633

Dellon ES, Collins MH, Bredenoord AJ, Philpott H, Biedermann L, Dulcine M, Nguyen-Cleary T, Su C, Yu J, Tan H, Cataldi F, Wu J, Wang W, Clax P, Woolcott JC, Hirano I

Etrasimod as a treatment for eosinophilic oesophagitis (VOYAGE): A double-blind, placebo-controlled, randomised, phase 2 trial

Background: Novel treatments are needed for eosinophilic oesophagitis. Etrasimod is an oral, once-daily, selective sphingosine 1-phosphate $(S1P)_{1,4,5}$ receptor modulator in development for the treatment of immune-mediated inflammatory diseases. The authors assessed efficacy and safety of etrasimod versus placebo in adults with eosinophilic oesophagitis.
Methods: In this double-blind, randomised, phase 2 trial, patients aged 18–65 years with a previous diagnosis of eosinophilic oesophagitis and histologically active disease from 64 clinical sites (in Australia, Belgium, Spain, Switzerland, and the USA) were randomly assigned (3:3:2) using an interactive web response system to receive oral etrasimod 2 mg or 1 mg or matching placebo for 24 weeks (centrally randomly assigned and double-blind; placebo-controlled period); they continued assigned etrasimod doses or were randomly assigned (1:1) from placebo to etrasimod 2 mg or 1 mg for 28 weeks (extension period). Randomisation was stratified by history of oesophageal dilation and concurrent proton pump inhibitor therapy. The full analysis set and safety set consisted of all randomly assigned patients who received at least one study treatment dose. The primary endpoint was percentage change from baseline in oesophageal peak eosinophil count (PEC) at week 16. Safety was assessed up to week 52. Patients were analysed according to treatment received in the placebo-controlled period and extension period.
Findings: Between December 15, 2020, and May 27, 2022, 41 patients were randomly assigned to etrasimod 2 mg (20 [49%] females and 21 [51%] males), 39 to etrasimod 1 mg (17 [44%] females and 22 [56%] males), and 28 to placebo (14 [50%] females and 14 [50%] males). 85 (79%) of 108 patients completed the double-blind period, entering the extension period. Median percentage changes from baseline in PEC at week 16 were -58.4% (IQR, -86.2 to -26.3) for etrasimod 2 mg (p = 0.010 vs. placebo), -39.4% (-71.1 to 79.0) for etrasimod 1 mg (p = 0.29 vs. placebo) and -21.5% (-57.2 to 55.4) for placebo. In the placebo-controlled period, the most common treatment-emergent adverse events were gastrointestinal disorders (11 [27%] of 41 patients in the etrasimod 2 mg group, 13 [33%] of 39 patients in the etrasimod 1 mg group, and 14 [50%] of 28 patients in the placebo group). Bradycardia events, reported by 3 patients (2 [5%] patients in the etrasimod 2 mg group and 1 [4%] in the placebo group) in the placebo-controlled period, were mild or moderate in severity. No serious treatment-emergent adverse events or deaths occurred.

Interpretation: Etrasimod led to sustained histological and endoscopic improvements in eosinophilic oesophagitis over 52 weeks, symptom improvement in patients without dilation, and was well tolerated. This trial provides the first evidence that targeting the sphingosine 1-phosphate (S1P) pathway can improve disease activity in patients with eosinophilic oesophagitis and that S1P receptor modulation is a viable treatment target for this disease.

E.S. Dellon, Center for Esophageal Diseases and Swallowing, and Center for Gastrointestinal Biology and Disease, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC, USA, e-mail: evan_dellon@med.unc.edu

DOI: 10.1016/S2468-1253(25)00062-7

Barrett's Esophagus, Esophageal and Gastric Cancer

Lancet. 2025;405(10494):2049-2060

Qi C, Liu C, Peng Z, Zhang Y, Wei J, Qiu W, Zhang X, Pan H, Niu Z, Qiu M, Qin Y, Fang W, Ye F, Li N, Liu T, Liu A, Zhang X, Hu C, Zhang J, Cui J, Lin X, Wang S, Zhang J, Lin T, Qu X, Yuan X, Gong J, Li J, Gao W, Gai L, Wang Y, Yuan D, Li Z, Shen L

Claudin-18 isoform 2-specific CAR T-cell therapy (satri-cel) versus treatment of physician's choice for previously treated advanced gastric or gastro-oesophageal junction cancer (CT041-ST-01): A randomised, open-label, phase 2 trial

Background: Claudin-18 isoform 2 (CLDN18.2) has emerged as a promising therapeutic target in gastric or gastro-oesophageal junction cancer. Satricabtagene autoleucel (satri-cel; also known as CT041), an autologous CLDN18.2-specific chimeric antigen receptor (CAR) T-cell therapy, showed encouraging activity in previously treated patients with advanced gastric or

gastro-oesophageal junction cancer in phase 1 clinical trials. In this article, the authors report the primary results from the phase 2 pivotal trial (CT041-ST-01) investigating the efficacy and safety of satri-cel for gastric or gastro-oesophageal junction cancer.
Methods: In this open-label, multicentre, randomised controlled trial conducted in China, patients with CLDN18.2-positive (immunohistochemistry expression intensity ≥ 2+ and positive tumour cells ≥ 40%) advanced gastric or gastro-oesophageal junction cancer, who were refractory to at least two previous lines of treatment, were randomly allocated (2:1) to receive satri-cel or treatment of physician's choice (TPC). In the satri-cel group, satri-cel was infused up to three times at a dose of 250×10^6 cells. For the TPC group, one of the standard-of-care drugs (nivolumab, paclitaxel, docetaxel, irinotecan, or rivoceranib [apatinib]) was given, per the physician's decision. Those who had disease progression or drug intolerance in the TPC group could receive subsequent satri-cel, if eligible. The primary endpoint was progression-free survival, assessed by an independent review committee, in the intention-to-treat population.
Findings: Between March 22, 2022, and July 29, 2024, 266 patients were screened, of whom 156 were randomly allocated to the satri-cel group (n = 104) or TPC group (n = 52). 88 (85%) patients in the satri-cel group and 48 (92%) patients in the TPC group received study drug. In the satri-cel group, 28 (27%) patients had previously received three or more lines of treatment and 72 (69%) patients had peritoneal metastasis. In the TPC group, 10 (19%) patients had previously received three or more lines of treatment and 31 (60%) patients had peritoneal metastasis. The median follow-up time for progression-free survival was 9.07 months (95% confidence interval [CI]: 6.21–13.01) in the satri-cel group and 3.45 months (2.89–not estimable) in the TPC group, based on the reverse Kaplan-Meier method. In the intention-to-treat population, median progression-free survival was 3.25 months (95% CI: 2.86–4.53) in the satri-cel group and 1.77 months (1.61–2.04) in the TPC group (hazard ratio = 0.37 [95% CI: 0.24–0.56]; one-sided log-rank p < 0.0001). In the safety analysis set (all patients who received at least one dose of study drug), grade 3 or higher treatment-emergent adverse events occurred in 87 (99%) of 88 patients in the satri-cel group and 30 (63%) of 48 patients in the TPC group. The most common grade 3 or worse treatment-emergent adverse events related to treatment were decreased lymphocyte count (86 [98%] of 88 patients), decreased white blood cell count (68 [77%] patients), and decreased neutrophil count (58 [66%] patients) in the satri-cel group. Cytokine release syndrome occurred in 84 (95%) of 88 patients in the satri-cel group.

Interpretation: This is the first randomised controlled trial of CAR T-cell therapy in solid tumours globally. Satri-cel treatment resulted in a significant improvement in progression-free survival, with a manageable safety profile. These results support satri-cel as a new third-line treatment for advanced gastric or gastro-oesophageal junction cancer patients.

C. Qi, Beijing Key Laboratory of Cell & Gene Therapy for Solid Tumour, State Key Laboratory of Holistic Integrative Management of Gastrointestinal Cancers, Department of Early Drug Development Centre, Peking University Cancer Hospital & Institute, Beijing, China, e-mail: changsongqi@bjmu.edu.cn

or

L. Shen, Beijing Key Laboratory of Cell & Gene Therapy for Solid Tumour, State Key Laboratory of Holistic Integrative Management of Gastrointestinal Cancers, Beijing Key Laboratory of Carcinogenesis and Translational Research, Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China, e-mail: shenlin@bjmu.edu.cn

DOI: 10.1016/s0140-6736(25)00860-8

EXPERT OPINION

Prof. Dr. Michael Quante

CLDN18.2 CAR-T cell therapy for gastric and gastroesophageal junction cancer: A promising new approach with challenges

In a randomized, open-label phase 2 study published in *The Lancet* in 2025, Qi et al. investigated the CLDN18.2-specific CAR-T cell therapy satri-cel in 156 patients with advanced gastric or gastroesophageal junction (GEJ) cancer refractory to at least two prior lines of therapy. Patients were randomly assigned in a 2:1 ratio to receive either satri-cel or treatment of physician's choice (TPC). The primary endpoint, progression-free survival (PFS), was significantly prolonged with satri-cel: median 3.25 months versus 1.77 months in the TPC arm (hazard ratio [HR] = 0.37; p < 0.0001). The objective response rate (ORR) was 22% (95% CI: 15–31) in the satri-cel arm compared with 4% (95% CI: 0–13) under TPC. In the intention-to-treat (ITT) population, overall survival (OS) showed a favorable trend (7.92 vs 5.49 months; HR = 0.69), which became more pronounced after adjustment for crossover of 20 patients to satri-cel (7.92 vs. 4.37 months; HR = 0.47; 95% CI: 0.30–0.72). Notably, patients who received satri-cel only after crossover achieved an ORR of 20%, further underscoring the biological activity of the therapy.
These results are noteworthy, as they represent the first randomized study in solid tumors to demonstrate a clear signal of superiority for a CAR-T cell therapy. While CAR-T cells are well established in hematologic malignancies, their success in solid tumors has thus far been limited.
However, interpretation of these findings requires a nuanced perspective: The cutoff for CLDN18.2 expression in this study was set at ≥ 40% of tumor cells with 2+/3+ expression, lower than the ≥ 75% cutoff used in previous zolbetuximab studies. This broadened the potential target population but might have led to greater heterogeneous treatment responses. Moreover, the study population was limited to Chinese patients, and the TPC arm included therapies such as apatinib, which are not standard in Western countries. This limits the generalizability of the results to European and North American populations.
The practical implementation of this therapy is also complex, requiring apheresis, lymphodepletion, and CAR-T cell infusion in specialized centers. Sixteen patients in the CAR-T arm did not receive the infusion due to disease progression during manufacturing, underscoring the logistical challenges inherent to personalized cell therapies.

The safety profile was consistent with that observed for other CAR-T cell products: hematologic toxicities grade ≥ 3 occurred in nearly all patients, and cytokine release syndrome (CRS) was reported in 95%, predominantly of mild to moderate severity. Immune effector cell-associated neurotoxicity syndrome (ICANS) was not observed.
In summary, the CT041-ST-01 study provides compelling evidence that CLDN18.2-targeted CAR-T cell therapy represents a promising treatment approach for carefully selected patients with refractory gastric or GEJ cancer. The results support the initiation of phase 3 studies in earlier lines of therapy but underscore the need for precise biomarker definitions, careful patient selection, and administration in experienced CAR-T referral centers. ■

N Engl J Med. 2025;393(3):217-230

Janjigian YY, Al-Batran SE, Wainberg ZA, Muro K, Molena D, Van Cutsem E, Hyung WJ, Wyrwicz L, Oh DY, Omori T, Moehler M, Garrido M, Oliveira SCS, Liberman M, Oliden VC, Smyth EC, Stein A, Bilici M, Alvarenga ML, Kozlov V, Rivera F, Kawazoe A, Serrano O, Heilbron E, Negro A, Kurland JF, Tabernero J; MATTERHORN Investigators

Perioperative durvalumab in gastric and gastroesophageal junction cancer

Background: Perioperative FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) is a standard therapy for resectable gastric and gastroesophageal junction adenocarcinomas, but recurrence rates remain high. Immunotherapy plus chemotherapy may improve outcomes.
Methods: In a phase 3, multinational, double-blind, randomized trial, the authors assigned participants with resectable gastric or gastroesophageal junction adenocarcinoma, in a 1:1 ratio, to receive durvalumab at a dose of 1500 mg or placebo every 4 weeks plus FLOT for 4 cycles (2 cycles each of neoadjuvant and adjuvant therapy), followed by durvalumab or placebo every 4 weeks for 10 cycles. The primary end point was event-free survival; secondary end points included overall survival and pathological complete response.
Results: A total of 474 participants were randomly assigned to the durvalumab group, and 474 to the placebo group (median follow-up, 31.5 months; interquartile range, 26.7–36.6). Two-year event-free survival (Kaplan-Meier estimate) was 67.4% among the participants in the durvalumab group and 58.5% among those in the placebo group (hazard ratio for event or death, 0.71; 95% confidence interval [CI]: 0.58–0.86; $p < 0.001$). Two-year overall survival was 75.7% in the durvalumab group and 70.4% in the placebo group (piecewise hazard ratio for death during months 0–12, 0.99 [95% CI: 0.70–1.39], and during the period from month 12 onward, 0.67 [95% CI: 0.50–0.90]; $p = 0.03$ by a stratified log-rank test [exceeding the significance threshold of $p < 0.0001$]). The percentage of participants with a pathological complete response was 19.2% in the durvalumab group and 7.2% in the placebo group (relative risk = 2.69 [95% CI: 1.86–3.90]). Adverse events with a maximum grade of 3 or 4 were reported in 340 participants (71.6%) in the durvalumab group and in 334 (71.2%) in the placebo group. The percentage of participants with delayed surgery was 10.1% and 10.8%, respectively, and the percentage with delayed initiation of adjuvant treatment was 2.3% and 4.6%.

Conclusions: Perioperative durvalumab plus FLOT led to significantly better event-free survival outcomes than FLOT alone among participants with resectable gastric or gastroesophageal junction adenocarcinoma.

Y.Y. Janjigian, Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA, e-mail: janjigiy@mskcc.org

DOI: 10.1056/nejmoa2503701 ■

Lancet. 2025;406(10500):271-282

Tan WK, Ross-Innes CS, Somerset T, Markert G, Markowetz F, O'Donovan M, di Pietro M, Sasieni P, Fitzgerald RC; DELTA consortium

Biomarker risk stratification with capsule sponge in the surveillance of Barrett's oesophagus: Prospective evaluation of UK real-world implementation

Background: Endoscopic surveillance is the clinical standard for Barrett's oesophagus, but its effectiveness is inconsistent. The authors have developed a test comprising a pan-oesophageal cell collection device coupled with biomarkers to stratify patients into three risk groups. The study aimed to prospectively evaluate the prespecified risk stratification tool to establish whether it can identify those at highest risk of dysplasia or cancer to prioritise the timing of endoscopy; and safely be used to follow up the low-risk group, thus sparing patients from unnecessary endoscopies.
Methods: Participants were recruited as part of two multicentre, prospective, pragmatic implementation studies from 13 hospitals in the UK. Patients with non-dysplastic Barrett's oesophagus had a capsule-sponge test which was assessed in an ISO-accredited laboratory. Patients were included if they were aged at least 18 years with a non-dysplastic Barrett's oesophagus diagnosis at their last endoscopy who were undergoing surveillance according to the published UK guidelines. Patients were assigned as low (clinical and capsule-sponge biomarkers negative), moderate (negative for capsule-sponge biomarkers, positive clinical biomarkers—age, sex, and segment length), or high risk (p53 abnormality or glandular atypia regardless of clinical biomarkers, or both). The primary outcome was a diagnosis of high-grade dysplasia or cancer necessitating treatment, according to the risk group assignment.
Findings: 910 patients recruited between August 2020 and December 2024 participated, of whom 138 (15%) were classified as high risk, 283 (31%) moderate risk and 489 (54%) low risk. The positive predictive value for any dysplasia or worse in the high-risk group was 37.7% (95% CI: 29.7–46.4). Patients with both atypia and aberrant p53 had the highest risk of high-grade dysplasia or cancer (relative risk = 135.8 [95% CI: 32.7–564.0] relative to the low-risk group). The prevalence of high-grade dysplasia or cancer in the low-risk group was 0.4% (95% CI: 0.1–1.6); the negative predictive value for any dysplasia or cancer was 97.8% (95% CI: 95.9–98.8). Applying a machine learning algorithm as part of a digital-pathology workflow reduces the proportion needing p53 pathology review to 32% without missing any positive cases.

Interpretation: The risk-panel substantially enriches for dysplasia and capsule-sponge-based surveillance could be used in low-risk Barrett's oesophagus in lieu of endoscopy.

R.C. Fitzgerald, Early Cancer Institute, University of Cambridge, Cambridge, UK, e-mail: rcf29@cam.ac.uk

DOI: 10.1016/s0140-6736(25)01021-9

N Engl J Med. 2025;393(4):336-348

Shitara K, Van Cutsem E, Gümüş M, Lonardi S, de la Fouchardière C, Coutzac C, Dekervel J, Hochhauser D, Shen L, Mansoor W, Liu B, Fornaro L, Ryu MH, Lee J, Faustino C, Metges JP, Tabernero J, Franke F, Janjigian YY, Souza F, Jukofsky L, Zhao Y, Kamio T, Zaanan A, Pietrantonio F; DESTINY-Gastric04 Trial Investigators

Trastuzumab deruxtecan or ramucirumab plus paclitaxel in gastric cancer

Background: On the basis of phase 2 studies, trastuzumab deruxtecan was approved for patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic gastric cancer or gastroesophageal junction adenocarcinoma who had previously received trastuzumab-based therapy. Ramucirumab plus paclitaxel is also a standard second-line treatment option regardless of HER2 status.
Methods: The authors conducted an international, randomized, phase 3 trial comparing second-line trastuzumab deruxtecan at a dose of 6.4 mg per kilogram of body weight with ramucirumab plus paclitaxel in patients with HER2-positive metastatic gastric cancer or gastroesophageal junction adenocarcinoma confirmed on tumor biopsy conducted after the patient had progression while receiving trastuzumab-based therapy. The primary end point was overall survival. Secondary end points included progression-free survival, confirmed objective response (complete or partial response lasting ≥ 4 weeks), disease control, duration of response, and safety.
Results: Among 494 patients who had undergone randomization, overall survival was significantly longer with trastuzumab deruxtecan than with ramucirumab plus paclitaxel (median, 14.7 vs. 11.4 months; hazard ratio for death, 0.70; 95% confidence interval [CI]: 0.55–0.90; p = 0.004). Significant results were also seen with regard to progression-free survival (hazard ratio for disease progression or death, 0.74; 95% CI: 0.59–0.92) and confirmed objective response (in 44.3% of the patients in the trastuzumab deruxtecan group vs. 29.1% of those in the ramucirumab-paclitaxel group). The incidence of drug-related adverse events of any grade was 93.0% with trastuzumab deruxtecan and 91.4% with ramucirumab plus paclitaxel; the incidence of drug-related adverse events of grade 3 or higher was 50.0% and 54.1%, respectively. Adjudicated drug-related interstitial lung disease or pneumonitis occurred in 13.9% of the patients who received trastuzumab deruxtecan (grade 1 or 2 in 33 patients and grade 3 in 1) and in 1.3% of those who received ramucirumab plus paclitaxel (grade 3 in 2 patients and grade 5 in 1).

Conclusions: Trastuzumab deruxtecan led to significantly longer overall survival than ramucirumab plus paclitaxel among patients with HER2-positive metastatic gastric cancer or gastroesophageal junction adenocarcinoma. Adverse events were common in both groups. Events of interstitial lung disease or pneumonitis with trastuzumab deruxtecan, a known risk, were mainly low-grade.

K. Shitara, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, e-mail: kshitara@east.ncc.go.jp

DOI: 10.1056/nejmoa2503119

Lancet Oncol. 2025;26(6):732-744

Zaanan A, Bouché O, de la Fouchardière C, Le Malicot K, Pernot S, Louvet C, Artru P, Le Brun Ly V, Aldabbagh K, Khemissa-Akouz F, Lecomte T, Castanie H, Laly M, Botsen D, Roth G, Samalin E, Muller M, Breysacher G, Manfredi S, Phelip JM, Taieb J

TFOX versus FOLFOX in first-line treatment of patients with advanced HER2-negative gastric or gastro-oesophageal junction adenocarcinoma (PRODIGE 51-FFCD-GASTFOX): An open-label, multicentre, randomised, phase 3 trial

Background: Perioperative FLOT (fluorouracil, oxaliplatin, and docetaxel) triplet chemotherapy is the standard of care for localised and resectable gastric and gastro-oesophageal junction adenocarcinoma. The authors aimed to compare a modified FLOT regimen (also known as TFOX) with FOLFOX as first-line treatment for patients with HER2-negative advanced gastric and gastro-oesophageal junction adenocarcinoma.
Methods: PRODIGE 51-FFCD-GASTFOX is an open-label, multicentre, randomised, phase 3 trial conducted at 96 medical centres in France. Eligible individuals were aged 18 years or older, had histologically confirmed, HER2-negative adenocarcinoma of the stomach or gastro-oesophageal junction that was locally advanced unresectable or metastatic and previously untreated, measurable disease per Response Evaluation Criteria in Solid Tumours, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function. Patients were randomly assigned (1:1), using the minimisation method, to receive FOLFOX (folinic acid 400 mg/m^2, oxaliplatin 85 mg/m^2, and 5-fluorouracil bolus 400 mg/m^2 then 5-fluorouracil 2,400 mg/m^2 as a continuous 46 h infusion every 2 weeks) or TFOX (docetaxel 50 mg/m^2, folinic acid 400 mg/m^2, and oxaliplatin 85 mg/m^2 then 5-fluorouracil 2,400 mg/m^2 as a continuous 46 h infusion every 2 weeks). Randomisation was stratified by centre, ECOG performance status, (neo)adjuvant chemotherapy or chemoradiotherapy, tumour stage, tumour location, and pathological histological subtype. The primary endpoint was progression-free survival (assessed in the intention-to-treat population), defined as time from randomisation to the first radiological or clinical progression (or both), or death due to any cause, whichever occurred first. Secondary endpoints included overall survival (defined as time from randomisation to death due to any cause) and objective response rate (defined as the proportion of patients with a best overall complete or partial response). Hazard ratio and 95% CIs were estimated using an unstratified Cox proportional hazards model.

When the proportional hazards assumption was violated, the restricted mean survival time was used to estimate the treatment effect size.
Findings: Between December 19, 2016, and December 26, 2022, 507 patients were randomly assigned (254 to the TFOX group and 253 to the FOLFOX group [intention-to-treat population]). The median age was 64.2 years (IQR, 56.7–70.8), and 399 (79%) participants were male and 108 (21%) were female. At median follow-up of 42.8 months (25.8–49.9), the median progression-free survival was 7.59 months (95% CI: 7.06–7.95) in the TFOX group versus 5.98 months (5.65–6.97) in the FOLFOX group. The assumption of proportional hazards was violated (p = 0.013); therefore, the 12-month restricted mean progression-free survival was calculated: 7.52 months (7.06–7.97) in the TFOX group versus 6.62 months (6.16–7.09) in the FOLFOX group (p = 0.0072). The median overall survival was 15.08 months (13.70–16.72) in the TFOX group versus 12.65 months (10.94–14.00) in the FOLFOX group (proportional hazards assumption was confirmed; HR = 0.82 [0.68–0.99]; p = 0.048) and the objective response rate was 62.3% (56.0–68.3) versus 53.4% (47.0–59.8; p = 0.045). The most common grade 3 and 4 treatment-emergent adverse events were diarrhoea (37 [15%] in the TFOX group vs. 18 [7%] in the FOLFOX group), peripheral neuropathy (80 [32%] vs. 49 [20%]), neutropenia (67 [27%] vs. 44 [18%]), and fatigue (40 [16%] vs. 20 [8%]). Serious treatment-related adverse events occurred in 66 (27%) participants in the TFOX group and 33 (13%) in the FOLFOX group. There were 2 (< 1%) treatment-related deaths in the TFOX group (1 due to septic shock and 1 due to gastro-intestinal perforation) and 1 (< 1%) in the FOLFOX group (due to septic shock).

Interpretation: The modified FLOT/TFOX regimen significantly improved progression-free survival, overall survival, and objective response rate compared with FOLFOX in previously untreated patients with advanced HER2-negative gastric and gastro-oesophageal junction adenocarcinoma. The modified FLOT/TFOX regimen might represent a new first-line treatment option for patients eligible for this docetaxel triplet chemotherapy.

A. Zaanan, Department of Gastroenterology and Digestive Oncology, European Georges Pompidou Hospital, Assistance Publique Hôpitaux de Paris, University of Paris Cité, Paris, France,
e-mail: aziz.zaanan@aphp.fr

DOI: 10.1016/s1470-2045(25)00130-5 ■

Nutrition and Obesity

N Engl J Med. 2025;393(1):26-36

Aronne LJ, Horn DB, le Roux CW, Ho W, Falcon BL, Gomez Valderas E, Das S, Lee CJ, Glass LC, Senyucel C, Dunn JP; SURMOUNT-5 Trial Investigators

Tirzepatide as compared with semaglutide for the treatment of obesity

Background: Tirzepatide and semaglutide are highly effective medications for obesity management. The efficacy and safety of tirzepatide as compared with semaglutide in adults with obesity but without type 2 diabetes is unknown.
Methods: In this phase 3b, open-label, controlled trial, adult participants with obesity but without type 2 diabetes were randomly assigned in a 1:1 ratio to receive the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or the maximum tolerated dose of semaglutide (1.7 mg or 2.4 mg) subcutaneously once weekly for 72 weeks. The primary end point was the percent change in weight from baseline to week 72. Key secondary end points included weight reductions of at least 10%, 15%, 20%, and 25% and a change in waist circumference from baseline to week 72.
Results: A total of 751 participants underwent randomization. The least-squares mean percent change in weight at week 72 was -20.2% (95% confidence interval [CI]: -21.4 to -19.1) with tirzepatide and -13.7% (95% CI: -14.9 to -12.6) with semaglutide (p < 0.001). The least-squares mean change in waist circumference was -18.4 cm (95% CI: -19.6 to -17.2) with tirzepatide and -13.0 cm (95% CI: -14.3 to -11.7) with semaglutide (p < 0.001). Participants in the tirzepatide group were more likely than those in the semaglutide group to have weight reductions of at least 10%, 15%, 20%, and 25%. The most common adverse events in both treatment groups were gastrointestinal, and most were mild to moderate in severity and occurred primarily during dose escalation.

Conclusions: Among participants with obesity but without diabetes, treatment with tirzepatide was superior to treatment with semaglutide with respect to reduction in body weight and waist circumference at week 72.

L.J. Aronne, Comprehensive Weight Control Center, Division of Endocrinology, Diabetes, and Metabolism, Weill Cornell Medicine, New York, NY, USA,
e-mail: ljaronne@med.cornell.edu

DOI: 10.1056/nejmoa2416394 ■

N Engl J Med. 2025;393(7):635-647

Garvey WT, Blüher M, Osorto Contreras CK, Davies MJ, Winning Lehmann E, Pietiläinen KH, Rubino D, Sbraccia P, Wadden T, Zeuthen N, Wilding JPH; REDEFINE 1 Study Group

Coadministered cagrilintide and semaglutide in adults with overweight or obesity

Background: Semaglutide at a dose of 2.4 mg has established weight-loss and cardiovascular benefits, and cagrilintide at a dose of 2.4 mg has shown promising results in early-phase trials; the efficacy of the combination (known as CagriSema) on weight loss in persons with either overweight and coexisting conditions or obesity is unknown.
Methods: In a phase 3a, 68-week, multicenter, double-blind, placebo-controlled and active-controlled trial, adults without diabetes who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher or a BMI of 27 or higher with at least one obesity-related complication were enrolled. Participants were randomly assigned in a ratio of 21:3:3:7 to receive the combination of semaglutide at a dose of 2.4 mg and cagrilintide at a dose of 2.4 mg, semaglutide alone at a dose of 2.4 mg, cagrilin-

tide alone at a dose of 2.4 mg, or placebo, plus lifestyle interventions for all groups. The coprimary end points were the relative change in body weight and a reduction of 5% or more in body weight from baseline to week 68 with cagrilintide-semaglutide as compared with placebo. Body-weight reductions of 20% or more, 25% or more, and 30% or more were assessed as confirmatory secondary end points. Effect estimates were assessed with the treatment-policy estimand (consistent with the intention-to-treat principle). Safety was assessed.
Results: A total of 3,417 participants underwent randomization, with 2,108 assigned to receive cagrilintide-semaglutide, 302 to receive semaglutide, 302 to receive cagrilintide, and 705 to receive placebo. The estimated mean percent change in body weight from baseline to week 68 was -20.4% with cagrilintide-semaglutide as compared with -3.0% with placebo (estimated difference, -17.3 percentage points; 95% confidence interval: -18.1 to -16.6; p < 0.001). Participants receiving cagrilintide-semaglutide were more likely than those receiving placebo to reach weight-loss targets of 5% or more, 20% or more, 25% or more, and 30% or more (p < 0.001 for all comparisons). Gastrointestinal adverse events (affecting 79.6% in the cagrilintide-semaglutide group and 39.9% in the placebo group), including nausea, vomiting, diarrhea, constipation, or abdominal pain, were mainly transient and mild-to-moderate in severity.

Conclusions: Cagrilintide-semaglutide provided significant and clinically relevant body-weight reductions in adults with overweight or obesity, as compared with placebo.

W.T. Garvey, Department of Nutrition Sciences, University of Alabama at Birmingham, Birmingham, AL, USA, e-mail: garveyt@uab.edu

DOI: 10.1056/nejmoa2502081

N Engl J Med. 2025;393(11):1077-1087

Wharton S, Lingvay I, Bogdanski P, Duque do Vale R, Jacob S, Karlsson T, Shaji C, Rubino D, Garvey WT; OASIS 4 Study Group

Oral semaglutide at a dose of 25 mg in adults with overweight or obesity

Background: Oral semaglutide at a dose of 25 mg may provide an alternative treatment option to injectable semaglutide (2.4 mg) and higher-dose oral semaglutide (50 mg) for persons with overweight or obesity.
Methods: In a 71-week, double-blind, randomized, placebo-controlled trial conducted at 22 sites in four countries, persons without diabetes who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher or a BMI of 27 or higher with at least one obesity-related complication were enrolled. The participants were randomly assigned in a 2:1 ratio to receive oral semaglutide (25 mg) or placebo once daily, plus lifestyle interventions. The coprimary end points at week 64 were the percent change in body weight and a reduction of 5% or more in body weight; confirmatory secondary end points included reductions in body weight of 10% or more, 15% or more, and 20% or more and the change in the Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT) Physical Function score.
Results: A total of 205 participants were randomly assigned to receive oral semaglutide, and 102 to receive placebo. The estimated mean change in body weight from baseline to week 64 was -13.6% in the oral semaglutide group and -2.2% in the placebo group (estimated difference: -11.4 percentage points; 95% confidence interval: -13.9 to -9.0; p < 0.001). Participants in the oral semaglutide group were significantly more likely than those in the placebo group to have body-weight reductions of 5% or more, 10% or more, 15% or more, and 20% or more (p < 0.001 for all comparisons) and to have an improved IWQOL-Lite-CT Physical Function score (p < 0.001). Gastrointestinal adverse events were more common with oral semaglutide than with placebo (74.0% vs. 42.2%).

Conclusions: Oral semaglutide at a dose of 25 mg once daily resulted in a greater mean reduction in body weight than placebo in participants with overweight or obesity.

S. Wharton, Wharton Weight Management Clinic, Burlington, ON, Canada,
e-mail: sean@whartonmedicalclinic.com

DOI: 10.1056/nejmoa2500969

Crohn's Disease

Gastroenterology. 2025;169(1):85-93.e3

Ben-Horin S, Lahat A, Ungar B, Ukashi O, Yablecovitch D, Amitai MM, Haberman Y, Selinger L, Talan-Asher A, Kriger-Sharabi O, Naftali T, Ron Y, Yanai H, Dotan I, Kopylov U, Eliakim R; Israeli IBD Research Nucleus (IIRN)

Capsule endoscopy-guided proactive treat-to-target versus continued standard care in patients with quiescent Crohn's disease: A randomized controlled trial

Background and aims: Optimal treat-to-target strategies for Crohn's disease (CD) are still being sought. The value of video capsule endoscopy (VCE) to guide proactive treat-to-target optimization in CD was examined.
Methods: A randomized controlled trial of patients with small bowel-involved (L1/L3) CD in corticosteroid-free clinical remission (Crohn's Disease Activity Index < 150). Patients ingested a VCE at baseline and those with a Lewis inflammatory score (LS) ≥ 350 were designated "high risk" and randomized to either treat-to-target treatment optimization or continued standard care. Treat-to-target was optimized by means of repeat VCE results every 6 months. Patients with LS < 350 ("low risk") continued standard care. The primary outcome was the rate of disease exacerbation (Crohn's Disease Activity Index increase > 70 points and score > 150 or hospitalization/surgery) in high-risk standard care versus treat-to-target groups at 24 months.
Results: Of 118 patients screened, 60 were enrolled. Treatment intensification in patients in the high-risk group allocated to proactive strategy comprised biologic dose escalation (n = 11 of 20), starting a biologic (n = 8 of 20), or swapping biologics (n = 1 of 20). The primary outcome, clinical flare by 24 months, occurred in 5 of 20 (25%) of high-risk treat-to-target patients

versus 14 of 20 (70%) of the high-risk standard-care group (odds ratio [OR] = 0.14; 95% confidence interval [CI]: 0.04–0.57; p = 0.006). Mucosal healing was significantly more common among the treat-to-target group when determined by a cutoff LS < 350 (OR = 4.5; 95% CI: 1.7–17.4; nominal p value = 0.03), but not by the combined scores of total LS < 450 and highest-segment LS < 350. Among all patients continuing standard care (n = 40), baseline LS was numerically higher among relapsers versus non-relapsers (450, 225–900 vs. 225, 135–600, respectively; p = 0.07). Of 221 VCEs ingested, there was a single (0.4%) temporarily retained spontaneously resolved event.

Conclusions: A video capsule endoscopy-guided treat-to-target strategy for patients with Crohn's disease in remission confers superior clinical outcomes compared with continued standard care.

S. Ben-Horin, Department of Gastroenterology, Sheba Medical Center, Ramat-Gan, Israel, e-mail: shomron.benhorin@gmail.com

DOI: 10.1053/j.gastro.2025.02.031

Lancet Gastroenterol Hepatol. 2025;10(8):715-725

Feagan BG, Sands BE, Siegel CA, Dubinsky MC, Longman RS, Sabino J, Laurent O, Luo A, Lu J, Nguyen DD, Muñoz-Elias EJ, Llewellyn H, Wang Y, Jang I, Bilsborough J, Marchelletta R, Towfic F, Yen M, Anderson JK, DuVall A, Kierkus J, Woynarowski M, Al Kharrat H, Targan SR, McGovern DPB

Safety and efficacy of the anti-TL1A monoclonal antibody tulisokibart for Crohn's disease: A phase 2a induction trial

Background: TNF-like cytokine 1A (TL1A) is a key mediator of inflammation and fibrosis. The efficacy and safety of the anti-TL1A monoclonal antibody tulisokibart as induction treatment was assessed in adults with moderately to severely active Crohn's disease with a history of insufficient response, loss of response, or intolerance to conventional or approved biological therapies.
Methods: In the phase 2a, multicentre, open-label APOLLO-CD study, participants aged 18 years or older with moderately to severely active Crohn's disease, as defined by a Crohn's Disease Activity Index (CDAI) of 220–450 and a Simple Endoscopy Score for Crohn's Disease (SES-CD) of at least 6 for ileocolonic or colonic disease or at least 4 for isolated ileal disease, received intravenous tulisokibart (1,000 mg on day 1 and 500 mg at weeks 2, 6, and 10). This article reports the results of the primary analysis of the induction period. The primary endpoints were safety and the proportion of participants with endoscopic response at week 12, defined as a decrease in SES-CD of at least 50% from baseline. Safety was analysed in all participants treated with tulisokibart, and endoscopic response was analysed in the per-protocol analysis set, which included all participants treated with tulisokibart with baseline CDAI and SES-CD scores, except those with prespecified important protocol deviations.
Findings: Of 101 participants screened for eligibility, 55 eligible participants were enrolled and received tulisokibart. The mean age of participants was 39.1 years (standard deviation [SD] 15.7), 34 (62%) were male, 21 (38%) were female, and 39 (71%) had received previous biological therapy. At week 12, endoscopic response was observed in 13 (26.0% [95% CI: 15.9–39.6]) of 50 participants receiving tulisokibart in the per-protocol analysis set. Adverse events occurred in 43 (78%) of 55 participants, with most adverse events being mild to moderate in severity. The most frequently occurring adverse events (≥ 5% of participants) were COVID-19 (6 [11%] participants), urinary tract infection (5 [9%]), Crohn's disease (5 [9%]), anaemia (4 [7%]), nasopharyngitis (3 [5%]), and fatigue (3 [5%]). Eight (15%) participants had serious adverse events, none of which were considered related to the study drug by the investigator. There were no deaths.

Interpretation: This proof-of-concept study showed that tulisokibart is potentially efficacious in moderately to severely active Crohn's disease and is well tolerated. Randomised controlled trials with longer duration are needed to confirm these results; a double-blind, placebo-controlled, phase 3 trial is currently underway.

B.G. Feagan, Department of Medicine, Division of Gastroenterology, Western University, London, ON, Canada, e-mail: brian.feagan@alimentiv.com

DOI: 10.1016/s2468-1253(25)00071-8

Gastroenterology. 2025;169(2):308-325

Hart A, Panaccione R, Steinwurz F, Danese S, Hisamatsu T, Cao Q, Ritter T, Seidler U, Olurinde M, Vetter ML, Yee J, Yang Z, Wang Y, Johanns J, Han C, Sahoo A, Terry NA, Sands BE, D'Haens G; GRAVITI Study Group

Efficacy and safety of guselkumab subcutaneous induction and maintenance in participants with moderately to severely active Crohn's disease: Results from the phase 3 GRAVITI study

Background and aims: Subcutaneous (SC) induction and maintenance with guselkumab was evaluated in adult participants with moderately to severely active Crohn's disease.
Methods: The phase 3 double-blind, placebo-controlled, treat-through GRAVITI study randomized 347 participants 1:1:1 to guselkumab 400 mg SC every 4 weeks→100 mg SC every 8 weeks (n = 115), guselkumab 400 mg SC every 4 weeks→200 mg SC every 4 weeks (n = 115), or placebo (n = 117). Placebo participants meeting rescue criteria received guselkumab from week 16 onward. Co-primary endpoints were clinical remission at week 12 and endoscopic response at week 12. Additional multiplicity-controlled endpoints were Patient-Reported Outcome-2 remission (week 12), clinical response (week 12), clinical remission (week 24), clinical remission (week 48), and endoscopic response (week 48). Safety was assessed through week 48.
Results: All multiplicity-controlled endpoints were met. At week 12, significantly greater proportions of participants receiving guselkumab 400 mg achieved clinical remission versus placebo (56.1% vs. 21.4%; Δ = 34.9; p < 0.001), and endoscopic response versus placebo

(41.3% vs. 21.4%; Δ = 19.9; p < 0.001). At week 48, significantly greater proportions of participants in both guselkumab groups (100 mg SC every 8 weeks: 60.0%, Δ = 42.8; 200 mg SC every 4 weeks: 66.1%, Δ = 48.9) achieved clinical remission versus placebo (17.1%; p < 0.001 each) and endoscopic response (44.3%, Δ = 37.5; 51.3%, Δ = 44.6; versus placebo 6.8%; p < 0.001 each). Efficacy was observed in both bionaive participants and those with inadequate response or intolerance to biologics. Adverse event rates were not greater in guselkumab groups versus placebo.

Conclusion: Subcutaneous guselkumab for both induction and maintenance was efficacious in treating participants with moderately to severely active Crohn's disease. Safety findings were consistent with those of guselkumab in approved indications, including ulcerative colitis.

G.R. D'Haens, Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, Amsterdam, The Netherlands,
e-mail: g.dhaens@amsterdamumc.nl

DOI: 10.1053/j.gastro.2025.02.033

Lancet. 2025;406(10501):358-375

Panaccione R, Feagan BG, Afzali A, Rubin DT, Reinisch W, Panés J, Danese S, Hisamatsu T, Terry NA, Salese L, Van Rampelbergh R, Sahoo A, Vetter ML, Yee J, Han C, Frustaci ME, Wan KYY, Yang Z, Johanns J, Andrews JM, D'Haens GR, Sands BE; GALAXI 2 and 3 Study Group

Efficacy and safety of intravenous induction and subcutaneous maintenance therapy with guselkumab for patients with Crohn's disease (GALAXI-2 and GALAXI-3): 48-week results from two phase 3, randomised, placebo and active comparator-controlled, double-blind, triple-dummy trials

Background: Despite the availability of biological therapies, suboptimal disease control remains a problem for patients with Crohn's disease. The authors report the results of the GALAXI-2 and GALAXI-3 studies, which aimed to assess the efficacy and safety of intravenous induction followed by subcutaneous maintenance therapy with guselkumab over 48 weeks in adults with moderately to severely active Crohn's disease.
Methods: GALAXI-2 and GALAXI-3 were identically designed, phase 3, randomised, double-blind, triple-dummy, treat-through trials with active and placebo comparators. Adult patients with moderately to severely active Crohn's disease (≥ 3 months duration) were enrolled at 257 sites across 40 countries. Eligible participants were randomly assigned (2:2:2:1) by use of a centralised computer-generated schedule to one of four treatment groups: (1) 200 mg intravenous guselkumab at weeks 0, 4, and 8, then 200 mg subcutaneous guselkumab every 4 weeks from week 12 to week 44 (guselkumab 200 mg group); (2) 200 mg intravenous guselkumab at weeks 0, 4, and 8, then 100 mg subcutaneous guselkumab every 8 weeks from week 16 to week 40 (guselkumab 100 mg group); (3) approximately 6 mg/kg intravenous ustekinumab at week 0, then 90 mg subcutaneous ustekinumab every 8 weeks from week 8 to week 40 (ustekinumab group); or (4) intravenous placebo every 4 weeks at weeks 0, 4, and 8 (placebo group). At week 12, participants without a clinical response to placebo received masked rescue therapy with ustekinumab; all other participants remained on their randomised regimen irrespective of response status at week 12. Participants, investigators, site personnel, and the funder were masked to study treatment until all participants had either completed the follow-up visit at week 48 or terminated study participation before week 48. Coprimary composite endpoints (comparing each guselkumab regimen with placebo) were (1) clinical response at week 12 and clinical remission at week 48 and (2) clinical response at week 12 and endoscopic response at week 48, measured in the primary analysis population of all randomly assigned participants who received at least one dose of the study agent and satisfied the Simple Endoscopic Score for Crohn's Disease (SES-CD) eligibility criteria introduced with the third protocol amendment as per health authority request. Safety was assessed in participants who received at least one dose of study treatment (all-treated analysis population).
Findings: From January 8, 2020, to October 20, 2023, 1,048 participants were randomly assigned, treated, and followed up until week 48, of whom 1,021 participants were included in the primary analysis population: 508 (49.8%) in GALAXI-2 and 513 (50.2%) in GALAXI-3. Both guselkumab regimens were superior to placebo for the endpoint of clinical response at week 12 and clinical remission at week 48 in GALAXI-2, which was observed in 80 of 146 (55%) participants in the guselkumab 200 mg group, 70 of 143 (49%) in the guselkumab 100 mg group, and 9 of 76 (12%) in the placebo group (adjusted treatment difference 43% [95% confidence interval [CI]: 32–54] in the guselkumab 200 mg group and 38% [27–49] in the guselkumab 100 mg group; p < 0.0001), and in GALAXI-3, observed in 72 of 150 (48%) participants in the guselkumab 200 mg group, 67 of 143 (47%) in the guselkumab 100 mg group, and 9 of 72 (13%) in the placebo group (35% [24–46] and 34% [23–45]; p < 0.0001). Similarly, both guselkumab regimens were superior to placebo for the endpoint of clinical response at week 12 and endoscopic response at week 48 in GALAXI-2, observed in 56 (38%) participants in the guselkumab 200 mg group, 56 (39%) in the guselkumab 100 mg group, and 4 (5%) in the placebo group (33% [24–42] in the guselkumab 200 mg group and 34% [24–43] in the guselkumab 100 mg group; p < 0.0001), and in GALAXI-3, observed in 54 (36%) participants in the guselkumab 200 mg group, 48 (34%) in the guselkumab 100 mg group, and 4 (6%) in the placebo group (31% [21–40] and 28% [19–37]; p < 0.0001). Serious adverse events occurred in 21 (7%) participants in the guselkumab 200 mg group (incidence rate 9.7 events per 100 participant-years), 32 (11%) in the guselkumab 100 mg group (14.9 events per 100 participant-years), 35 (12%) in the ustekinumab group (18.4 events per 100 participant-years), and 23 (15%) in the placebo group (23.8 events per 100 participant-years). No deaths were reported.

Interpretation: Intravenous induction followed by subcutaneous maintenance therapy with guselkumab was efficacious in participants with moderately to severely active Crohn's disease, showing superiority to placebo and ustekinumab at week 48 across multiple endpoints. Safety outcomes were favourable and

consistent with the known profile of guselkumab in approved indications.

B.E. Sands, Dr. Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA, e-mail: bruce.sands@mssm.edu

DOI: 10.1016/s0140-6736(25)00681-6 ■

Lancet Gastroenterol Hepatol. 2025;10(9):818-830

Joustra VW, Li Yim AYF, Henneman P, Hageman I, de Waard T, Levin E, Noble AJ, Chapman TP, Mol F, van Zon S, Lee D, McGregor CGC, Hulshoff MS, Satsangi JJ, de Jonge WJ, D'Haens GR

Development and validation of peripheral blood DNA methylation signatures to predict response to biological therapy in adults with Crohn's disease (EPIC-CD): An epigenome-wide association study

Background: Biological therapeutics are widely used in Crohn's disease, with evidence of efficacy from randomised trials and real-world experience. Primary non-response is a common, poorly understood problem. The authors aimed to assess blood methylation as a predictor of response to adalimumab, vedolizumab, or ustekinumab in patients with Crohn's disease.
Methods: This epigenome-wide association study used data from two ongoing biobanks (one from the Amsterdam University Medical Centre, University of Amsterdam, Amsterdam, Netherlands [discovery cohort] and the other from the John Radcliffe Hospital, Oxford, UK [validation cohort]) that recruited patients between October 1, 2009, and June 17, 2022. Adult participants (age ≥ 18 years) with active symptomatic and endoscopic Crohn's disease who were scheduled to start adalimumab, vedolizumab, or ustekinumab treatment were included. Patients with ongoing malignancy or serious concomitant inflammatory diseases were excluded. Treatment response was assessed after a median of 28 weeks of treatment (IQR, 18–36). Response was defined as a combination of endoscopic criteria (50% or more reduction in the Simple Endoscopic Score for Crohn's Disease) with either clinical or biochemical criteria (corticosteroid-free clinical response: ≥ 3 point decrease in Harvey-Bradshaw Index [HBI] score or remission [HBI ≤ 4] and no systemic steroids at follow up; biochemical response: C-reactive protein reduction ≥ 50% or ≤ 5 mg/L and faecal calprotectin reduction ≥ 50% or ≤ 250 µg/g) compared with baseline. Epigenome-wide DNA methylation and transcriptome-wide gene expression analyses were done on whole peripheral blood leukocyte samples that were collected before the start of treatment. To identify baseline DNA methylation markers associated with response or non-response to treatment, the authors performed supervised machine learning through stability selected gradient boosting. In a post-hoc analysis, the authors compared their DNA methylation-based prediction model with clinical decision support tools (CDSTs).
Findings: The authors profiled the peripheral blood DNA methylome of 273 adults with Crohn's disease scheduled to start adalimumab, vedolizumab, or ustekinumab in the discovery (Amsterdam, n = 183; 108 [59.0%] female and 75 [41.0%] male) and the validation cohort (Oxford, n = 90; 46 [51.1%] female and 44 [48.9%] male). In the discovery cohort, the authors defined a panel of DNA methylation biomarkers that were associated with combined endoscopic and clinical or biochemical response to adalimumab (18 markers), vedolizumab (25 markers), or ustekinumab (68 markers), with an area under the curve (AUC) of 0.86 (95% CI: 0.58–0.97) for adalimumab, 0.87 (0.67–0.98) for vedolizumab, and 0.89 (0.76–1.00) for ustekinumab. Validation in the Oxford cohort yielded an AUC of 0.25 (0.10–0.35) for adalimumab, 0.75 (0.65–0.85) for vedolizumab, and 0.75 (0.65–0.87) for ustekinumab. In comparison, implementing the CDSTs in the validation cohort yielded an AUC of 0.56 (0.44–0.68) for vedolizumab and 0.66 (0.54–0.77) for ustekinumab. Previous anti-TNF exposure was associated with a reduction in accuracy of the methylation models for vedolizumab (0.66 [0.55–0.73]) and ustekinumab (0.63 [0.52–0.70]) when analysed in the validation cohort.

Interpretation: The findings provide evidence for the potential use of DNA methylation as a modality for personalised medicine for Crohn's disease by predicting response to vedolizumab and ustekinumab. The models were more accurate in biologically naive patients and outperform available vedolizumab and ustekinumab clinical decision support tools (CDSTs). The authors were unable to predict response to adalimumab. The vedolizumab and ustekinumab prediction models are currently being tested in a multicentre randomised clinical trial.

G.R. D'Haens, Department of Gastroenterology and Hepatology, Amsterdam University Medical Centre, University of Amsterdam, Amsterdam, The Netherlands, e-mail: g.dhaens@amsterdamumc.nl

DOI: 10.1016/s2468-1253(25)00102-5 ■

The **242nd International Symposium** of the Falk Foundation e.V., **"Advances in Hepatology – From Mechanistic Insights to Novel Therapeutic Concepts"**, held in October 2025 in Berlin, brought together medical experts from across the globe.

The meeting focused on molecular and cellular mechanisms of **liver disease**, novel **therapeutic approaches**, innovative **research methods**, and **diagnostic options**. Current advances in hepatology and the need for **non-invasive liver diagnostics** for the general population were among the topics discussed.

In the next issue of the FGR Journal, you will find a report on the symposium's **key topics** as well as an **interview** with one of the scientific organizers, Prof. Frank Tacke (Director of the Department of Hepatology and Gastroenterology at Charité, Berlin).

COLON TO RECTUM

Ulcerative Colitis, Crohn's Colitis

Nature. 2025;642(8067):458-466

Hracs L, Windsor JW, Gorospe J, Cummings M, Coward S, Buie MJ, Quan J, Goddard Q, Caplan L, Markovinović A, Williamson T, Abbey Y, Abdullah M, Abreu MT, Ahuja V, Raja Ali RA, Altuwaijri M, Balderramo D, Banerjee R, Benchimol EI, Bernstein CN, Brunet-Mas E, Burisch J, Chong VH, Dotan I, Dutta U, El Ouali S, Forbes A, Forss A, Gearry R, Dao VH, Hartono JL, Hilmi I, Hodges P, Jones GR, Juliao-Baños F, Kaibullayeva J, Kelly P, Kobayashi T, Kotze PG, Lakatos PL, Lees CW, Limsrivilai J, Lo B, Loftus EV, Jr., Ludvigsson JF, Mak JWY, Miao Y, Ng KK, Okabayashi S, Olén O, Panaccione R, Paudel MS, Quaresma AB, Rubin DT, Simadibrata M, Sun Y, Suzuki H, Toro M, Turner D, Iade B, Wei SC, Yamamoto-Furusho JK, Yang SK, Ng SC, Kaplan GG; Global IBD Visualization of Epidemiology Studies in the 21st Century (GIVES-21) Research Group

Global evolution of inflammatory bowel disease across epidemiologic stages

During the twentieth century, inflammatory bowel disease (IBD) was considered a disease of early industrialized regions in North America, Europe and Oceania. At the turn of the twenty-first century, IBD incidence increased in newly industrialized and emerging regions in Africa, Asia and Latin America, while the prevalence in early industrialized regions continued to grow steadily. Changes in the incidence and prevalence denote the evolution of IBD across four epidemiologic stages: stage 1 (emergence), characterized by low incidence and prevalence; stage 2 (acceleration in incidence), marked by rapidly rising incidence and low prevalence; and stage 3 (compounding prevalence), where the incidence decelerates, plateaus or declines while the prevalence steadily increases. A fourth stage (prevalence equilibrium) has been proposed in which the prevalence slope plateaus due to demographic shifts in an ageing IBD population, but it has not yet been evidenced. To date, these stages have remained theoretical, lacking specific numerical indicators to define transition points. Here, using real-world data from 522 population-based studies encompassing 82 global regions and spanning more than a century (1920–2024), the authors show spatiotemporal transitions across stages 1–3 and model stage 4 progression. Understanding the evolution of IBD across epidemiologic stages enables healthcare systems to better anticipate the future worldwide burden of IBD.

S.C. Ng, Department of Medicine and Therapeutics, Institute of Digestive Disease, State Key Laboratory of Digestive Diseases, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China, e-mail: siewchienng@cuhk.edu.hk

or

G.G. Kaplan, Division of Gastroenterology and Hepatology, Department of Medicine, University of Calgary, Calgary, AB, Canada, e-mail: ggkaplan@ucalgary.ca

DOI: 10.1038/s41586-025-08940-0

EXPERT OPINION

Prof. Dr. Peter Hasselblatt

Epidemiology of inflammatory bowel disease: What does the future hold?

The incidence of inflammatory bowel disease (IBD) increases significantly in parallel with industrialization, a development that can be described in 4 epidemiological phases. Phase 1 is characterized by the sporadic occurrence of IBD, with low incidence and prevalence rates. As industrialization progresses, Western lifestyle and dietary patterns become more common, phase 2 emerges, marked by a significant rise in incidence while prevalence remains low. After reaching a plateau, incidence starts to decline in phase 3, whereas prevalence continues to increase due to the chronic nature of the disease. Phase 4, which remains hypothetical, may eventually be characterized by a decrease in prevalence within an aging IBD population as age-related mortality rises.

In a study published in *Nature*, Hracs et al. evaluated this epidemiological framework using data from 522 population-based studies conducted across 82 countries between 1920 and 2024. Their analysis confirmed marked regional variability in IBD epidemiology. For example, in Scandinavian countries, incidence increased approximately 5-fold between 1970 and 2010, followed by stabilization of incidence and a continuous rise in prevalence. These epidemiological patterns, first observed in Western industrialized countries, now appear to be emerging in developing and newly industrialized countries, where IBD incidence is currently on the rise. Interestingly, some regions reported a markedly elevated incidence. Further studies of these populations may yield important insights into potential genetic risk factors contributing to disease development. Several environmental determinants such as Western diet, level of health care, economic development, and urbanization correlated closely with the occurrence of the respective epidemiological phases 1 to 3. Since phase 4 has not yet been observed in any country, the authors used their dataset to mathematically model transitions from phase 3 to phase 4. Once incidence stabilizes in an aging population, prevalence is expected to decline due to increased mortality. In several countries such as Canada, Scotland and Denmark, IBD prevalence has risen more sharply among older individuals than in younger cohorts. According to the authors' calculations, however, an equilibrium in prevalence is unlikely to occur before 2040. In the long term, we must therefore prepare ourselves for a significant increase in the number of individuals affected by IBD, with prevalence projected to rise to between 1.0% and 1.7%.

These calculations are crucial for anticipating the future global burden of IBD and to better allocate health care resources. At the same time, this worrying increase in IBD prevalence underlines the need to improve early identification of individuals at risk, enhance preventive measures, and to develop more effective and affordable therapies. ■

Aliment Pharmacol Ther. 2025;62(1):59-71

Casanova MJ, Rubín de Célix C, Riestra S, Lucendo AJ, Benítez JM, Navarro-Llavat M, Barrio J, Morales-Alvarado VJ, Rivero M, Busquets D, Leo-Carnerero E, Nantes-Castillejo O, Navarro P, Van Domselaar M, Gutiérrez-Casbas A, Alonso-Abreu I, Barreiro-de Acosta M, Fernández-Salazar L, Iborra M, Martín-Arranz MD, García-Morales N, Guardiola J, Bouhmidi-Assakali A, Esteve M, Muñoz-Villafranca C, Rodríguez-Lago I, Ceballos D, Guerra I, Mañosa M, Marín-Jiménez I, Vera-Mendoza I, Garre A, Chaparro M, Gisbert JP; EXIT long-term study group of GETECCU

Long-term outcomes following withdrawal of anti-tumour necrosis factor treatment in inflammatory bowel disease patients in remission: The exit long-term study of GETECCU

Background: The EXIT trial found no difference in sustained remission at 12 months between inflammatory bowel disease (IBD) patients in remission who withdrew anti-TNF therapy (withdrawal arm [WA]) and those who maintained treatment (maintenance arm [MA]).
Aims: To compare the long-term risk of relapse between these groups and assess the response to anti-TNF resumption.
Methods: This was a follow-up extension of the EXIT trial. The authors analysed long-term outcomes of patients in sustained clinical remission from the start of EXIT.
Results: 125 patients (63 in MA and 62 in WA) were included. Median follow-up was 12 months for MA and 26 months for WA. The cumulative incidence of relapse (95% CI) was 35% (23–48%) in MA and 47% (34–60%) in WA; p = 0.3. In MA, relapses occurred in 8% of patients by 12 months and 47% by 24 months. In WA, relapses occurred in 16% by 12 months and 39% by 24 months. The incidence rate of relapse per patient-year was 22% in MA and 19% in WA. Baseline faecal calprotectin > 250 µg/g was the only variable associated with a higher risk of relapse. Of the 29 patients who relapsed in WA, 26 (90%) resumed anti-TNF therapy; of these, 69% regained clinical remission.

Conclusion: In this extended analysis of patients included in the EXIT trial, withdrawing anti-TNF therapy in patients with IBD in remission was not associated with a higher long-term relapse risk.

M.J. Casanova, Department of Gastroenterology, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Universidad Autónoma de Madrid (UAM), Madrid, Spain, e-mail: mjcasanova.g@gmail.com

DOI: 10.1111/apt.70172 ■

Aliment Pharmacol Ther. 2025;62(4):430-439

Osty M, Altwegg R, Serrero M, Benezech A, Lecomte A, Cadiot G, Vuitton L, Wampach A, Nancey S, Buisson A, le Berre C, Rouillon C, Gilletta C, Goutorbe F, Fumery M, Hammoudi N, Caillo L, Vidon M, Arab N, Sickersen G, Cavicchi M, Vieujean S, Charkaoui M, Richard N, Wils P, Caron B, Amiot A, Nuzzo A, Laharie D, Kirchgesner J, Uzzan M; GETAID-J2J group

Effectiveness and safety of a second JAK inhibitor in ulcerative colitis: The J2J multicentre study

Background: While three Janus kinase inhibitors (JAKi) have demonstrated efficacy in ulcerative colitis (UC), scarce data exist regarding JAKi intraclass switching.
Aim: To evaluate the effectiveness and safety of a second JAK inhibitor in UC.
Methods: This was a multicentre, retrospective, observational cohort including patients with moderate to severe UC who received a second-line of JAKi after failure or intolerance of a first. The primary outcome was steroid-free clinical remission (SFCR) at weeks 8–14, defined as a partial Mayo score of 2 or less with no individual subscore above 1.
Results: Among the 169 patients from 28 participating centres, 105 received upadacitinib, 54 filgotinib and 10 tofacitinib as a second-line of JAKi. Overall, 81/169 achieved SFCR at weeks 8–14: 58/105 with upadacitinib, 18/54 with filgotinib and 5/10 with tofacitinib (p = 0.03). In the multivariate analysis, upadacitinib was independently associated with higher odds of SFCR than filgotinib (OR = 3.15, 95% CI: 1.52–6.79). With a median follow-up duration of 96 days, drug persistence at 6 months was 72.8% with upadacitinib, 57.2% with filgotinib and 66.7% with tofacitinib (p = 0.099). 24.3% of patients (41/169) experienced at least one adverse event leading to treatment withdrawal in 9 patients (5%). No cases of death, cancer, or major acute cardiovascular events were reported.

Conclusion: A second-line of JAKi provided clinical remission in about half of patients after induction, and was well tolerated.

M. Uzzan, Gastroenterology Department, Hôpital Henri Mondor, APHP, Créteil, France, e-mail: mathieu.uzzan@aphp.fr

DOI: 10.1111/apt.70199 ■

EXPERT OPINION

Dr. Lena Sophie Mayer

Use of a second Janus kinase inhibitor in multi-refractory patients with ulcerative colitis

Janus kinase (Jak) inhibitors are small molecules that inhibit pro-inflammatory signaling pathways and the production of multiple cytokines by blocking the Jak-STAT signaling pathway intracellularly. Tofacitinib,

an unselective Jak inhibitor, as well as filgotinib and upadacitinib, both selective Jak1 inhibitors, are approved for the treatment of ulcerative colitis. The various Jak inhibitors differ in their potency and selectivity. Advantages include oral administration, rapid onset of action, and good efficacy, including effectiveness in managing extraintestinal manifestations. Reported adverse events include an increased risk of infection, cardiovascular events, and a potentially elevated risk of cancer.
Despite the growing number of therapeutic options, many patients fail to respond to treatment. In patients who are refractory to multiple therapeutic agents, one possible strategy is to reintroduce a previously used mechanism of action. In particular, anti-TNF antibodies are often re-administered, sometimes very successfully. However, it remains unclear to what extent retreatment with Jak inhibitors is effective and safe.
This multicenter, retrospective observational study included patients who had previously been treated with one of the three approved Jak inhibitors and had active ulcerative colitis (partial Mayo score ≥ 3). The primary endpoint was steroid-free clinical remission after induction (weeks 8–14, defined as partial Mayo score ≤ 2, no subscore > 1). Data from 169 patients with a median follow-up period of 96 days were analyzed. 38% were female, and the mean age at inclusion was 34.6 years. The mean disease duration was 7.4 years. A total of 93.5% of patients had been pretreated with at least two biologics (in addition to a Jak inhibitor). 67.5% had received tofacitinib, 27.2% filgotinib, and 5.3% upadacitinib as their first Jak inhibitor. Discontinuation of first-line Jak inhibitor therapy occurred in 57% of cases due to secondary loss of response and in 39% due to primary nonresponse. The mean treatment duration with the first Jak inhibitor was 162 days. Approximately 62% received upadacitinib, 32% filgotinib, and 6% tofacitinib in the second line.
Steroid-free clinical remission at weeks 8–14 was achieved in 47.9% of patients (55.2% with upadacitinib, 33.3% with filgotinib, and 50% with tofacitinib). The overall clinical response rate was 69.8%, with 61.5% achieving a steroid-free clinical response. During follow-up, 30.8% of patients discontinued Jak inhibitor therapy due to primary or secondary loss of response. Treatment persistence after six months was 72.8% for upadacitinib, 57.2% for filgotinib, and 66.7% for tofacitinib. Although no head-to-head trials are available, other small observational studies and real-world data analyses have also shown the highest effectiveness for upadacitinib compared with filgotinib or tofacitinib. Interestingly, the effectiveness of upadacitinib appeared to be independent of prior Jak inhibitor exposure.
Baseline steroid use and the presence of an ileorectal anastomosis were associated with poorer outcomes. Adverse events occurred in 24.3% of patients, most commonly infections and skin lesions/acne. Serious adverse events occurred in 5% of patients. No deaths, cancer, or cardiovascular events were observed. However, the cohort mainly included young patients and only a small proportion of active smokers, limiting conclusions regarding higher-risk populations. Two cases of ophthalmic herpes zoster were reported, both occurring in unvaccinated patients.
In summary, this study demonstrates that the use of a second Jak inhibitor in the second line appears to be both effective and safe, at least in individuals without pre-existing risk factors. These results are directly translatable to clinical practice: in particular, treatment with upadacitinib in patients who have previously received multiple advanced therapies, including Jak inhibitors, is promising. However, larger cohorts are needed to further evaluate the efficacy and safety of different Jak inhibitor sequencing strategies, especially outcomes after upadacitinib used as first-line therapy would be of interest. To assess the durability of response/remission and long-term safety, a substantially longer follow-up period and a prospective study design would be desirable. ■

Clin Gastroenterol Hepatol. 2025;23(8):1387-1397

Danese S, Rothenberg ME, Lim JJ, Ding HT, McBride JM, Chen Y, Dash A, Mar JS, Keir M, Peyrin-Biroulet L, Panes J, Colombel JF, Feagan B, Valentine JF, Schreiber S

A randomized phase 2 study of efmarodocokin alfa, an interleukin-22 agonist, versus vedolizumab in patients with ulcerative colitis

Background and aims: Efmarodocokin alfa is an interleukin (IL)-22 agonist, with favorable pharmacokinetic properties and an acceptable safety profile. This study further explored the therapeutic potential of efmarodocokin alfa compared with vedolizumab in patients with ulcerative colitis (UC).
Methods: This randomized phase 2 trial evaluated the efficacy, safety, pharmacokinetics, and pharmacodynamics of 3 doses of efmarodocokin alfa administered intravenously every 4 weeks (30 µg/kg [n = 43], 60 µg/kg [n = 44], and 90 µg/kg [n = 43]) compared with placebo (n = 22) and with vedolizumab (n = 43) in the treatment of moderate to severe UC. Key clinical outcomes were assessed through the modified Mayo Clinic Score, and endoscopic evaluations by a central reader.
Results: Efmarodocokin alfa was adequately tolerated with an acceptable safety profile. Although efmarodocokin alfa did not show statistically significant improvement in clinical remission, clinical response, endoscopic healing, or endoscopic remission at week 8 compared with placebo, vedolizumab demonstrated some efficacy. Clinical remission was achieved by 12%, 9%, and 12% of patients in the 30, 60, and 90 µg/kg dose arms, respectively, compared with 9% and 26% of patients in the placebo and vedolizumab arms at week 8. Similarly, endoscopic healing at week 8 was achieved by 14%, 14%, and 12% of patients in the 30, 60, and 90 µg/kg dose arms, respectively, compared with 14% and 33% of patients in the placebo and vedolizumab arms. A dose-dependent increase in pharmacodynamic biomarkers was observed (regenerating islet-derived protein 3-alpha and C-reactive protein levels).

Conclusion: Efmarodocokin alfa did not demonstrate efficacy compared with placebo, and this phase 2 study was ended early for futility; however, there was evidence of target engagement (skin adverse events, regenerating islet-derived protein 3-alpha levels).

S. Danese, Department of Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele, Milan, Italy,
e-mail: sdanese@hotmail.com

DOI: 10.1016/j.cgh.2024.11.013 ■

United European Gastroenterol J. 2025;13(5):710-718

Dignass A, Blumenstein I, Schwedhelm C, Strassen K, Kunk L, Marquardt S, Seiffert A, Kulchytska N, Hänsel I, Benson A, Kisser A

Inadequate therapy response on advanced therapy in ulcerative colitis adult patients: A retrospective analysis of German health claims data

Background: The treatment landscape for active ulcerative colitis is rapidly evolving and current real-world evidence on response to advanced therapy is limited. This study aimed to determine indicators of inadequate therapeutic response among patients with ulcerative colitis in Germany initiating advanced therapy.
Methods: This retrospective analysis used German claims data (2015–2022) from adult patients (≥ 18 years). The prevalence and incidence of ulcerative colitis (ICD-10-GM: K51.X) were estimated. Inadequate response to therapy was evaluated in patients initiating advanced therapy based on eight predefined indicators observed for 12 months following dispensation of index treatment.
Results: Mean ulcerative colitis patient age in 2016–2022 ranged from 49.6 to 51.5 years, 47.6–48.3% were female. Administrative prevalence ranged from 0.45% in 2016 to 0.53% in 2022. The number of patients initiating advanced treatment ranged from 157 to 347 across the study years (3.2–4.9% of overall treated study population). On average from 2016–2021, 78.8% had inadequate response in the 12 months following index treatment. Common indicators included prolonged use of corticosteroids (46.2%) and augmentation with conventional therapies (43.9%).

Conclusions: Adult ulcerative colitis patients showed a high prevalence of inadequate response to advanced therapies. These findings reveal a need for improved UC advanced therapy options, providing insight into inadequate response patterns. This may help identify patients who could benefit from a change in therapy to improve long-term outcomes.

C. Schwedhelm, Pfizer Pharma GmbH, Berlin, Germany, e-mail: carolina.schwedhelm@pfizer.com

DOI: 10.1002/ueg2.12755 ■

J Crohns Colitis. 2025;19(6):jjaf080

D’Haens G, Danese S, Panaccione R, Rubin DT, Peyrin-Biroulet L, Matsuoka K, Loftus EV, Jr., Kobayashi T, Elsharkawi W, Miceli R, Ahmed S, Luo Y, Napoli A, Vaile J, Dornic Q, Patel A, Schreiber S

Deucravacitinib in patients with inflammatory bowel disease: 12-week efficacy and safety results from 3 randomized phase 2 studies in Crohn’s disease and ulcerative colitis

Background and aims: Tyrosine kinase 2 is a downstream intracellular mediator of interleukin-23 signaling, which has a key role in the pathogenesis of inflammatory bowel disease. Deucravacitinib is a novel, oral, selective, allosteric tyrosine kinase 2 inhibitor currently approved for the treatment of adults with moderate to severe plaque psoriasis.
Methods: Here the authors describe 3 randomized, double-blind, placebo-controlled phase 2 studies of deucravacitinib in patients with moderately to severely active Crohn’s disease (LATTICE-CD) or ulcerative colitis (LATTICE-UC and IM011-127). Patients were randomized to receive placebo or twice-daily deucravacitinib 3 or 6 mg (LATTICE-CD), 6 mg (LATTICE-UC), or 12 mg (IM011-127) for 12 weeks. Coprimary endpoints for LATTICE-CD were clinical remission and endoscopic response at week 12. The primary endpoint was clinical remission (per modified Mayo score) at week 12 for LATTICE-UC and clinical response (per modified Mayo score) at week 12 for IM011-127.
Results: A total of 239 (LATTICE-CD), 131 (LATTICE-UC), and 38 (IM011-127) patients were randomized. The primary endpoints were not met for all 3 studies, which resulted in early study termination for LATTICE-CD and IM011-127. High efficacy rates were observed in placebo groups throughout the studies. In all studies, the safety profile of deucravacitinib was consistent with the known safety profile observed in patients with psoriasis, and no new safety signals were observed.

Conclusions: Deucravacitinib at multiple doses did not demonstrate significant clinical benefit versus placebo in moderately to severely active Crohn’s disease or ulcerative colitis. Deucravacitinib was safe and well tolerated.

G. D’Haens, Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, Amsterdam, The Netherlands,
e-mail: g.dhaens@amsterdamumc.nl

or

S. Danese, Department of Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele and Vita-Salute San Raffaele University, Milan, Italy,
e-mail: sdanese@hotmail.com

or

S. Schreiber, Department of Internal Medicine I, University Hospital Schleswig-Holstein, Kiel University, Kiel, Germany, e-mail: s.schreiber@ikmb.uni-kiel.de

DOI: 10.1093/ecco-jcc/jjaf080 ■

IBS, Functional and Motility Disorders

Gastroenterology. 2025;168(6):1128-1136.e4

Singh P, Chey WD, Takakura W, Cash BD, Lacy BE, Quigley EMM, Randall CW, Lembo A

A novel, IBS-specific IgG ELISA-based elimination diet in irritable bowel syndrome: A randomized, sham-controlled trial

Background and aims: Personalized dietary therapies for irritable bowel syndrome (IBS) are needed and an immunoglobulin (Ig)G-antibody-based elimination diet presents a potential solution. However, existing studies

have serious methodological limitations. This study aimed to assess the efficacy of an elimination diet by using a novel IBS-specific IgG assay.
Methods: The authors conducted a randomized, double-blind, sham-controlled trial enrolling subjects with IBS from 8 centers. Subjects positive for ≥ 1 food on an 18-food IgG assay and an average daily abdominal pain intensity score between 3.0 and 7.5 on an 11.0-point scale during a 2-week run-in period were randomized to either an experimental antibody-guided diet or sham diet for 8 weeks. The primary outcome was a ≥ 30% decrease in abdominal pain intensity for ≥ 2 of the last 4 weeks of the treatment period.
Results: Among 238 randomized subjects with IBS, 223 were included in the modified intention-to-treat analysis. A significantly greater proportion of subjects in the experimental diet group met the primary outcome than those in the sham diet group (59.6% vs. 42.1%, p = 0.02). Subgroup analysis revealed that a higher proportion of subjects with constipation-predominant IBS and IBS with mixed bowel habits in the experimental diet group met the primary endpoint versus the sham group (67.1% vs. 35.8% and 66% vs. 29.5%, respectively).

Conclusions: Subjects on an IgG-guided elimination diet were more likely to achieve the primary endpoint than those on a sham elimination diet. Subgroup analysis suggests a more robust benefit for subjects with constipation-predominant IBS and IBS with mixed bowel habits. This highlights the potential effectiveness of a personalized elimination diet based on a novel IBS-specific IgG assay. A larger study is warranted to validate these observations.

P. Singh, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Michigan Medicine, Ann Arbor, MI, USA, e-mail: singhpr@med.umich.edu

DOI: 10.1053/j.gastro.2025.01.223 ■

Am J Gastroenterol. 2025;120(7):1605-1614

Balsiger LM, Santos J, Serra J, Piessevaux H, Baert D, Storr M, Basilisco G, Mazzetti A, Moro L, Gerloni M, Longo L, Gentili A, Tack J

A phase 2, multicentric, randomized, double-blind, placebo-controlled, proof of concept study of efficacy and safety of rifamycin SV-MMX 600 mg tablets administered three or two times daily to patients with diarrhea-predominant irritable bowel syndrome

Introduction: Treatment with nonresorbable antibiotics is effective in diarrhea-predominant irritable bowel syndrome (IBS-D). Multimatrix (MMX) formulations ensure targeted drug delivery to the mid-distal small bowel and colon-traditionally considered the origin of IBS symptoms. To assess the efficacy of rifamycin SV-MMX for the treatment of IBS-D.
Methods: Randomized controlled trial in patients with IBS-D (Rome IV). Patients received rifamycin SV-MMX 600 mg (b.i.d = 1200 mg/day or t.i.d = 1800 mg/day) or placebo for 2 weeks. Primary end point was responder rate in the first treatment week on the full analysis set (FAS). Response was defined as decrease in average abdominal pain ≥ 30% and ≥ 50% reduction of days with stool type 6 or 7 based on daily reporting.
Results: A total of 279 patients were randomized (= intention-to-treat [ITT]), and 264 of were included in the FAS. More patients with rifamycin SV-MMX b.i.d (22/88, 25.00%) met the primary end point than t.i.d (10/81, 12.35%) or placebo (9/95, 9.47%) in both FAS and ITT. Adjusted odds ratio (AOR) for b.i.d. versus placebo was 3.26 (95% confidence interval [CI]: 1.39–7.67; p = 0.007) and for t.i.d. versus b.i.d. 0.40 (95% CI: 0.17–0.92; p = 0.031). After treatment, the percentage of monthly global responders was higher in the b.i.d. group versus placebo in the first month (64.2% vs. 46.6%, AOR = 2.14; 95% CI: 1.15–4.00; p = 0.0173) and first 2 months.

Discussion: Rifamycin SV-MMX 600 mg b.i.d. was more effective than placebo and t.i.d. dosing in the first week of treatment. Two months after treatment, rifamycin SV-MMX 600 mg b.i.d. provided more global symptom relief than placebo.

J. Tack, Translational Research Center for Gastrointestinal Disorders, University of Leuven, Leuven, Belgium, e-mail: jan.tack@kuleuven.be

DOI: 10.14309/ajg.0000000000003236 ■

Lancet Gastroenterol Hepatol. 2025;10(9):794-805

Seiler CL, Rueda GH, Miranda PM, Nardelli A, Borojevic R, Hann A, Rahmani S, De Souza R, Caminero A, Curella V, Neerukonda M, Vanner S, Schuppan D, Moayyedi P, Collins SM, Verdu EF, Pinto-Sanchez MI, Bercik P

Effect of gluten and wheat on symptoms and behaviours in adults with irritable bowel syndrome: A single-centre, randomised, double-blind, sham-controlled crossover trial

Background: Many patients with irritable bowel syndrome (IBS) believe gluten or wheat triggers their symptoms. The study compared symptomatic responses to wheat and gluten with gluten-free sham challenge in patients with IBS who previously perceived benefit from a gluten-free diet.
Methods: The authors conducted this randomised, double-blind, sham-controlled crossover study at McMaster University Medical Centre, Ontario, Canada. Eligible participants were adults aged 18 years or older who met Rome IV criteria for IBS and had previously self-reported improvement on a gluten-free diet, which was implemented for at least 3 weeks before enrolment. Eligible participants were randomly assigned (1:1:1:1:1:1) to receive one of six sequences of wheat, gluten, and sham (containing gluten and wheat free flour) in three periods of 7 days, separated by 14-day washout periods. Randomisation was done using the randomizeBE package in R and the cereal bars were designed to have the same appearance, taste, and smell to maintain blinding. The primary outcome was worsening of IBS symptoms of at least 50 points on the IBS Symptom Severity Score (IBS-SSS) after dietary challenges. Outcome and safety analyses were done in all patients who completed all three challenges.
Findings: Between November 15, 2018, and June 19, 2023, 101 people were assessed for eligibility. 72 people

were excluded due to ineligibility (n = 15), refusing screening (n = 42), and refusing participation (n = 15). 29 participants were enrolled and randomly assigned to wheat-gluten-sham (n = 5), wheat-sham-gluten (n = 5), gluten-wheat-sham (n = 5), gluten-sham-wheat (n = 5), sham-wheat-gluten (n = 5), and sham-gluten-wheat (n = 4). One participant in the wheat-sham-gluten group completed the first challenge but withdrew without providing a reason. In the 28 patients completing the study, there were no statistically significant differences in the proportion of participants with a worsening of IBS-SSS of at least 50 points after wheat (11 [39%] of 28 participants, risk difference vs. sham 0.11; 95% CI: -0.16 to 0.35) or gluten (10 participants [36%], 0.07; -0.19 to 0.32) versus sham (8 participants [29%]). Adverse events were reported in 26 (93%) of 28 patients after wheat, 26 patients (93%) after gluten, and 26 patients (93%) after sham. Study emergent adverse events were similar between challenges (5 [18%] of 28 participants after wheat, 5 [18%] after gluten, and 7 [25%] after sham). No patients reported severe adverse events.

Interpretation: IBS patients with self-perceived gluten sensitivity reacted similarly to gluten, wheat, and sham challenges. These findings suggest that expectations played a major role in symptom generation, and that only some of these patients could benefit from gluten or wheat restriction. Identifying this subset of patients while destigmatising wheat and gluten in the remaining ones should be considered for effective management of patients with IBS.

P. Bercik, Department of Medicine, Farncombe Family Digestive Research Institute, McMaster University, Hamilton, ON, Canada, e-mail: bercikp@mcmaster.ca

DOI: 10.1016/s2468-1253(25)00090-1

Colorectal Cancer

JAMA. 2025;334(2):136-148

Feng Q, Yuan W, Li T, Tang B, Jia B, Zhou Y, Zhang W, Zhao R, Zhang C, Cheng L, Zhang X, Wei Y, Liang F, He G, Xu J; REAL Study Group

Robotic versus laparoscopic surgery for middle and low rectal cancer: The REAL randomized clinical trial

Importance: Robotic surgery for rectal cancer is widely used, but data on long-term oncological outcomes are still lacking.
Objective: To compare the 3-year locoregional recurrence rates of middle and low rectal cancer in patients who underwent robotic surgery versus conventional laparoscopic surgery.
Design, setting, and participants: In this multicenter, superiority, randomized clinical trial, patients with middle or low rectal adenocarcinoma (cT1–T3, N0–N1, or ycT1–T3 Nx) and no distant metastasis were enrolled at 11 centers across 8 provinces in China from July 2016 to December 2020. Among the 1,742 consecutive patients assessed for eligibility, 1,240 were eligible and randomized. Follow-up continued until December 31, 2023.
Interventions: Patients were randomized 1:1 to undergo robotic or conventional laparoscopic rectal cancer resection.
Main outcomes and measures: The primary outcome was the 3-year locoregional recurrence rate. The primary analysis was performed as randomized, but excluded patients deemed ineligible after randomization. The secondary outcomes included disease-free survival; overall survival; and urinary, sexual, and defecation function.
Results: Of the 1,240 patients enrolled, 1,171 were included in the primary analysis (586 in the robotic surgery group; mean age, 59.1 [standard deviation {SD} 11.0] years; and 356 were men [60.8%] vs. 585 in the laparoscopic surgery group; mean age, 60.7 [SD 9.8] years; and 354 were men [60.5%]). The median follow-up time was 43.0 months (interquartile range, 36.7–60.0 months). The 3-year locoregional recurrence rate was 1.6% (95% confidence interval [CI]: 0.6–2.6%) in the robotic group versus 4.0% (95% CI: 2.4–5.6%) in the laparoscopic group (hazard ratio [HR] = 0.45 [95% CI: 0.22–0.92], log-rank p = 0.03; adjusted HR = 0.39 [95% CI: 0.19–0.80]). The 3-year disease-free survival rate was higher in the robotic group (87.2%) versus the laparoscopic group (83.4%) (HR = 0.74 [95% CI: 0.56–0.98], log-rank p = 0.04; adjusted HR = 0.67 [95% CI: 0.50–0.89]). No significant between-group difference was observed in 3-year overall survival (94.7% in the robotic group vs. 93.0% in the laparoscopic group). Patients in the robotic group also had better urinary function, male and female sexual function, and defecation function at 3 and 6 months after surgery and better urinary function and male sexual function at 12 months after surgery.

Conclusions and relevance: Compared with conventional laparoscopic surgery, robotic surgery significantly improved long-term oncological outcomes in patients with middle or low rectal cancer. With additional real-world clinical data and modern, improved training programs for surgeons, robotic surgery could be the preferred choice for patients with middle or low rectal cancer.

G. He and J. Xu, Department of Colorectal Surgery, Zhongshan Hospital Fudan University, and Shanghai Engineering Research Center of Colorectal Cancer Minimally Invasive Technology, Shanghai, China,
e-mail: angelhgd@163.com and
e-mail: xujmin@aliyun.com

DOI: 10.1001/jama.2025.8123

N Engl J Med. 2025;392(24):2425-2437

Elez E, Yoshino T, Shen L, Lonardi S, Van Cutsem E, Eng C, Kim TW, Wasan HS, Desai J, Ciardiello F, Yaeger R, Maughan TS, Morris VK, Wu C, Usari T, Laliberte R, Dychter SS, Zhang X, Tabernero J, Kopetz S; BREAKWATER Trial Investigators

Encorafenib, cetuximab, and mFOLFOX6 in *BRAF*-mutated colorectal cancer

Background: First-line treatment with encorafenib plus cetuximab (EC) with or without chemotherapy (oxaliplatin, leucovorin, and fluorouracil [mFOLFOX6])

for *BRAF* V600E-mutated metastatic colorectal cancer, an aggressive subtype with a poor prognosis, was compared with standard care (chemotherapy with or without bevacizumab) in an open-label, phase 3 trial, which showed significance regarding one of the two primary end points, objective response according to blinded independent central review (odds ratio for EC+mFOLFOX6 vs. standard care, 2.44; one-sided $p < 0.001$). This result led to accelerated Food and Drug Administration approval of this investigational combination therapy for *BRAF* V600E-mutated metastatic colorectal cancer, including as first-line therapy. Data on progression-free survival (the second primary end point) and an updated interim analysis of overall survival are now available.
Methods: The authors randomly assigned patients with untreated *BRAF* V600E-mutated metastatic colorectal cancer to receive EC, EC+mFOLFOX6, or standard care. The two primary end points were objective response (reported previously) and progression-free survival according to blinded independent central review in the EC+mFOLFOX6 group and the standard-care group. The key secondary end point was overall survival.
Results: Significantly longer progression-free survival was seen with EC+mFOLFOX6 than with standard care (median, 12.8 vs. 7.1 months; hazard ratio for progression or death, 0.53; 95% confidence interval [CI]: 0.41–0.68; $p < 0.001$). In an interim analysis, overall survival was significantly longer with EC+mFOLFOX6 than with standard care (median, 30.3 vs. 15.1 months; hazard ratio for death, 0.49; 95% CI: 0.38–0.63; $p < 0.001$). The incidence of serious adverse events during treatment was 46.1% with EC+mFOLFOX6 and 38.9% with standard care. Safety profiles were consistent with those known for each agent.

Conclusions: This trial showed significantly longer progression-free survival and overall survival with first-line treatment with EC+mFOLFOX6 than with standard care among patients with *BRAF* V600E-mutated metastatic colorectal cancer.

S. Kopetz, University of Texas MD Anderson Cancer Center, Houston, TX, USA,
e-mail: skopetz@mdanderson.org

DOI: 10.1056/nejmoa2501912

N Engl J Med. 2025;393(1):13-25

Courneya KS, Vardy JL, O'Callaghan CJ, Gill S, Friedenreich CM, Wong RKS, Dhillon HM, Coyle V, Chua NS, Jonker DJ, Beale PJ, Haider K, Tang PA, Bonaventura T, Wong R, Lim HJ, Burge ME, Hubay S, Sanatani M, Campbell KL, Arthuso FZ, Turner J, Meyer RM, Brundage M, O'Brien P, Tu D, Booth CM; CHALLENGE Investigators

Structured exercise after adjuvant chemotherapy for colon cancer

Background: Preclinical and observational studies suggest that exercise may improve cancer outcomes. However, definitive level 1 evidence is lacking.
Methods: The phase 3, randomized trial conducted at 55 centers assigned patients with resected colon cancer who had completed adjuvant chemotherapy to participate in a structured exercise program (exercise group) or to receive health-education materials alone (health-education group) over a 3-year period. The primary end point was disease-free survival.
Results: From 2009 through 2024, a total of 889 patients underwent randomization to the exercise group (445 patients) or the health-education group (444 patients). At a median follow-up of 7.9 years, disease-free survival was significantly longer in the exercise group than in the health-education group (hazard ratio [HR] for disease recurrence, new primary cancer, or death, 0.72; 95% confidence interval [CI]: 0.55–0.94; $p = 0.02$). The 5-year disease-free survival was 80.3% in the exercise group and 73.9% in the health-education group (difference, 6.4 percentage points; 95% CI: 0.6–12.2). Results support longer overall survival in the exercise group than in the health-education group (HR for death, 0.63; 95% CI: 0.43–0.94). The 8-year overall survival was 90.3% in the exercise group and 83.2% in the health-education group (difference, 7.1 percentage points; 95% CI: 1.8–12.3). Musculoskeletal adverse events occurred more often in the exercise group than in the health-education group (in 18.5% vs. 11.5% of patients).

Conclusions: A 3-year structured exercise program initiated soon after adjuvant chemotherapy for colon cancer resulted in significantly longer disease-free survival and findings consistent with longer overall survival.

K.S. Courneya, Faculty of Kinesiology, Sport, and Recreation, College of Health Sciences, University of Alberta, Edmonton, AB, Canada,
e-mail: kerry.courneya@ualberta.ca

or

C.M. Booth, Department of Oncology, Queen's University, Kingston, ON, Canada,
e-mail: booth@queensu.ca

DOI: 10.1056/nejmoa2502760

N Engl J Med. 2025;392(23):2297-2308

Cercek A, Foote MB, Rousseau B, Smith JJ, Shia J, Sinopoli J, Weiss J, Lumish M, Temple L, Patel M, Wilde C, Saltz LB, Argiles G, Stadler Z, Artz O, Maron S, Ku G, Gu P, Janjigian YY, Molena D, Iyer G, Coleman J, Abida W, Cohen S, Soares K, Schattner M, Strong VE, Yaeger R, Paty P, Shcherba M, Sugarman R, Romesser PB, Zervoudakis A, Desai A, Segal NH, El Dika I, Widmar M, Wei I, Pappou E, Fumo G, Aparo S, Gonen M, Gollub M, Jayaprakasam VS, Kim TH, Garcia Aguilar J, Weiser M, Diaz LA, Jr.

Nonoperative management of mismatch repair-deficient tumors

Background: Among patients with mismatch repair-deficient (dMMR), locally advanced rectal cancer, neoadjuvant checkpoint blockade eliminated the need for surgery in a high proportion of patients. Whether this approach can be extended to all early-stage dMMR solid tumors, regardless of tumor site, is unknown.
Methods: In a phase 2 study, patients with stage I, II, or III dMMR solid tumors that were amenable to curative-intent surgery were treated with neoadjuvant dostarlimab, a programmed cell death 1 (PD-1) blocking agent,

for 6 months. The response to treatment was assessed in two cohorts: patients in cohort 1 had dMMR, locally advanced rectal cancer, and patients in cohort 2 had dMMR nonrectal solid tumors. Patients with a clinical complete response could elect to proceed with nonoperative management; those with residual disease were to undergo resection. In this analysis, the primary end point, assessed in cohort 1, was a sustained clinical complete response at 12 months. Recurrence-free survival and safety were evaluated.
Results: A total of 117 patients were included in the analysis. In cohort 1, all 49 patients who completed treatment had a clinical complete response and elected to proceed with nonoperative management. A total of 37 patients had a sustained clinical complete response at 12 months, a finding that met the criterion for efficacy. In cohort 2, a total of 35 of 54 patients who completed treatment had a clinical complete response, and 33 elected to proceed with nonoperative management. Among the 103 patients who completed treatment across both cohorts, 84 had a clinical complete response, and 82 did not undergo surgery. Among the 117 total patients, recurrence-free survival at 2 years was 92% (95% confidence interval: 86–99); the median follow-up for recurrence was 20.0 months (range, 0–60.8). The majority of patients (95%) had reversible, grade 1 or 2 adverse events (60%) or had no adverse events (35%). The option for curative resection was not compromised during or after treatment in any of the patients.

Conclusions: Among patients with early-stage dMMR solid tumors that were amenable to curative-intent surgery, neoadjuvant PD-1 blockade led to organ preservation in a high proportion of patients.

A. Cercek and L.A. Diaz, Jr., Memorial Sloan Kettering Cancer Center, New York, USA,
e-mail: cerceka@mskcc.org and
e-mail: diaz15@mskcc.org

DOI: 10.1056/nejmoa2404512

Colorectal Cancer Screening/ Endoscopy

Gut. 2025;74(7):1104-1112

Drews J, Zachäus M, Kleemann T, Schirra J, Cahyadi O, Möschler O, Schulze C, Steinbrück I, Wedi E, Pech O, Weismüller TJ, Küllmer A, Abdelhafez M, Wedemeyer J, Beyna T, Riedel J, Halm UP, Güther C, Vasapolli R, Torres Reyes C, Quast DR, Bachmann O, Dedonaki E, Ulrich J, Marchuk I, Frahm C, Steffen T, Wohlmuth P, Bunde T, Geßler N, von Hahn T

Multicentre randomised controlled trial of a self-assembling haemostatic gel to prevent delayed bleeding following endoscopic mucosal resection (PURPLE trial)

Background: Prophylactic application of a haemostatic gel to the resection field may be an easy way to prevent delayed bleeding, a frequent complication after endoscopic mucosal resection (EMR).
Objective: The study aimed to evaluate if the prophylactic application of a haemostatic gel to the resection field directly after EMR can reduce the rate of clinically significant delayed bleeding events.
Design: The authors conducted a prospective randomised trial of patients undergoing hot-snare EMR of flat lesions in the duodenum (≥ 10 mm) and colorectum (≥ 20 mm) at 15 German centres. Prophylactic clip closure was not allowed, but selective clipping or coagulation could be used prior to randomisation to treat intraprocedural bleeding or for prophylactic closure of visible vessels. Patients were randomised to haemostatic gel application or no prophylaxis. The primary endpoint was delayed bleeding within 30 days.
Results: The trial was stopped early due to futility after an interim analysis. The primary endpoint was analysed in 232 patients (208 colorectal, 26 duodenal). Both groups were comparable in age, sex, comorbidities and lesion characteristics. Preventive measures, such as selective clipping or coagulation, were applied prior to randomisation in 51.9% of cases, with no difference between groups. Delayed bleeding occurred in 14 cases (11.7%; 95% CI: 7.1–18.6%) after haemostatic gel and in 7 cases (6.3%; 95% CI: 3.1–12.3%) in the control group ($p = 0.227$), with no difference between colorectal and duodenal subgroups.

Conclusion: The application of a haemostatic gel following EMR of large flat lesions in the duodenum and colorectum does not reduce the rate of delayed bleeding.

T. von Hahn, Gastroenterology, Hepatology and Interventional Endoscopy, Asklepios Klinik Barmbek, Hamburg, Germany, e-mail: t.hahn@asklepios.com

DOI: 10.1136/gutjnl-2024-334229

JAMA. 2025;334(1):56-63

Shaukat A, Burke CA, Chan AT, Grady WM, Gupta S, Katona BW, Ladabaum U, Liang PS, Liu JJ, Putcha G, Robertson DJ, Schoen RE, Meng Z, Piscitello A, Sun CK, Xu C, Lin CJ, Lee LC, Baldo L, Levin TR; PREEMPT CRC Investigators

Clinical validation of a circulating tumor DNA-based blood test to screen for colorectal cancer

Importance: Colorectal cancer screening is widely recommended but underused. Blood-based screening offers the potential for higher adherence compared with endoscopy or stool-based testing but must first be clinically validated in a screening population.
Objective: To evaluate the clinical performance of an investigational blood-based circulating tumor DNA test for colorectal cancer detection in an average-risk population using colonoscopy with histopathology as the reference method.
Design, setting, and participants: Prospective, multicenter, cross-sectional observational study enrolling participants between May 2020 and April 2022 who were asymptomatic adults aged 45 to 85 years, at average risk of colorectal cancer, and willing to undergo a standard-of-care screening colonoscopy. Participants, staff, and pathologists were blinded to blood test

results, and laboratory testing was performed blinded to colonoscopy findings. The study was conducted at 201 centers across 49 US states and the United Arab Emirates. Site-based and mobile phlebotomy were used for blood collection.
Exposures: Participants were required to complete a screening colonoscopy after blood collection.
Main outcomes and measures: The primary end points were sensitivity for colorectal cancer, specificity for advanced colorectal neoplasia (colorectal cancer or advanced precancerous lesions), negative predictive value for advanced colorectal neoplasia, and positive predictive value for advanced colorectal neoplasia. The secondary end point was sensitivity for advanced precancerous lesions.
Results: The median age of participants in the evaluable cohort (n = 27,010) was 57.0 years, and 55.8% were women. Sensitivity for colorectal cancer was 79.2% (57/72; 95% confidence interval [CI]: 68.4–86.9%) and specificity for advanced colorectal neoplasia was 91.5% (22,306/24,371; 95% CI: 91.2–91.9%). The negative predictive value for advanced colorectal neoplasia was 90.8% (22,306/24,567; 95% CI: 90.7–90.9%) and the positive predictive value for advanced colorectal neoplasia was 15.5% (378/2,443; 95% CI: 14.2–16.8%). All primary end points met prespecified acceptance criteria. The sensitivity for advanced precancerous lesions was 12.5% (321/2,567; 95% CI: 11.3–13.8%), which did not meet the prespecified acceptance criterion.

Conclusions and relevance: In an average-risk colorectal cancer screening population, a blood-based test demonstrated acceptable accuracy for colorectal cancer detection, but detection of advanced precancerous lesions remains a challenge, and ongoing efforts are needed to improve test sensitivity.

T.R. Levin, Kaiser Permanente Division of Research, Pleasanton, CA, USA, e-mail: theodore.levin@kp.org

DOI: 10.1001/jama.2025.7515

Gastroenterology. 2025;169(2):337-345.e2

Toyoshima N, Sakamoto T, Shinmura K, Hotta K, Misawa M, Tamai N, Uraoka T, Matsuda T, Shibata T, Mizuguchi Y, Takamaru H, Nakamura K, Kakugawa Y, Shiroyama M, Kawagoe R, Tsuchiya K, Ikematsu H, Inaba A, Minakata N, Imai K, Takada K, Ito S, Wakamura K, Kudo SE, Sumiyama K, Ito M, Tomaru S, Fujimoto A, Saito Y

The efficacy of texture and color enhancement imaging observation in the detection of colorectal lesions: A multicenter, randomized controlled trial (deTXIon study)

Background and aims: Colonoscopy is the gold standard for detecting and resecting adenomas and early-stage cancers to reduce colorectal cancer (CRC) incidence and mortality rates. This study aimed to confirm the superiority of texture and color enhancement imaging (TXI) over white light imaging (WLI) in detecting colorectal lesions.
Methods: This randomized controlled trial was conducted at 8 Japanese institutions between March 2023 and October 2023. Participants aged 40 to 80 years old scheduled for CRC screening and nonscreening purposes, such as postpolypectomy surveillance, positive fecal occult blood test results, and abdominal symptoms, were included. The authors used only the latest model colonoscopes and performed observations in each arm of the TXI mode 1 and WLI. The primary end point was the mean number of adenomas detected per procedure. Secondary end points included the adenoma detection rate, polyp detection rate, flat polyp detection rate, and adverse events.
Results: A total of 956 patients were enrolled and randomized. After patients who did not meet the eligibility criteria were excluded, 451 and 445 patients were included in the TXI and WLI arms, respectively. The mean number of adenomas detected per procedure was 1.4 and 1.5 and the adenoma detection rate was 57.2% and 56.0% in TXI and WLI, respectively, and there were no statistically significant differences between the two arms. The polyp detection rate and flat polyp detection rate were significantly higher in TXI than in WLI, which were 82.5% versus 74.4% (p = 0.003), and 76.5% versus 70.3% (p = 0.036), respectively.

Conclusions: This study did not demonstrate the superiority of TXI over WLI in detecting neoplastic lesions. However, TXI may be effective in detecting flat polyps.

Y. Saito, Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan, e-mail: ytsaito@ncc.go.jp

DOI: 10.1053/j.gastro.2025.03.007

Gut. 2025;74(9):1430-1436

Digby J, Nobes J, Strachan JA, McCann R, Hall C, Fraser CG, Mowat C

Combining faecal haemoglobin, iron deficiency anaemia status, and age can improve colorectal cancer risk prediction in patients attending primary care with bowel symptoms: A retrospective observational study

Background: In primary care, National Institute for Health and Care Excellence suspected cancer guidelines recommend measuring faecal haemoglobin (f-Hb) if colorectal cancer (CRC) is suspected, with a referral threshold of ≥ 10 µg Hb/g faeces defining a 3% risk, but most have a normal colonoscopy.
Objective: Examine whether combining f-Hb, patient age and iron-deficient anaemia (IDA) status improves risk prediction.
Design: Retrospective single-centre observational study of symptomatic patients who submitted contemporaneous f-Hb and full blood count (FBC) samples between December 2015 and December 2019. f-Hb was estimated using HM-JACKarc (Hitachi Chemical Diagnostics Systems). Patients were categorised by presence/absence of IDA. Incident CRC was identified via record linkage to the Scottish Cancer Registry. Kaplan-Meier estimates determined cumulative 1-year CRC risk by patient age, f-Hb result, and presence of IDA.
Results: Of 34,647 valid f-Hb results retrieved, 7,889 (22.8%) had f-Hb ≥ 10 µg Hb/g. Of these, 33,285 samples (96.1%) had associated FBC results of which 3,000 (9.0%)

had IDA. Overall, 571 incident CRC were recorded. The risk of CRC breached 3% in patients with f-Hb > 99 µg Hb/g aged > 40 years and reached 30% (19.4–41.0) with f-Hb > 99 µg Hb/g in age > 55 years plus IDA. 2,029 f-Hb results (25.7%) were in the 10–19 µg Hb/g range of which 27 (1.3%) had CRC. In this subgroup, CRC risk did not exceed 3% in patients < 85 years and no IDA.

Conclusion: Combining f-Hb, patient age and IDA status improves CRC risk prediction, identifies a low-risk group with f-Hb < 20 µg Hb/g and no IDA and could inform revised referral guidance.

C. Mowat, Division of Respiratory Medicine and Gastroenterology, University of Dundee, Dundee, UK, e-mail: cmowat@dundee.ac.uk

DOI: 10.1136/gutjnl-2024-334248

Lancet Gastroenterol Hepatol. 2025;10(10):915-923

Antonelli G, Desideri F, Scarozza P, Andrisani G, Zerboni G, Furnari M, Bevilacqua N, Cossignani M, Di Fonzo M, Cereatti F, Navazzotti G, Antenucci C, Di Matteo FM, Bevivino G, Caruso A, Spadaccini M, Schiavone S, Grossi C, Rizkala T, Comberlato M, Bretthauer M, Sharma P, Von Renteln D, Rex DK, Correale L, Repici A, Mori Y, Iacopini F, Hassan C

Safety of artificial intelligence-assisted optical diagnosis for leaving colorectal polyps in situ during colonoscopy (PRACTICE): A non-inferiority, randomised controlled trial

Background: Guidelines recommend leaving in situ rectosigmoid polyps diagnosed during colonoscopy that are 5 mm or smaller if the endoscopist optically predicts them to be non-neoplastic. However, no randomised controlled trial has been done to examine the efficacy and safety of this strategy.
Methods: This open-label, multicentre, non-inferiority, randomised controlled trial enrolled adults age 18 years or older undergoing colonoscopy for screening, surveillance, or clinical indications across four Italian centres. Eligible patients were randomised 1:1 (with stratification by patient sex, age, and previous adenoma removal) via a central web-based system, to either the leave-in-situ group, in which endoscopists could leave non-neoplastic lesions in place after optical diagnosis, or the resect-all group, in which all detected polyps were systematically removed, regardless of optical diagnosis. Patients and endoscopists were not masked to group allocation but pathologists and investigators assessing outcomes were masked. All procedures in both groups were done with the assistance of a computer-aided detection and diagnosis system. Endoscopists optically diagnosed lesions through a combination of white light, blue light, and computer-aided detection. The primary outcome was the adenoma detection rate (ADR), defined as the proportion of participants with at least one adenoma detected (per-patient analysis), assessed by intention-to-treat, to determine whether the leave-in-situ strategy was non-inferior to the resect-all approach, with an absolute 10% non-inferiority margin.
Findings: Between October 1, 2022, and April 30, 2024, 1,147 patients were recruited and 895 patients (507 [57%] females, 388 [43%] males, mean age 61.1 years [SD 9.8]) were randomly assigned to either the leave-in-situ group (n = 441) or resect-all group (n = 454). 197 adenomas or colorectal cancers were detected in the leave-in-situ group and 211 in the resect-all group; the ADR was 44.7% (95% CI: 40.4–49.5) in the leave-in-situ group and 46.5% (41.8–51.2) in the resect-all group (absolute difference -1.8 percentage points, 95% CI: -8.9 to 4.9; $p_{\text{non-inferiority}}$ = 0.013). No colonoscopy-related complications, including perforation and bleeding, were reported in either group.

Interpretation: The leave-in-situ strategy through optical diagnosis with computer-assisted diagnosis support does not reduce oncological safety of colonoscopy, as measured by ADR. By reducing unnecessary polypectomies, this strategy could be considered as an attractive option in colonoscopy practice.

Y. Mori, Clinical Effectiveness Research Group, University of Oslo, Oslo, Norway, e-mail: yuichi.mori@medisin.uio.no

DOI: 10.1016/S2468-1253(25)00140-2

EXPERT OPINION

PD Dr. Armin Küllmer

Diminutive polyps without suspicion of adenoma in the rectosigmoid: Do not remove!

A common recommendation in national and international guidelines is to leave in situ small polyps (< 5 mm) in the rectosigmoid colon when there is no suspicion of adenoma based on visual assessment. However, this is still not widely implemented in clinical practice. This is largely because the design of the studies underpinning this recommendation required removal of all polyps —including those diagnosed as "non-adenomatous"— for histological confirmation, potentially introducing examiner bias.
The present randomized controlled trial (n = 895 patients) avoids this bias by investigating, for the first time, the effect of the "leave-in-situ" strategy when polyps are not removed. If the strategy were unreliable, the control group would have shown a higher adenoma detection rate. This was not observed, because the polyps removed in the control group were "non-neoplastic." These findings demonstrate that, in clinical practice, consistent application of the strategy can avoid unnecessary polypectomies and their associated economic (e.g., cost of material, diagnostics) and social (unnecessary anxiety for patients) consequences, without compromising the quality of cancer screening.
The second aspect of the study concerns the role of artificial intelligence. The study protocol required use of the CADx system, which assesses dignity ("non-neoplastic" vs. "neoplastic"), in both study arms. Given the high adenoma detection rate (> 40%) in each group and the known limited added benefit of AI in this context, the effect is likely to have been minimal.
Nevertheless, the study makes an important contribution to cancer screening. With or without AI support, diminutive rectosigmoid polyps that do not appear to be suspicious for adenoma should not be removed.

Gastrointestinal Infections, Diverticular Disease, Other Inflammatory Disorders

N Engl J Med. 2025;393(3):255-266

Freedman SB, Williamson-Urquhart S, Plint AC, Dixon A, Beer D, Joubert G, Pechlivanoglou P, Finkelstein Y, Heath A, Zhang JZ, Wallace A, Offringa M, Klassen TP; Pediatric Emergency Research Canada Innovative Clinical Trials Study Group

Multidose ondansetron after emergency visits in children with gastroenteritis

Background: Ondansetron improves outcomes when administered in emergency departments to children with acute gastroenteritis-associated vomiting. It is commonly prescribed at discharge to reduce symptoms, but evidence to support this practice is limited.
Methods: The authors conducted a double-blind, randomized superiority trial involving children 6 months to less than 18 years of age with acute gastroenteritis-associated vomiting in six pediatric emergency departments. Caregivers were provided with 6 doses of oral ondansetron or placebo to administer in response to ongoing vomiting during the first 48 hours after enrollment. The primary outcome was moderate-to-severe gastroenteritis, defined by a score of 9 or higher on the modified Vesikari scale (scores range from 0 to 20, with higher scores indicating greater severity), during the 7 days after enrollment. Secondary outcomes included the presence of vomiting, the duration of vomiting (defined as the time from enrollment to the last vomiting episode), the number of vomiting episodes within 48 hours after enrollment, unscheduled physician visits within 7 days after enrollment, and receipt of intravenous fluids.
Results: A total of 1,030 children underwent randomization. Moderate-to-severe gastroenteritis occurred in 5.1% (23/452 participants for whom data were available) in the ondansetron group and 12.5% (55/441) in the placebo group (unadjusted risk difference, -7.4 percentage points; 95% confidence interval [CI]: -11.2 to -3.7). After adjustment for site, weight, and missing data, ondansetron was associated with a lower risk of moderate-to-severe gastroenteritis than placebo (adjusted odds ratio [aOR] = 0.50; 95% CI: 0.40–0.60). Although the authors did not observe any meaningful difference between the groups in the presence or median duration of vomiting, the total number of vomiting episodes within 48 hours after enrollment was lower with ondansetron than with placebo (aOR = 0.76; 95% CI: 0.67–0.87). The percentage of children who had unscheduled health care visits and the percentage who received intravenous fluids after enrollment did not differ substantially between the groups. The incidence of adverse events also did not differ meaningfully between the groups (OR = 0.99; 95% CI: 0.61–1.61).

Conclusions: Among children with gastroenteritis-associated vomiting, the provision of ondansetron after an emergency department visit led to lower risk of moderate-to-severe gastroenteritis during the subsequent 7 days than the provision of placebo.

S.B. Freedman, Sections of Emergency Medicine and Gastroenterology, Department of Pediatrics, Alberta Children's Hospital, University of Calgary, Calgary, AB, Canada,
e-mail: stephen.freedman@albertahealthservices.ca

DOI: 10.1056/nejmoa2503596

Lower Gastrointestinal Bleeding

Endoscopy. 2025;57(8):839-848

Dajti E, Frazzoni L, Castellet-Farrús S, Guardiola J, Sinagra E, Anderloni A, Ferrara F, Gkolfakis P, Camus Duboc M, Mandarino FV, Sadeghi A, Lorenzo-Zúñiga V, Perez S, Triantafyllou K, Curado MP, Facciorusso A, Collatuzzo G, Hassan C, Radaelli F, Fuccio L; ALIBI Study Group

In-hospital mortality in patients with lower gastrointestinal bleeding: Development and validation of a prediction score

Background: Lower gastrointestinal bleeding (LGIB) is a common condition linked to increased morbidity, healthcare costs, and mortality. Currently, no prospectively validated prognostic model exists to predict mortality in patients with LGIB. The aim was to develop and validate a risk score that could accurately predict in-hospital mortality of patients admitted for LGIB.
Methods: Patient data from a nationwide cohort study in 15 centers in Italy (2019–2020) were used to derive the risk score, the Acute Lower gastrointestinal Bleeding and In-hospital mortality (ALIBI) score; the model was then externally validated in a cohort of consecutive patients hospitalized for LGIB in 12 centers from 6 countries (Italy, Spain, France, Greece, Iran, and Brazil) from 2022 to 2024. The main outcome was in-hospital mortality; the authors also reported rebleeding rates and the in-hospital mortality rate stratified by risk score and timing of colonoscopy.
Results: Among 1,198 patients in the derivation cohort, 105 (8.8%) re-bled and 41 (3.4%) died. Age, Charlson Co-morbidity Index, in-hospital onset, hemodynamic instability, and creatinine level were independent predictors of in-hospital mortality. The model demonstrated excellent discrimination (area under the receiver operating curve [AUROC] 0.81, 95% CI: 0.75–0.87) and calibration. In the validation cohort (n = 752 patients), the model's good discrimination (AUROC 0.79, 95% CI: 0.72–0.86) and calibration were confirmed. Patients were categorized as low (0–4 points; 1% mortality), intermediate (5–9 points; 4.6% mortality), or high risk (10–13 points; 19.1% mortality).

Conclusion: A new validated score effectively predicts in-hospital mortality in patients with LGIB, aiding in their risk stratification and management.

L. Fuccio, Gastroenterology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, e-mail: lorenzo.fuccio3@unibo.it

DOI: 10.1055/a-2541-2312

Microscopic Colitis

J Crohns Colitis. 2025;19(7):jjaf110

Verhaegh BPM, Münch A, Guagnozzi D, Wildt S, Cebula W, Pedersen N, Kiudelis V, Lucendo AJ, Lyutakov I, Tontini GE, Pigò F, Russo E, Hjortswang H, Munck LK; European Microscopic Colitis Group (EMCG)

The long-term disease course of microscopic colitis: A European prospective incident cohort study

Background and aims: The disease course of microscopic colitis is largely unknown and current knowledge is based on retrospective data. The aim of the PRO-MC Collaboration is to prospectively describe the long-term disease course and prognostic factors.
Methods: Incident patients of microscopic colitis were included in a prospective, European, multicenter, web-based registry. Data on patient characteristics, symptoms, treatment, and quality of life were systematically registered at baseline and during fixed follow-up intervals. Four disease course phenotypes were defined.
Results: Of 422 registered incident patients, 220 had a complete 5-year follow-up. After 5 years, 6% had a quiescent disease course, 54% achieved remission after treatment, 33% had a relapsing disease course, and 7% a chronic active disease course. Patients with a relapsing or chronic active disease course had a more impaired quality of life and were more often in need for long-term budesonide treatment. The disease course in the first year after diagnosis was the only predictor of the disease course.

Conclusions: Microscopic colitis is a chronic condition with relapsing or continuous disease course in nearly half of the patients during the first 5 years after diagnosis. The disease course in the first year predicts the long-term disease course.

B.P.M. Verhaegh, Department of Gastroenterology, Laurentius Hospital Roermond, Roermond, The Netherlands, e-mail: bas.verhaegh@lzr.nl

DOI: 10.1093/ecco-jcc/jjaf110

PANCREAS

Pancreatic Tumors

Lancet Gastroenterol Hepatol. 2025;10(7):634-647

Mahajan UM, Oehrle B, Goni E, Strobel O, Kaiser J, Grützmann R, Werner J, Friess H, Gress TM, Seufferlein TW, Uhl W, Will U, Neoptolemos JP, Wittel UA, Vornhülz M, Sirtl S, Beyer G, Regel I, Boeck S, Heinemann V, Frost F, Steveling A, Völzke H, Petersmann A, Nauck M, Weber E, Kamlage B, Lerch MM, Mayerle J; METAPAC trial investigators

Validation of two plasma multimetabolite signatures for patients at risk of or with suspected pancreatic ductal adenocarcinoma (METAPAC): A prospective, multicentre, investigator-masked, enrichment design, phase 4 diagnostic study

Background: Earlier diagnosis of pancreatic ductal adenocarcinoma is key to improving overall survival in patients with this hard-to-treat cancer. The authors independently validated two previously identified plasma-based metabolic signatures for exclusion of pancreatic ductal adenocarcinoma in cohorts with an increased annual risk.
Methods: The METAPAC study was a prospective, multicentre, investigator-masked, enrichment design, phase 4 trial done in 23 centres in Germany. Patients with pancreatic lesions identified by diagnostic imaging that required further diagnostic assessment were recruited and followed up for 24 months. Targeted quantitative plasma metabolite analysis was done on a liquid chromatography-tandem mass spectrometry platform. The improved metabolic (i-Metabolic) signature consisted of 12 analytes plus carbohydrate antigen (CA) 19-9, and the minimalistic metabolic (m-Metabolic) signature consisted of four analytes plus CA 19-9. The primary endpoint of the study was the exclusion of pancreatic ductal adenocarcinoma with an 85% specificity and the highest possible diagnostic accuracy. All statistical analyses were done per protocol.
Findings: Between September 9, 2016, and April 8, 2022, 1,370 patients with CT-identified pancreatic lesions necessitating further diagnostic assessment were screened, of whom 1,129 patients (489 with pancreatic ductal adenocarcinoma, 640 controls) were included in the primary analysis (median age 67 years [IQR, 58–75]; 556 [49%] female, 572 [51%] male). The control group consisted of high-risk individuals with acute pancreatitis (11 [1%] of 1,129 participants), chronic pancreatitis (113 [10%]), intraductal papillary mucinous neoplasms (232 [21%]), cystic lesions other than intraductal papillary mucinous neoplasms (271 [24%]), and metastases of extrapancreatic origin (13 [1%]). The i-Metabolic signature detected pancreatic ductal adenocarcinoma with an area under the curve (AUC) of 0.846 (95% CI: 0.842–0.849), specificity of 90.4% (89.8–91.1), sensitivity of 67.5% (66.9–68.0), and balanced accuracy of 80.5% (80.2–80.8), compared with CA 19-9 alone (AUC 0.799 [0.797–0.802], p < 0.0001; specificity 79.1% [78.7–79.4]; sensitivity 81.8% [81.5–82.0]; balanced accuracy 80.6% [80.4–80.9]). The m-Metabolic signature detected pancreatic ductal adenocarcinoma with an AUC of 0.846 (95% CI: 0.842–0.849; p < 0.0001 vs. CA 19-9 alone), specificity of 93.6% (93.1–94.0), sensitivity of 59.9% (59.3–60.4), and accuracy of 79.0% (78.8–79.2). In a population of 242 individuals with new-onset diabetes (three cases of incident pancreatic ductal adenocarcinoma), the m-Metabolic signature (without CA 19-9) significantly discriminated patients with pancreatic ductal adenocarcinoma from those without (p = 0.038). AUC, specificity, and sensitivity remained constant after random bootstrapping for a prevalence of pancreatic ductal adenocarcinoma between 1% and 20%.

Interpretation: Two plasma-based metabolic signatures showed significant improvement in performance compared with CA 19-9 alone in excluding pancreatic ductal adenocarcinoma in a prospective real-world cohort. These findings could offer a surveillance tool in patients with an annual risk of pancreatic ductal adenocarcinoma of 1% to reduce unnecessary invasive procedures and facilitate earlier detection of resectable disease.

J. Mayerle, Department of Medicine II, LMU University Hospital, LMU Munich, Munich, Germany,
e-mail: julia.mayerle@med.uni-muenchen.de

DOI: 10.1016/S2468-1253(25)00056-1

J Clin Oncol. 2025;43(20):2255-2264

Ducreux M, Desgrippes R, Rinaldi Y, Di Fiore F, Guimbaud R, Evesque L, Bachet JB, Vanelslander P, Lecomte T, Capitain O, Parzy A, Bolliet M, Etienne PL, Forestier J, El Hajbi F, Bignon AL, Lebrun-Ly V, De Sousa Carvalho N, Texier M, Bouche O

PRODIGE 29-UCGI 26 (NEOPAN): A phase 3 randomized trial comparing chemotherapy with FOLFIRINOX or gemcitabine in locally advanced pancreatic carcinoma

Purpose: More than 30% of patients with pancreatic cancer are unresectable because of the local extension with a median overall survival (OS) of < 1 year. Combination of fluorouracil (FU), oxaliplatin, and irinotecan (FOLFIRINOX) is superior to gemcitabine in the treatment of metastatic pancreatic cancer, but standard of care remains gemcitabine in locally advanced pancreatic cancer (LAPC).
Methods: Patients with histologically proven LAPC not suitable for surgery, Eastern Cooperative Oncology Group WHO performance status (PS) ≤ 1 were eligible. Random assignment was stratified by center, tumor localization (pancreas head yes/no), WHO PS (0 vs. 1), and age (≤ 60 years vs. > 60 years). Patients received FOLFIRINOX or gemcitabine for 6 months. The primary end point was progression-free survival (PFS). Main secondary end points were OS, time to treatment failure, quality of life, and safety. 170 patients (142 events) were

needed to detect an increase of 3 months in PFS with 80% power (log-rank test, 5% two-sided α).
Results: 171 patients age 35–84 years were included and followed for a maximum of 5 years. With a median follow-up of 59.6 months (95% CI: 42.3 to not reached), 168 events were observed and the median PFS was 9.7 months (95% CI: 7.0–11.7) with FOLFIRINOX versus 7.7 months (95% CI: 6.2–9.2) with gemcitabine, hazard ratio (HR) = 0.7 (95% CI: 0.5–1.0), p = 0.04. The median OS was 15.7 months (95% CI: 11.9–20.4) in the FOLFIRINOX group versus 15.4 months (95% CI: 11.7–18.6) in the gemcitabine group, HR = 1.02 (95% CI: 0.73–1.43), p = 0.95.

Conclusion: Results confirm that FOLFIRINOX improves PFS significantly compared with gemcitabine and is well tolerated in LAPC. No significant difference in OS was observed between both groups.

M. Ducreux, Gustave Roussy Cancer Center, Tumor Cells Dynamics, INSERM U1279, Université Paris-Saclay, Villejuif, France, e-mail: michel.ducreux@gustaveroussy.fr

DOI: 10.1200/JCO-24-02210

Acute/Chronic Pancreatitis

Gut. 2025;74(9):1467-1475

Huang L, Feng Z, Yang W, Zhu Y, Li J, Huang L, Wang R, Peng L, He M, Tang Y, Chen P, Lan C, Zhou X, Zhou L, Ye C, Zhang L, Jiang J, Ye Y, Wang R, He Y, Liu Y, Gong H, Xiong H, Xia L, Xu H, Zhang B, Tu R, Du C, Cui L, Gao J, Huang Z, Tang C

Parecoxib sequential with imrecoxib for occurrence and remission of severe acute pancreatitis: A multicentre, double-blind, randomised, placebo-controlled trial

Background: There is no effective drug treatment for organ failure (OF) caused by severe acute pancreatitis (SAP).
Objective: The aim of this trial was to evaluate the efficacy of cyclooxygenase-2 inhibitors (COX-2-Is) in the treatment of SAP and its safety.
Design: In this multicentre, double-blind, randomised, placebo-controlled, investigator-initiated trial, 348 patients with acute pancreatitis aged 18–75 years, < 1 week from onset of illness to admission, and Acute Physiology and Chronic Health Evaluation II Score ≥ 7 or modified Marshall Score ≥ 2, were randomly assigned (1:1) to the COX-2-Is group (parecoxib sequential with imrecoxib) or the placebo group. SAP occurrence, duration of OF, local complications, clinical outcomes and serum inflammatory mediators were measured.
Results: Compared with the placebo group, SAP occurrence was reduced by 20.7% (77.6% vs. 61.5%, p = 0.001) and the persistent OF duration in SAP was shortened by 2 days (p < 0.001) after COX-2-Is treatment. For patients enrolled within or after 48 hours from symptom onset, SAP occurrence was reduced by 23.8% (p = 0.001) and 8.5% (p = 0.202), and the persistent OF duration in SAP was shortened by 3 days (p = 0.001) and 2 days (p = 0.010) after COX-2-Is treatment, respectively. The occurrence of local complications in the COX-2-Is group was significantly lower than those in the placebo group, 33.7% versus 49.1%, p = 0.004. The serum levels of inflammatory mediators and 30-day mortality (from 8.6% to 3.4%) were significantly reduced after COX-2-Is treatment, p < 0.05. The incidence of adverse events was similar between the two treatment groups.

Conclusion: Parecoxib sequential with imrecoxib was effective and well tolerated in reducing the occurrence and duration of SAP and local complications through suppression of systemic inflammatory response, leading to decreased morbidity.

C. Tang and Z. Huang, Department of Gastroenterology, West China Hospital of Sichuan University, Chengdu, Sichuan, China, e-mail: shcqcdmed@163.com and e-mail: huang-zhiyin@qq.com

DOI: 10.1136/gutjnl-2024-334038

United European Gastroenterol J. 2025;13(4):631-639

Davidsen L, Knoph CS, Cook ME, Drewes AM, Olesen SS

Increased early post-discharge mortality in patients with acute pancreatitis

Background: Emerging evidence suggests that individuals who recover from acute pancreatitis may face a significant risk of mortality during the early post-discharge period. Despite these concerns, comprehensive population-based studies on this issue are lacking.
Objectives: To study in-hospital and post-discharge mortality in patients with acute pancreatitis and how it has changed over time.
Methods: In a Danish nationwide population-based cohort study, the authors included all adults discharged after an incident episode of acute pancreatitis between 2002 and 2017. For each patient, five individuals from the general population, matched by age and sex, were selected as controls. The authors used Cox regression analysis to assess all-cause mortality at 90 days, 1, 2, and 5 years post-discharge and to examine trends in in-hospital and post-discharge mortality over the study period. Models were adjusted for comorbidities, heavy smoking, alcohol abuse and sociodemographic factors.
Results: Of 28,759 adults with incident acute pancreatitis, 956 (3.3%) died in hospital. The 27,803 patients discharged from the hospital following an incident episode of acute pancreatitis were matched with 139,035 individuals (mean age 58.1 years, 51.1% men). The cumulative post-discharge mortality at 90 days was 5.0% for the acute pancreatitis cohort and 0.55% for controls. The mortality risk was significantly increased in acute pancreatitis patients at 90 days post-discharge (adjusted hazard ratio [aHR] = 7.62; 95% CI: 6.86–8.45); the risk attenuated over time but remained elevated for up to five years (aHR = 1.85; 95% CI: 1.79–1.92). In-hospital mortality decreased over the study period (aHR = 0.65; 95% CI: 0.53–0.81) from 2002–2005 to 2014–2017, while post-discharge mortality risk remained stable (aHR = 0.85; 95% CI: 0.72–1.01). Gastrointestinal and cardiovascular diseases accounted for 59.4% of 90-day post-discharge deaths.

Conclusions: In-hospital mortality for acute pancreatitis has improved in recent years. However, the risk of post-discharge mortality remains high, especially in the first 90 days after discharge.

S.S. Olesen, Centre for Pancreatic Diseases and Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark, e-mail: soso@rn.dk

DOI: 10.1002/ueg2.12766

Gut. 2025;74(7):1094-1102

Kang X, Xia M, Wang J, Wang X, Luo H, Qin W, Liang Z, Zhao G, Yang L, Sun H, Tao J, Ning B, Zhong L, Zhang R, Ma X, Zhao J, Yue L, Jin H, Kang C, Ren G, Liang S, Wang H, Wang L, Nie Y, Wu K, Fan DM, Pan Y

Rectal diclofenac versus indomethacin for prevention of post-ERCP pancreatitis (DIPPP): A multicentre, double-blind, randomised, controlled trial

Background: Recent meta-analyses suggested diclofenac may be superior to indomethacin in preventing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP). The aim of the study was to compare the efficacy of 100 mg rectal indomethacin versus diclofenac on PEP incidences.
Design: This multicentre, double-blinded, randomised controlled trial was conducted in nine tertiary centres in China. Patients with low and high risk for PEP and native papilla were randomly allocated (1:1) to receive 100 mg diclofenac or 100 mg indomethacin rectally before ERCP. The primary outcome was the occurrence of PEP defined by the Cotton consensus. The intention-to-treat principle was conducted for the analysis.
Results: The trial was terminated early for futility after the predetermined first interim analysis. Between June 2023 and May 2024, 1,204 patients were randomised into the diclofenac group (n = 600) or indomethacin group (n = 604). Baseline characteristics were balanced. The primary outcome occurred in 53 patients (8.8%) of 600 patients allocated to the diclofenac group and 37 patients (6.1%) of 604 patients allocated to the indomethacin group (relative risk = 1.44; 95% confidence interval [CI]: 0.96–2.16, p = 0.074). PEP occurred in 35 (14.2%) of 247 high-risk patients in the diclofenac group and 26 (9.8%) of 266 high-risk patients in the indomethacin group (p = 0.124). PEP incidences were also comparable in low-risk patients between the two groups (18/353 [5.1%] vs. 11/338 [3.3%], p = 0.227). Other ERCP-related complications did not differ between the two groups.

Conclusion: Pre-procedure 100 mg rectal diclofenac was not superior to the same dose of rectal indomethacin regarding preventing post-ERCP pancreatitis (PEP). These findings supported current clinical practice guidelines of 100 mg indomethacin or diclofenac for PEP prophylaxis in patients without contraindications.

Y. Pan, State Key Laboratory of Holistic Integrative Management of Gastrointestinal Cancers and National Clinical Research Center for Digestive Diseases, Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi’an, Shaanxi, China, e-mail: yanglinpan@hotmail.com

DOI: 10.1136/gutjnl-2024-334466

Dig Dis Sci. 2025;70(6):2204-2211

Munigala S, Subramaniam DS, Subramaniam DP, Xian H, Munigala SM, Kottapalli KC, Burroughs TE, Sheth SG

Decreased life expectancy in patients with acute and chronic pancreatitis

Background and aims: Population-based data on the life expectancy and mortality for acute (AP) and chronic pancreatitis (CP) in the United States are limited. This study evaluates the life expectancy, mortality rates and the cause of death in AP and CP patients.
Methods: Using the nationwide Veterans Administration database from 1999 to 2015, the authors identified AP and CP patients (using ICD-9 codes) and non-pancreatitis patients (controls). Age at the time of death was used as a surrogate indicator of life expectancy. Life expectancy in AP and CP patients was compared with the controls, using Cox-proportional hazards model. The mortality rates and cause of death for AP, CP, and controls were also assessed.
Results: Overall, the authors selected 35,550 AP and 12,545 CP patients and 100,000 controls. The life expectancy was significantly lower for both AP (69 years) and CP (71 years) patients compared to the controls (81 years, p < 0.001). The risk of mortality was higher for AP (adjusted hazard ratio [aHR] = 1.61, 95% CI: 1.58–1.65, p < 0.001) and CP (aHR = 1.64, 95% CI: 1.59–1.68, p < 0.001) than in controls. Approximately 42% of all patients died during the follow-up (AP -44.3%, CP -52.1% and controls -39.7%). Circulatory disorders, neoplasms, and respiratory disorders were the leading causes of death in AP and CP patients.

Conclusions: Acute (AP) and chronic pancreatitis (CP) are associated with decreased life span and higher mortality emphasizing their clinical importance. Although the deaths due to gastrointestinal/digestive system disorders were significantly higher, most of the deaths in AP and CP patients were primarily due to non-gastrointestinal causes.

S. Munigala, Department of Internal Medicine, Washington University in St. Louis, Saint Louis, MO, USA, e-mail: satish.munigala@slu.edu

DOI: 10.1007/s10620-025-08944-w

Symposium 241, Oxford (United Kingdom), July 10–12, 2025

Mucosal Immunology Days

Interview with Prof. Britta Siegmund

Lively discussions and open exchange bring the community of IBD researchers together

by Dr. Corinna Kolac

Gastroenterologist Prof. Britta Siegmund (Berlin, Germany) co-organized the symposium on mucosal immunology in IBD, drawing numerous leading experts. The event featured in-depth discussions on many aspects of mucosal immunology. Currently, a new IBD classification system is under review. We interviewed Prof. Siegmund during the symposium.

The Montreal classification for chronic inflammatory bowel disease (IBD) dates back to 2006 [1]. For Crohn's disease (CD), for example, it considers age at diagnosis, disease location, and disease behavior. The classification is now being revised. What factors might be important in the future?

Prof. Britta Siegmund: Unfortunately, I can't share specific details yet. However, it's becoming clear that disease localization will play a significant role and needs to be better defined—something we've learned from oncology and immunological research. Only by refining how we define localization can we truly understand its relevance and build on it. We'll also integrate perianal classification. The new system for clinical practice likely won't be overly complex—it needs to be practical and user-friendly. The Montreal classification isn't fundamentally wrong; the new version will simply be more granular. We're making sure these changes are practical—otherwise, the classification won't be adopted widely. At the same time, we're considering a research-focused classification that goes beyond clinical needs, allowing for more detailed data collection.

There's a lot of discussion around new models. How relevant are organoids in clinical practice today? Could patients with severe disease expect personalized treatment using these models soon?

Prof. Britta Siegmund: Organoids are an excellent tool for studying certain aspects of IBD. However, the intestinal wall contains many different cell types, while organoids are purely epithelial—all the supporting structures are missing. If the defect is in the epithelium, organoids can provide valuable insights. But once other cell types are involved, things get much more complicated. So, while organoids are a useful model, they have their limitations.

There's ongoing debate about whether biomarkers could indicate IBD long before symptoms appear. Does this suggest potential for screening?

Prof. Britta Siegmund: The idea of using biomarkers comes from studies of blood samples from US veterans, who regularly give blood and receive healthcare, creating large datasets. It's relatively easy to identify people who later developed IBD and analyze their earlier blood samples. There's a set of blood markers associated with a higher risk of developing IBD, but how meaningful these markers are is still unclear. Initial efforts are underway to identify individuals at increased risk and to treat those at very high risk before clinical symptoms appear, with the hope of preventing intestinal inflammation. These are exciting, but still experimental, approaches.

Monogenic IBD is receiving significant attention at this symposium. What's the current state of research?

Prof. Britta Siegmund: There are two types of monogenic IBD. The condition is more common in children and adolescents, especially before the age of one—here, the likelihood of a monogenic cause is very high. Pediatricians are therefore much more familiar with this topic. But there's also a second form in adults, often characterized by a particular phenotype or severe disease. In these cases, genetic sequencing is warranted.

How important is nutrition in the development of IBD?

Prof. Britta Siegmund: Nutrition is important not only in the development of IBD but also in its management. For example, research has shown that an emulsifier-free diet can help control mild to moderate Crohn's disease. Regarding the onset of IBD, we know that a "Western diet" is strongly associated with increased risk. Of course, diet likely plays a role in many other diseases as well. In my opinion, we, as a society, should do more to reduce our intake of processed foods and focus on fresh, unprocessed foods with as few emulsifiers as possible.

What has your personal highlight of this symposium been?

Prof. Britta Siegmund: For me, the highlight is the many lively discussions. I find them incredibly enriching. Everyone brings unique perspectives, and we can only make progress by sharing ideas and weighing options together. Identifying where the true gaps are and what needs urgent attention is invaluable. Moving forward requires collaboration. I really value the openness among researchers and the dialogue with clinicians. For all these reasons, I'm already looking forward to the next symposium, which will take place in Gothenburg in 2027.

Reference
1 Satsangi J, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006; 55(6):749–753.

LIVER AND BILE

Viral Hepatitis

Lancet. 2025;405(10491):1769-1780

Cooke GS, Hung LM, Flower B, McCabe L, Hang VTK, Thu VT, Thuan DT, Dung NT, Phuong LT, Khoa DB, An NTC, Thach PN, Huong VTT, Bich DT, Tuyen NK, Ansari MA, Le Ngoc C, Quang VM, Phuong NTN, Thao LT, Tran NB, Kestelyn E, Kingsley C, Van Doorn R, Rahman M, Pett SL, Thwaites GE, Barnes E, Day JN, Chau NVV, Walker AS

Treatment options to support the elimination of hepatitis C: An open-label, factorial, randomised controlled non-inferiority trial

Background: WHO recommends treating hepatitis C infection with one of three antiviral combinations for 8-12 weeks. No randomised trials have compared these regimens, and high cure rates might be achievable with shorter durations of therapy. The authors aimed to compare sofosbuvir-daclatasvir with sofosbuvir-velpatasvir, and to evaluate potential novel treatment strategies.
Methods: A multi-arm, open-label, randomised controlled non-inferiority trial in two public hospitals in Vietnam was conducted. Adults (aged ≥ 18 years) with chronic hepatitis C infection and mild-to-moderate liver fibrosis were eligible. Recruitment was stratified by centre and viral genotype (1–5 vs. 6) with 1:1 random allocation to an oral fixed-dose combination of sofosbuvir 400 mg plus daclatasvir 60 mg (sofosbuvir-daclatasvir) or sofosbuvir 400 mg plus velpatasvir 100 mg (sofosbuvir-velpatasvir). Participants were simultaneously factorially randomly assigned to one of four treatment strategies: 12 weeks' standard of care (SOC); 4 weeks' therapy with 4 weekly PEGylated interferon alfa-2a subcutaneous injections; induction and maintenance therapy with 2 weeks' standard therapy followed by 10 weeks' therapy 5 days a week; and response-guided therapy (RGT) for 4, 8, or 12 weeks determined by viral load on day 7. The primary outcome was sustained virological response (SVR) 12 weeks after treatment completion, analysed in all evaluable participants regardless of actual treatment received. The authors chose a 5% non-inferiority margin for the drug comparison, and a 10% non-inferiority margin for the treatment strategy comparisons. Safety was assessed in all randomised participants.
Findings: Between June 19, 2020, and May 10, 2023, 624 participants were randomised (470 [75%] were male and 154 [25%] were female). 296 (47%) had genotype 6 and 328 (53%) had genotypes 1–5. The primary outcome was assessable in 609 (98%) participants. SVR occurred in 294 (97%) of 302 participants in the sofosbuvir-daclatasvir group and 292 (95%) of 307 participants in the sofosbuvir-velpatasvir group (risk difference 2.2%, 90% credible interval [CrI]: -0.2 to 4.8, within the 5% non-inferiority margin; 93% probability that sofosbuvir-daclatasvir is superior to sofosbuvir-velpatasvir). SVR occurred in 148 (99%) of 150 in the SOC group, 143 (94%) of 152 in the 4-week antiviral plus interferon group (-4.5%, 90% CrI: -8.3 to -1.3), 151 (99%) of 152 in the induction-maintenance group (0.6%, -1.1 to 2.7), and 144 (93%) of 155 in the RGT group (-5.7%, -9.6 to -2.3); all risk differences were within the 10% non-inferiority margin. Serious adverse events were rare (11 [4%] of 313 participants in the sofosbuvir-velpatasvir group vs. 6 [2%] of 311 in the sofosbuvir-daclatasvir group; risk difference -1.6% [95% CrI: -4.2 to 0.8]) with no evidence of differences between regimens or strategies, but adverse reactions were very common in the 4-week antiviral plus interferon group compared with the other treatment strategies (risk difference vs. SOC group, 66.8% [59.2–74.0]; $p < 0.0001$).

Interpretation: Sofosbuvir-daclatasvir was non-inferior to sofosbuvir-velpatasvir. High efficacy was seen with novel strategies, which might help to inform approaches to treatment for harder-to-reach populations.

G.S. Cooke, Department of Infectious Disease, Imperial College London, London, UK,
e-mail: g.cooke@imperial.ac.uk

DOI: 10.1016/s0140-6736(25)00097-2 ■

Lancet Gastroenterol Hepatol. 2025;10(10):904-914

Trickey A, Artenie A, Feld JJ, Vickerman P

Estimating the annual number of hepatitis C virus infections through vertical transmission at country, regional, and global levels: A data synthesis study

Background: The burden of hepatitis C virus (HCV) among women of childbearing age remains high globally. Studies have estimated that 7–12% of children born to women with HCV infection will acquire HCV, although around two-thirds of children will then clear their HCV infection by 5 years of age. The authors aimed to estimate the annual number of vertically transmitted HCV infections and how many cases remain at 5 years of age at the country or territory, regional, and global levels.
Methods: In this data synthesis study, the authors produced estimates of vertical HCV transmission by combining data from several sources: data on the number of women, age-specific fertility rates, mortality rates among children aged 0–5 years, and HIV prevalence among women aged 15–49 years from the UN; modelled data on HCV prevalence among women aged 15–49 years; meta-analysis data on HCV-HIV co-infection prevalence; and recent estimates of the probabilities of vertical HCV transmission and subsequent clearance by age 5 years. The annual number of births with HCV was estimated by multiplying the number of women with HCV in 5-year age bands by age band-specific birth rates, separately by HIV status, and multiplying by HIV status-specific HCV vertical transmission probabilities.

The number of births with HCV was multiplied by the probability of spontaneous clearance of HCV by 5 years of age, accounting for mortality. All estimates were sampled 1,000 times from their uncertainty intervals (UIs) to produce 95% UIs.
Findings: The estimated annual global number of new HCV infections occurring through vertical transmission was 73,862 (95% UI: 69,808–78,279). Southern Asia (21,245 [18,095–24,847]), western Africa (16,482 [14,873–18,283]), and eastern Africa (8,182 [7,479–9,085]) were the regions with the most infections. Pakistan (16,350 [13,325–19,844]) and Nigeria (8,483 [6,944–10,184]) had the largest burden and together accounted for around a third of new infections. The authors estimated that 23,120 (20,596–25,813) of these children would be alive and still have HCV when aged 5 years.

Interpretation: Targeted screening policies that test and treat pregnant women with HCV could prevent substantial numbers of new HCV infections; however, data on the safety of HCV treatments in pregnant women are required.

A. Trickey, Population Health Sciences, University of Bristol, Bristol, UK, e-mail: adam.trickey@bristol.ac.uk

DOI: 10.1016/s2468-1253(25)00189-x

Gastroenterology. 2025;169(1):136-149

Ji Y, Le Bert N, Lai-Hung Wong G, Douglas MW, Lee A, Zhu C, Wang B, Lv J, Li D, Tan Y, Ma H, Chen J, Chen X, Zhu Q, Yuen MF, Bertoletti A

The impact of hepatitis B surface antigen reduction via small interfering RNA treatment on natural and vaccine (BRII-179)-induced hepatitis B virus-specific humoral and cellular immune responses

Background and aims: The impact of hepatitis B surface antigen (HBsAg) reduction from small interfering RNA (siRNA) treatments on hepatitis B virus (HBV)-specific immunity of individuals with chronic hepatitis B (CHB) has not been adequately analyzed in humans. The authors conducted a phase 2a study treating CHB participants with nine 4-weekly doses of HBV-targeted siRNA elebsiran (BRII-835), either alone (n = 10) or in combination with a virus-like particle-based therapeutic vaccine (BRII-179) containing Pre-S1, Pre-S2, and S antigens, co-administered with (n = 39) or without (n = 41) interferon alfa.
Methods: The study analyzed longitudinally for 72 weeks virologic, clinical, and immunologic parameters, including HBsAg, alanine aminotransferase, hepatitis B surface antibody (anti-HBs), the neutralizing activity of representative sera, and frequency and cytokine secretion ability of T cells specific for Pre-S1, Pre-S2, and S both directly ex vivo and after in vitro expansion.
Results: Combination therapy with elebsiran and BRII-179 was well tolerated. Although no sustained HBsAg seroclearance or notable difference in mean HBsAg reduction at the group level was observed, the authors detected marked heterogeneity in immunologic responses among groups. HBsAg reduction mediated by siRNA alone was associated with minimal HBV-specific immune response recovery. In contrast, combination of elebsiran with BRII-179 induced a significant modification of immune responses demonstrated by anti-HBs antibody production and an expansion of interleukin 2-producing helper T cells specific for Pre-S1/Pre-S2 antigens only. Importantly, anti-HBs antibodies persisted at ≥ 100 IU/L in ~40% of the participants for at least 32 weeks after combined treatment. Moreover, the neutralizing ability of the anti-HBs-positive sera was associated with HBsAg reduction.

Conclusions: siRNA-induced HBsAg reduction may contribute to the persistence and efficacy of the humoral arm of HBV-specific adaptive immunity in CHB participants receiving the therapeutic vaccine BRII-179.

A. Bertoletti, Programme in Emerging Infectious Diseases, Duke-NUS Medical School, Singapore, Singapore, e-mail: antonio@duke-nus.edu.sg

or

Q. Zhu, Brii Biosciences Inc, Durham, NC, USA, e-mail: qing.zhu@briibio.com

DOI: 10.1053/j.gastro.2025.02.016

Steatotic Liver Disease incl. MASLD

J Hepatol. 2025;83(1):21-30

Wallace C, Gamkrelidze I, Estes C, Razavi H, Sanyal AJ

Modeling the health and economic impact of pharmacologic therapies for MASLD in the United States

Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common condition leading to chronic liver disease, which generates substantial healthcare costs. The authors aimed to model the impact of a hypothetical pharmacologic therapy that halts MASLD fibrosis progression on disease and economic burden.
Methods: The US MASLD disease burden model is a Markov model which forecasts disease progression and the impact of diagnosis and treatment. Diagnostic costs for all patients and direct costs for patients with MASLD-related liver disease were also incorporated. MASLD disease burden and economic impacts were modeled for five scenarios: a no treatment case and four interventions incorporating the impact of gradually increasing awareness, screening, and diagnosis, and treatment with anti-steatotic therapy and a future, hypothetical therapy that halts fibrosis progression.
Results: Treatment with therapy which only reverses steatosis had minimal (< 1–2%) effect on cumulative chronic liver disease cases and healthcare costs averted. The scenarios in which a hypothetical therapy halts fibrosis progression resulted in reductions in cases of decompensated cirrhosis (11–39%), hepatocellular carcinoma (10–34%), and liver-related deaths (8–31%), a 9–31% reduction in cumulative DALYs, and $40.5 to $99.1B incremental healthcare costs averted.

Conclusions: Increasing diagnosis and treatment for the MASLD population with moderate-to-advanced

fibrosis will prevent advanced liver disease and death and will result in reducing the associated direct healthcare costs. Increasing awareness, screening and diagnosis along with introducing pharmacologic therapies that halt fibrosis progression are necessary to realize health and economic benefits for the MASLD population.

H. Razavi, Center for Disease Analysis Foundation, Lafayette, CO, USA, e-mail: hrazavi@cdafound.org

DOI: 10.1016/j.jhep.2025.01.009

Hepatology. 2025;82(1):127-139

Hsu CL, Wang L, Maestri E, Jacob AR, Do WL, Mayo S, Bosques-Padilla F, Verna EC, Abraldes JG, Brown RS, Jr., Vargas V, Altamirano J, Caballería J, Shawcross DL, Louvet A, Lucey MR, Mathurin P, Garcia-Tsao G, Stärkel P, Bataller R, Wang XW, Schnabl B; AlcHepNet Investigators

Viral antibody response predicts morbidity and mortality in alcohol-associated hepatitis

Background and aims: Alcohol-associated hepatitis (AH) is associated with very high mortality despite abstinence from alcohol; up to 40% of patients die within 6 months of diagnosis. Patients with AH are especially prone to infections, which can lead to multiorgan dysfunction and poorer prognosis.
Approach and results: The authors performed comprehensive serological profiling of the viral and bacterial infection history of 36 healthy controls, 48 patients with alcohol use disorder, and 224 patients with AH from 2 multicenter observational studies. The authors used systematic viral and bacterial epitope scanning by VirScan, a phage-display immunoprecipitation and sequencing technology that detects the peptides recognized by antibodies in patient sera, to comprehensively analyze antiviral and antibacterial antibodies and identify serologic biomarkers to predict patient outcomes. The authors found significant differences in the serological profiles of the 3 populations. The number of serum antibody epitopes in patients with alcohol use disorder during abstinence was increased compared with during active alcohol use. A decreased number and diversity of viral and bacterial antibody targets were detected in the sera of patients with AH, particularly those with a higher Child-Pugh score. In patients with AH, a decrease in the serum antiviral, but not antibacterial, antibody repertoire was associated with decompensation and mortality. Ninety-day mortality in AH could be predicted using a serum viral epitope signature.

Conclusions: Abstinence from alcohol is associated with a significant increase in serum viral and bacterial antibody response. Decreased serum antiviral antibody repertoire is predictive of decompensation of liver disease and mortality in patients with AH.

B. Schnabl, Department of Medicine, University of California San Diego, La Jolla, CA, USA, e-mail: beschnabl@health.ucsd.edu

DOI: 10.1097/hep.0000000000001046

EXPERT OPINION

Prof. Dr. Tobias Böttler

Loss of antimicrobial antibody diversity due to alcohol abuse – Reversible only as long as the liver still works

Advanced liver disease is associated with impaired immune competence and multiple infectious complications. The study by Hsu et al. demonstrates that alcohol abuse alone can profoundly alter the immune repertoire, even before the development of advanced liver disease. Using a high-throughput immunoserologic profiling approach, the authors show that both harmful alcohol consumption and alcohol-associated liver disease correlate with a reduced diversity of pathogen-specific antibody responses. Whereas alcohol abstinence in individuals without liver disease led to a marked recovery of antibody diversity, this effect was absent in those with advanced liver disease. Notably, the diversity of antiviral—but not antibacterial—antibodies was identified as an independent predictor of mortality and hepatic decompensation, whereas no such association was observed for antibacterial antibodies.
The study compellingly illustrates that alcohol abuse and the resulting liver disease represent two additive yet partly independent determinants of humoral immune dysfunction. This finding is particularly relevant with regard to the reversibility of immune dysregulation, which appears to be lost once advanced liver disease has developed. This observation is consistent with the concept of cirrhosis-associated immune dysfunction (CAID), a systemic immune dysregulation commonly observed in patients with cirrhosis and characterized by functional immune impairment, increased susceptibility to infections, and diminished vaccine responsiveness. Paradoxically, advanced liver disease is often accompanied by elevated serum levels of immunoglobulins (particularly IgG and IgA), although their antigen specificity remains largely undefined. Possible explanations include unspecific immune activation with reactivation of antibody-producing memory B cells or, alternatively, systemic exposure to intestinal antigens resulting from portal hypertension, leading to de novo immune responses against irrelevant peripheral targets. The observed decline in antimicrobial antibody diversity with progression of liver disease rather supports the latter mechanism. As the study primarily included patients with alcohol-associated steatohepatitis, it remains unclear to what extent the cohort also comprised individuals with advanced portal hypertension—an aspect of particular relevance for interpreting the immunological significance of these findings.
Another key observation is the selective association between reduced antiviral, but not antibacterial, antibody diversity and mortality and hepatic decompensation. Clinically, both bacterial and viral infections are well-known triggers of decompensating events, yet viral infections—such as herpesvirus reactivations, influenza, respiratory viruses, or hepatitis E virus—are rarely identified in a systematic manner. The present findings therefore highlight the need for more detailed differentiation between viral and bacterial triggers of decompensation, with important implications for vaccination

strategies and antiviral prophylaxis in high-risk patients with alcohol-associated liver disease. ■

Lancet Gastroenterol Hepatol. 2025;10(8):734-745

Loomba R, Kowdley KV, Rodriguez J, Kim NJ, Alvarez AM, Morrow L, Jeglinski B, Clawson A, Chowdhury S, Bain G, Odrljin T

Efimosfermin alfa (BOS-580), a long-acting FGF21 analogue, in participants with phenotypic metabolic dysfunction-associated steatohepatitis: A multicentre, randomised, double-blind, placebo-controlled, phase 2a trial

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive disease characterised by steatosis, inflammation, and liver fibrosis. Efimosfermin alfa (efimosfermin, formerly BOS-580) is a long-acting, engineered variant of FGF21 designed to have a prolonged half-life. The trial aimed to assess the safety and tolerability of multiple efimosfermin doses and dosing regimens compared with placebo and to evaluate exploratory biomarkers of efficacy in participants with phenotypic MASH.
Methods: This multicentre, randomised, double-blind, placebo-controlled, phase 2a trial was conducted at 12 centres in the USA. Individuals with phenotypic MASH, aged 18–75 years and with a BMI of 30–45 kg/m^2, were eligible for the study. Participants were randomly assigned, using a centralised interactive randomisation system with no stratification factors, to one of five dosing cohorts: efimosfermin 75 mg once every 4 weeks, 75 mg once every 2 weeks, 150 mg once every 4 weeks, 150 mg once every 2 weeks, or 300 mg once every 4 weeks, for a 12-week treatment period. Participants were assigned 1:1:1:1 to all cohorts except efimosfermin 150 mg once every 4 weeks, which was initiated after assignment to the other cohorts was complete. Within each cohort, participants were randomly assigned 4:1 to receive efimosfermin or placebo, via subcutaneous injection, in fixed blocks of size five. Investigators and participants were masked to group assignment and treatment allocation. The primary endpoint was safety and tolerability and was assessed throughout the 12-week treatment period and at the follow-up visit 4 weeks after the final dose in the full analysis set, defined as enrolled participants who received at least one dose of study medication. Part A (reported here) of this phase 2 study is complete, while other parts of the phase 2 study are ongoing.
Findings: Between August 27, 2021, and July 22, 2022, 360 individuals were screened, of whom 102 were eligible and were randomly assigned to receive placebo (n = 37) or efimosfermin 75 mg every 4 weeks (n = 8), 75 mg every 2 weeks (n = 14), 150 mg every 4 weeks (n = 15), 150 mg every 2 weeks (n = 15), or 300 mg every 4 weeks (n = 13), for a total of 12 weeks. 45 (44%) of the 102 participants were female and 57 (56%) were male, with a mean age of 53 years (SD 11) and mean BMI of 36.5 kg/m^2 (SD 4.1). Of 65 participants treated with efimosfermin, 43 (66%) had treatment-emergent adverse events (TEAEs): 4 (50%) of 8 participants receiving 75 mg every 4 weeks, 10 (71%) of 14 participants receiving 75 mg every 2 weeks, 6 (40%) of 15 participants receiving 150 mg every 4 weeks; 12 (80%) of 15 participants receiving 150 mg every 2 weeks, and 11 (85%) of 13 participants receiving 300 mg every 4 weeks; TEAEs were recorded in 18 (49%) of 37 participants receiving placebo. TEAEs were typically mild-to-moderate in severity and resolved spontaneously. The most frequent TEAEs were gastrointestinal in nature, reported by 9 (24%) of 37 participants in the placebo group and 26 (40%) of 65 participants who received efimosfermin: 2 (25%) of 8 participants receiving 75 mg every 4 weeks, 8 (57%) of 14 participants receiving 75 mg every 2 weeks, 2 (13%) of 15 participants receiving 150 mg every 4 weeks, 8 (53%) of 15 participants receiving 150 mg every 2 weeks, and 6 (46%) of 13 participants receiving 300 mg every 4 weeks. The most common gastrointestinal events were nausea, vomiting, and diarrhoea. There were no treatment-related deaths. At week 12, 47 (89%) of 53 participants receiving efimosfermin for whom data were available had at least a 30% reduction in hepatic fat fraction: 5 (63%) of 8 participants receiving 75 mg every 4 weeks, 11 (92%) of 12 participants receiving 75 mg every 2 weeks, 9 (90%) of 10 participants receiving 150 mg every 4 weeks, 11 (92%) of 12 participants receiving 150 mg every 2 weeks, and all 11 (100%) participants receiving 300 mg every 4 weeks, compared with 2 (7%) of 30 participants receiving placebo.

Interpretation: In participants with phenotypic MASH, efimosfermin had a favourable safety profile and showed improvements in indicators of hepatic steatosis. These results help to inform future studies of efimosfermin in this important disease state.

R. Loomba, MASLD Research Center, Division of Gastroenterology and Hepatology, Department of Medicine, University of California at San Diego, La Jolla, CA, USA, e-mail: roloomba@health.ucsd.edu

DOI: 10.1016/s2468-1253(25)00067-6 ■

Lancet. 2025;406(10505):821-831

Loomba R, Morgan E, Yousefi K, Li D, Geary R, Bhanot S, Alkhouri N; ION224-CS2 Investigators

Antisense oligonucleotide DGAT-2 inhibitor, ION224, for metabolic dysfunction-associated steatohepatitis (ION224-CS2): Results of a 51-week, multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

Background: ION224, a liver-directed antisense inhibitor of diacylglycerol O-acyltransferase 2 (DGAT2), suppresses de novo lipogenesis, an important metabolic pathway associated with lipotoxicity and the underlying inflammation, hepatocellular injury, and fibrosis in metabolic dysfunction-associated steatohepatitis (MASH). This study aimed to prospectively assess the safety and efficacy of ION224 in patients with MASH and fibrosis.
Methods: ION224-CS2 was an adaptive, two-part, multicentre, randomised, double-blind, placebo-controlled, phase 2 trial conducted at 43 clinical sites in the USA and Puerto Rico in patients aged 18–75 years with biopsy-confirmed MASH and fibrosis (stages F1, F2, and F3) and baseline liver steatosis ≥ 10%. In part 1, participants were randomly assigned (1:1:1) to subcutaneous injec-

tions of ION224 60 mg, 90 mg, or 120 mg, or placebo, once per month. In part 2, participants were randomly assigned (2:1) to ION224 90 mg and 120 mg or placebo after a pre-specified interim analysis of safety and efficacy (liver steatosis). The primary endpoint was ≥ 2-point reduction in Non-Alcoholic Fatty Liver Disease Activity Score (NAS) with ≥ 1-point improvement in hepatocellular ballooning or lobular inflammation, and without worsening of fibrosis at week 51. The primary analysis was in a predefined per-protocol set that included patients who received at least 10 of 13 doses of the study drug without missing 3 consecutive doses and completed the final liver biopsy at the end of treatment.
Findings: Between June 8, 2021, and December 27, 2022, 160 participants were randomly assigned to receive ION224 60 mg (n = 23), 90 mg (n = 45), or 120 mg (n = 46), or placebo (n = 46), of whom 123 were included in the per-protocol set. The primary endpoint was met in 18 (46%) of 39 participants in the 90-mg group (predicted risk 46.2% [95% CI: 30.5–61.8]; risk difference 27.4% [95% CI: 6.7–48.1], p = 0.0094) and 20 (59%) of 34 in the 120-mg group (58.8% [42.3–75.4]; 40.1% [18.7–61.4], p = 0.0002) compared with 6 (19%) of 32 in the placebo group (predicted risk 18.7% [95% CI: 5.2–32.3]). ION224 was safe and well tolerated. Adverse events were reported in 107 (94%) of participants treated with ION224 and 41 (89%) of 46 participants treated with placebo. There were no deaths and no treatment-related serious adverse events.

Interpretation: This study provides the first clinical evidence that antisense-mediated inhibition of DGAT2 with ION224 could be a safe and efficacious strategy for the treatment of MASH. The observed histological improvements were independent of changes in body weight, suggesting potential to combine with other therapies such as GLP-1 based treatments.

R. Loomba, MASLD Research Center, Division of Gastroenterology and Hepatology, Department of Medicine, University of California at San Diego, La Jolla, CA, USA, e-mail: roloomba@health.ucsd.edu

DOI: 10.1016/s0140-6736(25)00979-1

Lancet. 2025;406(10504):719-730

Noureddin M, Frias JP, Neff GW, Lucas KJ, Behling C, Bedossa P, Dubourg J, Chan D, Burch M, Fong E, de Temple B, Minerva M, Barrett K, Shringarpure R, Tillman EJ, Rolph T, Cheng A, Yale K

Safety and efficacy of once-weekly efruxifermin versus placebo in metabolic dysfunction-associated steatohepatitis (HARMONY): 96-week results from a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial

Background: Efruxifermin is a bivalent fibroblast growth factor 21 analogue in development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). This trial aimed to prospectively assess the safety and efficacy of efruxifermin administration for 96 weeks in individuals with MASH and moderate (stage 2; F2) or severe (stage 3; F3) fibrosis.

Methods: HARMONY is a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial conducted at 41 academic and community centres in the USA. Adults (aged 18–75 years) with biopsy-confirmed MASH (defined as non-alcoholic fatty liver disease activity score of 4 or higher and a score of 1 or higher for steatosis, ballooning, and lobular inflammation), with histological stage F2 or F3 fibrosis, were randomly assigned (1:1:1), via an interactive response system, to receive subcutaneous efruxifermin (28 mg or 50 mg) once per week or placebo. Participants, investigators, pathologists, site staff, and the sponsor were masked to group assignments. The primary endpoint was an improvement in liver fibrosis (decrease ≥ 1 stage) without worsening of MASH at week 24, which has been previously reported. End-of-treatment endpoints at week 96 included a final evaluation of the primary endpoint, as well as MASH resolution without fibrosis worsening.
Findings: Between March 22, 2021, and February 7, 2022, 128 participants were randomly assigned and 126 received at least one dose of efruxifermin or placebo and were included in the modified intention-to-treat analysis. 79 (62%) of 128 participants were female and 49 (38%) were male. The proportion of participants in the modified intention-to-treat population with ≥ 1-stage fibrosis improvement without MASH worsening at week 96 was 8 (19%) of 43 in the placebo group, 12 (30%) of 40 in the 28 mg group (difference vs. placebo: 12 percentage points [95% CI: -6 to 31]; p = 0.19), and 21 (49%) of 43 in the 50 mg group (difference: 31 percentage points [12–49]; p = 0.0030). Of 88 participants with week-96 biopsies, ≥ 1-stage fibrosis improvement without MASH worsening was observed in 8 (24%) of 34 participants in the placebo group, 12 (46%) of 26 in the 28 mg group (difference vs. placebo: 22 percentage points [95% CI: -1 to 45]; p = 0.070), and 21 (75%) of 28 in the 50 mg group (difference: 52 percentage points, [31–73]; p < 0.0001). 38 (95%) of 40 participants in the 28 mg group, 43 (100%) of 43 in the 50 mg group, and 42 (98%) of 43 in the placebo group reported an adverse event. Mild to moderate gastrointestinal adverse events were more common with efruxifermin than placebo. There were no reports of drug-induced liver injury or deaths across the groups.

Interpretation: Efruxifermin resulted in greater improvements in fibrosis than placebo after 96 weeks, warranting further investigation in phase 3 trials.

M. Noureddin, Houston Research Institute, Houston, TX, USA, e-mail: noureddinmd@houstonresearchinstitute.com

DOI: 10.1016/s0140-6736(25)01073-6

N Engl J Med. 2025;392(21):2089-2099

Sanyal AJ, Newsome PN, Kliers I, Østergaard LH, Long MT, Kjær MS, Cali AMG, Bugianesi E, Rinella ME, Roden M, Ratziu V; ESSENCE Study Group

Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis

Background: Semaglutide, a glucagon-like peptide-1 receptor agonist, is a candidate for the treatment of metabolic dysfunction-associated steatohepatitis (MASH).

Methods: In this ongoing phase 3, multicenter, randomized, double-blind, placebo-controlled trial, the authors assigned 1,197 patients with biopsy-defined MASH and fibrosis stage 2 or 3 in a 2:1 ratio to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo for 240 weeks. The results of a planned interim analysis conducted at week 72 involving the first 800 patients are reported here (part 1). The primary end points for part 1 were the resolution of steatohepatitis without worsening of liver fibrosis and reduction in liver fibrosis without worsening of steatohepatitis.
Results: Resolution of steatohepatitis without worsening of fibrosis occurred in 62.9% of the 534 patients in the semaglutide group and in 34.3% of the 266 patients in the placebo group (estimated difference, 28.7 percentage points; 95% confidence interval [CI]: 21.1–36.2; $p < 0.001$). A reduction in liver fibrosis without worsening of steatohepatitis was reported in 36.8% of the patients in the semaglutide group and in 22.4% of those in the placebo group (estimated difference, 14.4 percentage points; 95% CI: 7.5–21.3; $p < 0.001$). Results for the three secondary outcomes that were included in the plan to adjust for multiple testing were as follows: combined resolution of steatohepatitis and reduction in liver fibrosis was reported in 32.7% of the patients in the semaglutide group and in 16.1% of those in the placebo group (estimated difference, 16.5 percentage points; 95% CI: 10.2–22.8; $p < 0.001$). The mean change in body weight was -10.5% with semaglutide and -2.0% with placebo (estimated difference, -8.5 percentage points; 95% CI: -9.6 to -7.4; $p < 0.001$). Mean changes in bodily pain scores did not differ significantly between the two groups. Gastrointestinal adverse events were more common in the semaglutide group.

Conclusions: In patients with MASH and moderate or advanced liver fibrosis, once-weekly semaglutide at a dose of 2.4 mg improved liver histologic results.

A.J. Sanyal, Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, Virginia Commonwealth University School of Medicine, Richmond, VA, USA, e-mail: arun.sanyal@vcuhealth.org

DOI: 10.1056/nejmoa2413258

N Engl J Med. 2025;392(24):2413-2424

Noureddin M, Rinella ME, Chalasani NP, Neff GW, Lucas KJ, Rodriguez ME, Rudraraju M, Patil R, Behling C, Burch M, Chan DC, Tillman EJ, Zari A, de Temple B, Shringarpure R, Jain M, Rolph T, Cheng A, Yale K

Efruxifermin in compensated liver cirrhosis caused by MASH

Background: In phase 2 trials involving patients with stage 2 or 3 fibrosis caused by metabolic dysfunction-associated steatohepatitis (MASH), efruxifermin, a bivalent fibroblast growth factor 21 (FGF21) analogue, reduced fibrosis and resolved MASH. Data are needed on the efficacy and safety of efruxifermin in patients with compensated cirrhosis (stage 4 fibrosis) caused by MASH.
Methods: In this phase 2b, randomized, placebo-controlled, double-blind trial, the authors assigned patients with MASH who had biopsy-confirmed compensated cirrhosis (stage 4 fibrosis) to receive subcutaneous efruxifermin (at a dose of 28 mg or 50 mg once weekly) or placebo. The primary outcome was a reduction of at least one stage of fibrosis without worsening of MASH at week 36. Secondary outcomes included the same criterion at week 96.
Results: A total of 181 patients underwent randomization and received at least one dose of efruxifermin or placebo. Of these patients, liver biopsy was performed in 154 patients at 36 weeks and in 134 patients at 96 weeks. At 36 weeks, a reduction in fibrosis without worsening of MASH occurred in 8 of 61 patients (13%) in the placebo group, in 10 of 57 patients (18%) in the 28-mg efruxifermin group (difference from placebo after adjustment for stratification factors, 3 percentage points; 95% confidence interval [CI]: -11 to 17; $p = 0.62$), and in 12 of 63 patients (19%) in the 50-mg efruxifermin group (difference from placebo, 4 percentage points; 95% CI: -10 to 18; $p = 0.52$). At week 96, a reduction in fibrosis without worsening of MASH occurred in 7 of 61 patients (11%) in the placebo group, in 12 of 57 patients (21%) in the 28-mg efruxifermin group (difference from placebo, 10 percentage points; 95% CI: -4 to 24), and in 18 of 63 patients (29%) in the 50-mg efruxifermin group (difference from placebo, 16 percentage points; 95% CI: 2–30). Gastrointestinal adverse events were more common with efruxifermin; most events were mild or moderate.

Conclusions: In patients with compensated cirrhosis caused by MASH, efruxifermin did not significantly reduce fibrosis at 36 weeks.

M. Noureddin, Houston Methodist Hospital, Department of Medicine, Sherrie and Alan Conover Center for Liver Disease and Transplantation, Houston, TX, USA, or Houston Research Institute, Houston, TX, USA, e-mail: noureddinmd@houstonresearchinstitute.com

DOI: 10.1056/nejmoa2502242

Immune-mediated Liver Disease

Hepatology. 2025;81(6):1660-1670

Efe C, Lytvyak E, Eşkazan T, Liberal R, Androutsakos T, Turan Gökçe D, Terziroli Beretta-Piccoli B, Janik M, Bernsmeier C, Arvaniti P, Milkiewicz P, Batıbay E, Yüksekyayla O, Ergenç I, Arikan Ç, Stättermayer AF, Barutçu S, Cengiz M, Gül Ö, Heurgue A, Heneghan MA, Verma S, Purnak T, Törüner M, Akdogan Kayhan M, Hatemi I, Zachou K, Macedo G, Drenth JPH, Björnsson E, Montano-Loza AJ, Wahlin S, Higuera-de la Tijera F

Efficacy and safety of infliximab in patients with autoimmune hepatitis

Background and aims: A limited number of drugs are used as standard or alternative therapies in autoimmune hepatitis (AIH). No specific recommendations are available for patients failing to respond to these therapies. The authors analyzed the efficacy and safety of infliximab in patients with AIH.
Approach and results: The authors performed a retrospective study of 42 patients with AIH who received

infliximab at 21 liver centers in 12 countries. Patients were categorized according to the reason for infliximab therapy. Patients in group 1 (n = 20) had failed standard, second-line (mycophenolate mofetil and 6-mercaptopurine) or third-line (tacrolimus or cyclosporine) therapy. In group 2 (n = 22), infliximab was given for treatment of concomitant extrahepatic autoimmune diseases. Patients received a median of 17 (range, 3–104) infliximab infusions. Complete biochemical response (CR) was achieved or maintained in 33 (78%) patients during infliximab therapy. In group 1, infliximab induced CR in 11 of 20 (55%) patients. In group 2, 16 patients with CR prior to infliximab maintained remission, and the remaining 6 patients with active AIH (5 on standard and 1 on both second-line and third-line therapy) showed CR following infliximab therapy. Infliximab led to CR in 75% (6/8) of nonresponders to second-line and in 46% (6/13) of failing third-line therapy. Overall, 65% (17/26) of the patients with active AIH achieved CR on infliximab. Infliximab was discontinued in 3 patients of group 1. One patient had a severe allergic reaction and 2 developed anti-infliximab autoantibodies.

Conclusions: The study suggests that infliximab may be an effective and safe rescue therapy in AIH.

C. Efe, Department of Gastroenterology, Harran University Hospital, Osmanbey Yerleşkesi, Haliliye, Şanlıurfa, Turkey, e-mail: scumaliefe@gmail.com

DOI: 10.1097/hep.0000000000001089 ■

Gut. 2025;74(9):1486-1499

Röttele F, Zollner A, Mogler C, Yuksel M, Arikan C, Karl V, Aberle JH, Aberle SW, Kogler H, Vécsei A, Vodopiutz J, Salié H, Gräser A, Krimmel L, Martin P, Lurz E, Maier FI, Woelfle L, Nobre S, Goncalves I, Kern L, Schwemmle M, Boettler T, Hofmann M, Hasselblatt P, Thimme R, Tilg H, Müller T, Vogel GF, Bengsch B

Characteristic immune cell interactions in livers of children with acute hepatitis revealed by spatial single-cell analysis identify a possible postacute sequel of COVID-19

Background: A rise in paediatric cases of acute hepatitis of unknown origin (AHUO) was observed in 2022, some requiring liver transplantation. A link to adeno-associated virus 2 infection and CD4⁺T-cell mediated disease was reported in cohorts in the UK and USA but does not explain all cases.
Objective: To determine the intrahepatic immune cell interactions in the inflamed liver and a possible contribution of SARS-CoV-2 infection.
Design: Patients with acute non-A non-E hepatitis (10/12 AHUO, 2/12 subacute) during February 2022–December 2022 undergoing liver biopsy were recruited in a European patient cohort. Hepatological, virological, histopathological and highly multiplexed spatial and single-cell analyses of liver biopsies were performed.
Results: Patients were negative for adenoviral and SARS-CoV-2 PCR. Three patients had a positive adenoviral serology and 10/12 patients had a history or serological evidence of SARS-CoV-2 infection. Imaging mass cytometry identified significant intrahepatic immune infiltration with an enrichment of $CD8^{+}$T-cells. The highest CD8 infiltration and concomitant peripheral immune activation were observed in patients with the most severe hepatitis. $CD8^{+}$T-cell infiltration was connected to histomorphological interface hepatitis and bridging necrosis. Cellular neighbourhood analysis indicated disease-associated microanatomic interactions between $CX3CR1^{+}$ endothelial and myeloid cell populations, interacting with effector $CD8^{+}$T-cells suggesting a pathogenic cellular triad. Of note, the authors detected intrahepatic SARS-CoV-2 antigens in ACE2-expressing cells in the areas with significant pathology in 11/12 samples using several different detection methods. 10/12 patients were treated with corticosteroid therapy and no liver transplantation was required.

Conclusions: The authors identified a possible manifestation of an immune-mediated postacute sequel to COVID-19 associated with a characteristic immune infiltrate in children with AHUO. COVID-19 testing should be considered in paediatric AHUO.

B. Bengsch, Clinic for Internal Medicine II, Freiburg University Medical Center, Freiburg, Germany, e-mail: bertram.bengsch@uniklinik-freiburg.de

or

G.F. Vogel, Department of Paediatrics I, Medical University of Innsbruck, Innsbruck, Austria, e-mail: georg.vogel@i-med.ac.at

DOI: 10.1136/gutjnl-2024-333880 ■

Clinical Hepatology / Epidemiology

J Hepatol. 2025;83(3):662-669

Caballero-Gómez J, Casares-Jiménez M, Gallo-Marín M, Pereira-Pardo S, Beato-Benítez A, Poyato A, Guerra R, Avellón A, Schilling-Loeffler K, Freyre-Carrillo C, García-Bocanegra I, Jiménez-Martín D, Corona-Mata D, Viciana I, Fajardo T, Muñoz-Chimeno M, Quevedo MÁ, Ríos-Muñoz L, Pérez AB, Cano-Terriza D, Macías J, Fuentes A, Johne R, Rivero-Juarez A, Rivero A; GEHEP-014 Study Group

Rat hepatitis E virus as an aetiological agent of acute hepatitis of unknown origin

Background and aims: Rat hepatitis E virus (ratHEV) is an emerging cause of acute hepatitis worldwide. The limited number of ratHEV cases may be associated with the lack of a proper method for molecular diagnosis; thus, the clinical impact and breadth of ratHEV as a cause of acute hepatitis remain uncertain.
Methods: The study was carried out in four phases. I) Identification: molecular assays were identified through a literature search. II) Testing: the methods were evaluated in a rodent testing cohort, and the most suitable molecular diagnostic algorithm was established. III) Derivation: the established algorithm was tested in a larger rodent cohort. IV) Clinical validation: the algorithm was used in a cohort of individuals suffering from acute hepatitis of unknown aetiology, thus establishing the frequency of ratHEV as an aetiological agent of acute hepatitis and its clinical impact.

Results: The authors detected differences in the frequency of positive results among the assays evaluated. After comparing all available molecular methods, the authors established a molecular diagnostic algorithm, which revealed that 17.5% of the 103 rodents in the validation cohort were infected with ratHEV. In the clinical validation cohort, of 562 patients with acute hepatitis of unknown origin, 8 cases of ratHEV infection were identified during the 3 years of the study, representing a frequency of 1.4%. One (12.5%) case had severe acute hepatitis; 4 (50.0%) patients required hospitalization, one of whom (12.5%) died. The strains detected in these patients revealed a close phylogenetic relationship with those found in rats in Spain.

Conclusions: The study demonstrated that ratHEV is an emerging and underdiagnosed cause of acute hepatitis. The results provide evidence that ratHEV should be monitored and included in the differential diagnosis of acute hepatitis.

A. Rivero-Juarez, Grupo de Virología Clínica y Zoonosis, Unidad de Enfermedades Infecciosas, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Hospital Universitario Reina Sofía, Universidad de Córdoba, Córdoba, Spain, e-mail: arjvet@gmail.com

DOI: 10.1016/j.jhep.2025.02.027

Cirrhosis and Portal Hypertension

Hepatology. 2025;82(1):140-154

Alvarado-Tapias E, Brujats A, Puente A, Ardevol A, Rodriguez-Arias A, Fajardo J, Pavel O, Garcia-Guix M, Aracil C, Poca M, Cuyàs B, Cantó E, Montañés R, Garcia-Osuna A, Escorsell À, Torras X, Villanueva C

Hemodynamic effects of carvedilol plus simvastatin in cirrhosis with severe portal hypertension and suboptimal response to β-blockers: A double-blind, placebo-controlled, randomized trial

Background and aims: Carvedilol is a nonselective β-blocker (NSBB) with anti-α1-adrenergic activity, more effective than traditional NSBBs in reducing portal pressure hepatic venous pressure gradient (HVPG). However, 35–45% of patients still have insufficient HVPG decrease. Statins ameliorate endothelial dysfunction, reduce hepatic vascular resistance, and have pleiotropic effects. The authors investigated whether the addition of simvastatin improves the efficacy of carvedilol on HVPG in cirrhosis with severe portal hypertension and suboptimal response to traditional NSBBs.
Methods: Patients with cirrhosis and high-risk varices referred for primary prophylaxis were consecutively included. HVPG was measured at baseline and again after i.v. propranolol. Suboptimal responders (HVPG decrease < 20%) were treated with carvedilol and were randomized to double-blind administration of placebo or simvastatin. Chronic HVPG response was assessed after 4–6 weeks, repeating HVPG measurements after a standard liquid meal to estimate endothelial dysfunction. Plasma samples were obtained before each study to investigate inflammatory parameters.

Results: Of 184 eligible patients, 82 were randomized to carvedilol + simvastatin (n = 41) or carvedilol + placebo (n = 41). Baseline characteristics were similar. HVPG significantly decreased with both, carvedilol + simvastatin (18.6 ± 4 to 15.7 ± 4 mmHg, $p < 0.001$) and carvedilol + placebo (18.9 ± 3 to 16.9 ± 3 mmHg, $p < 0.001$). The decrease was greater with carvedilol + simvastatin (2.97 ± 2.5 vs. 2.05 ± 1.6 mmHg, $p = 0.031$). An HVPG decrease ≥ 20% occurred in 37% versus 15% of patients, respectively (OR = 3.37, 95% CI: 1.15–9.85; $p = 0.021$). With test meal, HVPG increased in both groups ($p < 0.01$), although carvedilol + simvastatin attenuated such increment (12 ± 8% vs. 23 ± 16%, $p < 0.001$). Cytokine levels (interleukin-6, monocyte-chemoattractant protein-1, and malondialdehyde) decreased significantly more with carvedilol + simvastatin ($p < 0.01$). The incidence of adverse events was similar.

Conclusions: In patients with severe portal hypertension (all with high-risk varices) and suboptimal hemodynamic response to traditional NSBBs, combined therapy with carvedilol + simvastatin significantly enhances the portal pressure reduction achieved with carvedilol monotherapy, improves endothelial dysfunction, and reduces proinflammatory cytokines.

C. Villanueva, Department of Gastroenterology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, e-mail: cvillanueva@santpau.cat

DOI: 10.1097/hep.0000000000001148

J Hepatol. 2025;83(1):81-91

Bajaj JS, Fagan A, Gavis EA, Sterling RK, Gallagher ML, Lee H, Matherly SC, Siddiqui MS, Bartels A, Mousel T, Davis BC, Puri P, Fuchs M, Moutsoglou DM, Thacker LR, Sikaroodi M, Gillevet PM, Khoruts A

Microbiota transplant for hepatic encephalopathy in cirrhosis: The THEMATIC trial

Background and aims: Preventing hepatic encephalopathy (HE) recurrence in cirrhosis, which is associated with an altered gut-liver-brain axis, is an unmet need. Benefits of fecal microbiota transplantation (FMT) have been shown in phase I studies, but route and dose-related questions remain.
Methods: The authors performed a phase 2 randomized, placebo-controlled, double-blind, clinical trial of capsule and enema FMT in patients with cirrhosis and HE on lactulose and rifaximin. Participants were randomized into four groups (3 active doses; 2 active and 1 placebo dose; 1 active and 2 placebo doses; 3 placebo doses). Each patient received two capsules and one enema (either placebo or FMT) and were followed for 6 months. The primary outcome was FMT-related (serious) adverse events ([S]AEs)/AEs using intention-to-treat analysis. Secondary outcomes were HE recurrence, all-cause hospitalizations, death, donor engraftment, and quality-of-life. FMT was from a vegan or omnivorous donor.
Results: They enrolled 60 patients (15/group) with similar baseline characteristics. FMT was safe, with no FMT-related SAEs/AEs reported. Overall SAEs ($p = 0.96$) or death ($p = 1.0$) were similar. There were significant differences in HE recurrence between groups ($p = 0.035$, Cramer's V = 0.39). On post hoc analysis, recurrence

was highest in the all-placebo versus any FMT group (40% vs. 9%; odds ratio = 0.15, 95% CI: 0.04–0.64). Within the FMT groups, HE recurrence rates were similar regardless of route, doses, or donor type. Quality of life improved in FMT-recipient groups. Engraftment was highest in those with high pre-FMT *Lachnospiraceae* and lower in those whose HE recurred.

Conclusions: Fecal microbiota transplantation (FMT) was safe in patients with cirrhosis and hepatic encephalopathy (HE) on maximal therapy, with no FMT-related adverse events reported, regardless of dose, route, or donor type. On post hoc analysis, HE recurrence was highest in the placebo-only group and linked with lower baseline *Lachnospiraceae* and reduced donor engraftment.

J.S. Bajaj, Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University and Richmond VA Medical Center, Richmond, VA, USA, e-mail: jasmohan.bajaj@vcuhealth.org

DOI: 10.1016/j.jhep.2024.12.047 ■

Lancet Gastroenterol Hepatol. 2025;10(8):726-733

Cervoni JP, Weil D, Desmarets M, Lannes A, D'Alteroche L, Bouzbib C, Larrue H, Lemaitre E, Faure S, Latournerie M, Jézéquel C, Billioud C, Carbonell N, Saliba F, Tanné F, Hiriart JB, Olivier-Hourmand I, Nguyen Khac E, Archambeaud I, Hilleret MN, Oberti F, Elkrief L, Meunier L, Gerster T, Rode A, Bardou-Jacquet E, Robic MA, Ozenne V, Sacleux SC, Reboux N, Chermak F, Calame P, Borentain P, Thevenot T, Di Martino V, Thabut D, Louvet A, Rudler M, Bureau C;
Club Francophone pour l'Etude de l'Hypertension Portale, GAVAPROSEC study group

Pre-emptive TIPS for gastric variceal bleeding in patients with cirrhosis (GAVAPROSEC): An open-label randomised clinical trial

Background: In patients with cirrhosis, variceal glue obliteration is recommended for the treatment of acute fundal variceal bleeding, and for the prevention of rebleeding in combination with non-selective β blockers (NSBB). The authors evaluated the efficacy of pre-emptive transjugular intrahepatic portosystemic shunt (p-TIPS) in this setting.
Methods: This open-label randomised trial was conducted at 17 tertiary centres in France. Patients with cirrhosis and acute fundal variceal bleeding (excluding type 1 gastro-oesophageal varices), who achieved initial haemostasis with endoscopic glue injection and vasoactive therapy, and remained stable for at least 12 h, were randomly assigned to receive either a covered p-TIPS within 72 h or to continue with on-demand glue obliteration sessions combined with NSBB. Randomisation was centralised, stratified by centre, and performed in blocks of four (1:1 ratio). The primary composite endpoint was all-cause mortality or clinically significant rebleeding within 1 year. Analyses were conducted in the modified intention-to-treat (mITT) population.
Findings: Between January 3, 2019, and February 25, 2023, 292 patients were screened, of whom 105 were enrolled and randomly assigned. After excluding 2 patients who were randomly assigned by error and 2 who withdrew consent, 101 patients were included in the mITT population (mean age 58.2 years [SD 9.7], 81 [80%] male, 91 [90%] alcohol-related cirrhosis, mean MELD score 14.3 [SD 5.0]). Of these 101 patients, 47 were allocated to p-TIPS and 54 to glue obliteration and NSBB. The 1-year probability of being free from death or rebleeding was 77% (95% CI: 62–87) in the p-TIPS group versus 37% (24–50) in the glue obliteration and NSBB group (hazard ratio = 0.25 [95% CI: 0.12–0.51]; $p < 0.0001$). Rescue TIPS was required in 20 (37%) patients in the control group. Glue migration was reported in 8 patients (3 [6%] in the p-TIPS group and 5 [9%] in the control group). One case of cardiac decompensation occurred in the p-TIPS group. The 1-year cumulative incidence of hepatic encephalopathy was similar between groups (35% [95% CI: 21–49] vs. 32% [19–45]).

Interpretation: In patients with cirrhosis and acute bleeding from fundal varices, p-TIPS significantly reduced the risk of rebleeding or death at 1 year and should be considered as first-line therapy.

C. Bureau, Service d'Hépatologie, Hôpital Rangueil, CHU Toulouse, and Université de Toulouse, Toulouse, France, e-mail: bureau.c@chu-toulouse.fr

DOI: 10.1016/s2468-1253(25)00156-6 ■

EXPERT OPINION

PD Dr. Michael Schultheiß

Pre-emptive TIPS: now for gastric variceal bleeding

The fact that in liver cirrhosis with clinically significant portal hypertension, transjugular intrahepatic portosystemic shunts (TIPS) should be inserted at an earlier stage has gained increasing acceptance in recent years. An early milestone in this development was a study published in the *New England Journal of Medicine* in 2010 on the early use of TIPS following esophageal variceal bleeding (DOI: 10.1056/nejmoa0910102), which, together with follow-up studies, established "early" or "pre-emptive" TIPS within 72 hours of esophageal variceal bleeding in patients with advanced liver cirrhosis (≥ Child-Pugh B) as the current standard of care in hepatology.
Using a similar study design, the French GAVAPROSEC study group led by Christophe Bureau has now focused on gastric fundal variceal bleeding (GOV2 and IGV1 varices). Such a study was long overdue: endoscopic therapy for gastric varices is technically demanding even for experienced gastroenterologists, recurrent bleeding is common, and more than 40% of patients die within one year. Previous guideline recommendations supported TIPS placement only as secondary prophylaxis—after failure of conventional therapy consisting of endoscopic glue injection and non-selective beta-blockers (NSBB). However, this approach has increasingly been questioned in favor of earlier use of TIPS.
In my opinion, the study is excellently designed. Despite the relatively rare occurrence of gastric variceal bleeding, 292 patients were screened in 17 French centers

over just more than 4 years, and 101 patients were ultimately randomly assigned to the two comparison groups: 47 patients received pre-emptive TIPS (pTIPS), while 54 patients underwent on-demand glue obliteration sessions combined with NSBB. Baseline data show that 90% of enrolled patients, with Child-Pugh A to C liver function, had alcohol-related cirrhosis. Complications occurred more frequently during endoscopic therapy, with 13 bleeding episodes and 8 cases of glue migration (including those from initial treatments before randomization). When interpreting the results, however, it is important to note the selection of NSBB: rather than carvedilol, which achieves a greater reduction in portal pressure gradient (PPG), considerably more patients received propranolol (n = 41), with fewer receiving carvedilol (n = 8) or nadolol (n = 1).
Although overall survival did not show a statistically significant advantage (one-year survival 84% in the pTIPS group vs. 77%), there were notable advantages for the pTIPS group: the one-year rebleeding rates were 3/47 versus 24/54 cases, and the overall mortality rates were 7/47 versus 11/54 cases. The combined primary endpoint of one-year mortality and rebleeding showed a statistically significant advantage for the pTIPS cohort (37% vs. 77%, $p < 0.0001$). The rate of crossover is also striking, with 20 of 54 patients in the conventional group ultimately requiring TIPS due to rebleeding.
In summary, the study impressively demonstrates a reduction in rebleeding rates in gastric fundal varices with pTIPS compared to conventional therapy. However, the study reports on a selected cohort of patients with alcohol-related liver cirrhosis, most of whom were treated with propranolol instead of carvedilol in the control group. Therefore, further follow-up studies on this topic are urgently needed. ■

J Hepatol. 2025;83(3):682-691

Schleicher EM, Karbannek H, Weinmann-Menke J, Galle PR, Stallmach A, Gairing SJ, Zipprich A, Ripoll C, Labenz C

Effect of albumin treatment duration on response rates and outcomes in patients with cirrhosis and acute kidney injury

Background and aims: Guidelines recommended volume expansion with albumin for 48 hours for patients with cirrhosis and acute kidney injury (AKI) to correct hypovolemia and rule out prerenal AKI. A recent update in the ADQI-ICA consensus guidelines suggested shortening this duration to 24 hours, primarily based on expert opinion. This study aimed to evaluate the response rates to albumin treatment after 24 and 48 hours and to compare and assess the prognostic significance of three different definitions of response to albumin therapy.
Methods: Data from 127 prospectively recruited patients with cirrhosis and AKI from two German centers were analyzed. The authors examined three response definitions after 24 and 48 hours: (1) serum creatinine (SCr) decrease > 0.3 mg/dL, (2) SCr decrease > 25%, and (3) SCr decrease in at least one AKI stage. Follow-up was prolonged until liver transplantation, death or hemodialysis.
Results: Overall, 30–54% of the patients responded to albumin treatment depending on the definition, and response rates were balanced across AKI stages. Notably, a relevant number of patients who responded at 48 hours did not respond within the first 24 hours. Additional responses to albumin during the second 24 hours according to definitions 1, 2, and 3 were 28%, 22%, and 18%, respectively. Response according to definition 3 was associated with higher hemodialysis- and transplantation-free survival rates.

Conclusion: A substantial proportion of patients require 48 hours to respond to albumin treatment. Shortening the duration of albumin therapy may lead to overtreatment with terlipressin.

C. Labenz, Department of Internal Medicine I, University Medical Center of the Johannes Gutenberg-University, Mainz, Germany,
e-mail: christian.labenz@unimedizin-mainz.de

DOI: 10.1016/j.jhep.2025.03.008 ■

Liver Tumors

J Hepatol. 2025;83(2):426-439

Ding W, Meng Y, Ma J, Pang C, Wu J, Tian J, Yu J, Liang P, Wang K

Contrast-enhanced ultrasound-based AI model for multi-classification of focal liver lesions

Background and aims: Accurate multi-classification is a prerequisite for appropriate management of focal liver lesions (FLLs). Ultrasound is the most common imaging examination but lacks accuracy. Contrast-enhanced ultrasound (CEUS) offers better performance but is highly dependent on operator experience. Therefore, the authors aimed to develop a CEUS-based artificial intelligence (AI) model for FLL multi-classification and evaluate its performance in multicenter clinical tests.
Methods: From January 2017 to December 2023, CEUS videos, immunohistochemical biomarkers and clinical information on solid FLLs > 1 cm in adults were collected from 52 centers to build and test the model. The model was developed to classify FLLs into six types: hepatocellular carcinoma, hepatic metastasis, intrahepatic cholangiocarcinoma, hepatic hemangioma, hepatic abscess and others. First, Module-Disease, Module-Biomarker and Module-Clinic were built in training set A and a validation set. Then, three modules were aggregated as Model^{-DCB} in training set B and an internal test set. Model^{-DCB} performance was compared with CEUS and MRI radiologists in three external test sets.
Results: In total, 3,725 FLLs from 52 centers were divided into training set A (n = 2,088), the validation set (n = 592), training set B (n = 234), the internal test set (n = 110), and external test sets A (n = 113), B (n = 276) and C (n = 312). In external test sets A, B and C, Model^{-DCB} achieved significantly better performance (accuracy from 0.85 to 0.86) than junior CEUS radiologists (0.59–0.73), and comparable performance to senior CEUS radiologists (0.79–0.85) and senior MRI radiologists (0.82–0.86). In multiple subgroup analyses on demographic characteristics, tumor characteristics and ultrasound devices, its accuracy ranged from 0.79 to 0.92.

Conclusions: CEUS-based Model^{-DCB} provides accurate multi-classification of FLLs. It holds promise for a wide range of populations, especially those in remote areas who have difficulty accessing MRI.

K. Wang or J. Tian, CAS Key Laboratory of Molecular Imaging, Institute of Automation, Chinese Academy of Sciences, Beijing, China, e-mail: kun.wang@ia.ac.cn or e-mail: jie.tian@ia.ac.cn

or

J. Yu or P. Liang, Department of Interventional Ultrasound, Chinese PLA General Hospital, Beijing, China, e-mail: jiemi301@163.com or e-mail: liangping301@hotmail.com

DOI: 10.1016/j.jhep.2025.01.011

Gut. 2025;74(10):1667-1679

Ma L, Hung MH, Rashidi Mehrabadi F, Wang L, Li Q, Forgues M, Wang KC, Budhu A, Candia J, Chaisaingmongkol J, Rabibhadana S, Pupacdi B, Ruchirawat M, Wang XW

Beneficial infections of the enterovirus genus in patients with liver cancer

Background: Hepatocellular carcinoma (HCC) is a significant global cancer burden, with rising incidence and lacking a unified prevention strategy due to complex aetiologies. Viral exposures may shape host immunity via specific reactive viral antigens that could induce immune responses against hepatocarcinogenesis.
Objective: The authors aimed to characterise viral exposure differences between HCC patients and healthy individuals and identify potentially protective viral antigens against HCC.
Design: The authors profiled pan-viral serological antibody repertoires using a microbial phage library among 2,647 study subjects and examined the biological activities of selective viral antigens on blood-derived immune cells from both healthy individuals and HCC patients.
Result: The study identified 153 viral antigens with a significantly reduced serological response in HCC patients compared with healthy individuals. The authors also observed that a higher serological response to 153 viral antigens is associated with better clinical outcomes of patients with chronic liver diseases and HCC. These findings are consistent across different populations across sex, ethnicity and aetiology. The authors identified a common epitope (CE1) shared among 39% of reactive viral antigens that belong to the rhinovirus and enterovirus families. The study demonstrated that CE1 could induce both CD4$^+$ and CD8$^+$ T-cell activation and CD8$^+$ T-cell-mediated HCC cell killing.

Conclusions: The results suggest that past exposures to members of the Enterovirus genus may be advantageous for cancer patients, highlighting the potential for a viral peptide-based HCC vaccine.

X.W. Wang, Laboratory of Human Carcinogenesis, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA, e-mail: xw3u@nih.gov

DOI: 10.1136/gutjnl-2024-334681

Lancet. 2025;405(10492):1851-1864

Yau T, Galle PR, Decaens T, Sangro B, Qin S, da Fonseca LG, Karachiwala H, Blanc JF, Park JW, Gane E, Pinter M, Peña AM, Ikeda M, Tai D, Santoro A, Pizarro G, Chiu CF, Schenker M, He A, Chon HJ, Wojcik-Tomaszewska J, Verset G, Wang QQ, Stromko C, Neely J, Singh P, Jimenez Exposito MJ, Kudo M; CheckMate 9DW investigators

Nivolumab plus ipilimumab versus lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma (CheckMate 9DW): An open-label, randomised, phase 3 trial

Background: Patients with unresectable hepatocellular carcinoma have a poor prognosis, and treatments with long-term benefits are needed. The authors report results from the preplanned interim analysis of the CheckMate 9DW trial assessing nivolumab plus ipilimumab versus lenvatinib or sorafenib for unresectable hepatocellular carcinoma in the first-line setting.
Methods: This open-label, randomised, phase 3 trial enrolled patients aged 18 years or older with unresectable hepatocellular carcinoma without previous systemic therapy at 163 hospitals and cancer centres across 25 countries in Asia, Australia, Europe, North America, and South America. Patients had at least one measurable untreated lesion per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, a Child-Pugh score of 5 or 6, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were randomly assigned (1:1) via an interactive response technology system to receive nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) intravenously every 3 weeks for up to 4 doses, followed by nivolumab 480 mg every 4 weeks or investigator's choice of either oral lenvatinib (8 mg or 12 mg daily depending on body weight) or oral sorafenib (400 mg twice daily). Randomisation was stratified by aetiology; the presence of macrovascular invasion, extrahepatic spread, or both; and baseline alpha-fetoprotein concentration. The primary endpoint was overall survival, which was assessed in all randomly assigned patients; safety was an exploratory endpoint and was assessed in all randomly assigned patients who received at least one dose of study medication.
Findings: Between January 6, 2020, and November 8, 2021, 668 patients were randomly assigned to nivolumab plus ipilimumab (n = 335) or lenvatinib or sorafenib (n = 333). Early crossing of the overall survival Kaplan-Meier curves reflected a higher number of deaths during the first 6 months after randomisation with nivolumab plus ipilimumab (hazard ratio [HR] = 1.65 [95% CI: 1.12–2.43]) but was followed by a sustained separation of the curves thereafter in favour of nivolumab plus ipilimumab (0.61 [0.48–0.77]). After a median follow-up of 35.2 months (IQR, 31.1–39.9), overall survival was significantly improved with nivolumab plus ipilimumab versus lenvatinib or sorafenib (median 23.7 months [95% CI: 18.8–29.4] vs. 20.6 months [17.5–22.5]; HR = 0.79 [0.65–0.96]; two-sided stratified log-rank p = 0.018); respective overall survival rates were 49% (95% CI: 44–55) versus 39% (34–45) at 24 months and 38% (32–43) versus 24% (19–30) at 36 months. Overall, 137 (41%) of 332 patients receiving nivolumab plus ipilimumab and 138 (42%) of 325 patients receiving lenvatinib or sorafenib had grade 3–4 treatment-related

adverse events. 12 deaths were attributed to treatment with nivolumab plus ipilimumab and 3 were attributed to treatment with lenvatinib or sorafenib.

Interpretation: Nivolumab plus ipilimumab showed a significant overall survival benefit versus lenvatinib or sorafenib and manageable safety in patients with previously untreated unresectable hepatocellular carcinoma. These results support nivolumab plus ipilimumab as a first-line treatment in this setting.

P.R. Galle, University Medical Center,
I Medical Department, Mainz, Germany,
e-mail: peter.galle@unimedizinmainz.de

DOI: 10.1016/s0140-6736(25)00403-9

Hepatology. 2025;81(6):1714-1727

Scheiner B, Kang B, Balcar L, Radu IP, Reiter FP, Adžić G, Guo J, Gao X, Yuan X, Cheng L, Gorgulho J, Schultheiss M, Peeters F, Hucke F, Ben Khaled N, Piseddu I, Philipp A, Sinner F, D'Alessio A, Pomej K, Saborowski A, Bathon M, Schwacha-Eipper B, Zarka V, Lampichler K, Nishida N, Lee PC, Krall A, Saeed A, Himmelsbach V, Tesini G, Huang YH, Vivaldi C, Masi G, Vogel A, Schulze K, Trauner M, Djanani A, Stauber R, Kudo M, Parikh ND, Dufour JF, Prejac J, Geier A, Bengsch B, von Felden J, Venerito M, Weinmann A, Peck-Radosavljevic M, Finkelmeier F, Dekervel J, Ji F, Wang HW, Rimassa L, Pinato DJ, Bouattour M, Chon HJ, Pinter M

Outcome and management of patients with hepatocellular carcinoma who achieved a complete response to immunotherapy-based systemic therapy

Background and aims: The outcome of patients with HCC who achieved complete response (CR) to immune-checkpoint inhibitor (ICI)-based systemic therapies is unclear.
Approach and results: Retrospective study of patients with HCC who had CR according to modified Response Evaluation Criteria in Solid Tumors (CR-mRECIST) to ICI-based systemic therapies from 28 centers in Asia, Europe, and the United States. Of 3,933 patients with HCC treated with ICI-based noncurative systemic therapies, 174 (4.4%) achieved CR-mRECIST, and 97 (2.5%) had CR according to RECISTv1.1 (CR-RECISTv1.1) as well. The mean age of the total cohort (male, 85%; Barcelona-Clinic Liver Cancer-C, 70%) was 65.9 ± 9.8 years. The majority (83%) received ICI-based combination therapies. Median follow-up was 32.2 (95% CI: 29.9–34.4) months. One- and 3-year overall survival rates were 98% and 86%. One- and 3-year recurrence-free survival rates were excellent in patients with CR-mRECIST-only and CR-RECISTv1.1 (78% and 55%; 70% and 42%). Among patients who discontinued ICIs for reasons other than recurrence, those who received immunotherapy for ≥ 6 months after the first mRECIST CR had a longer recurrence-free survival than those who discontinued immunotherapy earlier ($p = 0.008$). Of 9 patients who underwent curative surgical conversion therapy, 8 (89%) had pathological CR (CR-RECISTv1.1, n = 2/2; CR-mRECIST-only, n = 6/7).

Conclusions: Overall survival and recurrence-free survival of patients with CR-mRECIST-only and CR-RECISTv1.1 were excellent, and 6 of 7 patients with CR-mRECIST-only who underwent surgical conversion therapy had pathological CR. Despite potential limitations, these findings support the use of mRECIST in the context of immunotherapy for clinical decision-making. When considering ICI discontinuation, treatment for at least 6 months beyond CR seems advisable.

M. Pinter, Division of Gastroenterology and Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria,
e-mail: matthias.pinter@meduniwien.ac.at

or

H.J. Chon, Division of Medical Oncology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Bundang-gu Seongnam, South Korea,
e-mail: minidoctor@cha.ac.kr

DOI: 10.1097/hep.0000000000001163

Gastroenterology. 2025;168(6):1170-1177.e12

Rhee H, Kim MJ, Kim DY, An C, Kang W, Han K, Roh YH, Han KH, Ahn SH, Choi JY, Park JY, Chung YE, Kim SU, Kim BK, Lee S, Lee HW, Lee JS

Noncontrast magnetic resonance imaging versus ultrasonography for hepatocellular carcinoma surveillance: A randomized, single-center trial

Background and aims: This study aimed to compare ultrasonography (US) and noncontrast magnetic resonance imaging (MRI) in the surveillance of hepatic malignancy.
Methods: The authors conducted a randomized, non-blinded trial at a single center in South Korea. Eligible individuals were aged 20 to 70 years with liver cirrhosis, Child-Pugh class A, and no history of liver cancer or other recent malignancy. Participants were randomized 1:1 to receive up to 10 semiannual surveillance using US or noncontrast MRI with serum alpha-fetoprotein testing. The primary endpoints were the detection rates of Barcelona Clinic Liver Cancer (BCLC) stage 0 or A tumors, stage distribution at initial diagnosis, and false-positive referral rates.
Results: From June 2015 to November 2017, 416 patients were screened, and 414 were enrolled and assigned to the US (n = 207) or MRI (n = 207) group. In total, 23 participants in the US group and 25 in the MRI group were diagnosed with liver cancer by November 2022. The detection rates of BCLC stage 0 or A tumors were not different between the US and MRI groups (7% [95% confidence interval {CI}: 4–11%] vs. 12% [8–17%]). BCLC stage 0 tumors were more frequently detected in the MRI group than in the US group (8% vs. 2%). The MRI group had earlier BCLC stage ($p = 0.014$) and lower false-positive referral rate (0.7% [95% CI: 0.4–1.2%] vs. 3.1% [2.3–4.1%], $p < 0.001$) compared with the US group.

Conclusions: Noncontrast MRI is a better alternative to US for the surveillance of cirrhotic patients offering earlier stage at initial diagnosis and lower false-positive referral rate.

M.-J. Kim, Department of Radiology, Yonsei University College of Medicine, Seodaemun-gu, Seoul, South Korea, e-mail: kimnex@yuhs.ac

or

D.Y. Kim, Department of Internal Medicine, Yonsei University College of Medicine, Seodaemun-gu, Seoul, South Korea, e-mail: dyk1025@yuhs.ac

DOI: 10.1053/j.gastro.2024.12.035 ■

J Hepatol. 2025;83(2):358-366

Knox JJ, McNamara MG, Bazin IS, Oh DY, Zubkov O, Breder V, Bai LY, Christie A, Goyal L, Cosgrove DP, Springfeld C, Sjoquist KM, Park JO, Verdaguer H, Braconi C, Ross PJ, De Gramont A, Shroff RT, Zalcberg JR, Palmer DH, Smith JR, Oelmann E, Bruce T, Valle JW

A phase 3 randomized study of first-line NUC-1031/cisplatin versus gemcitabine/cisplatin in advanced biliary tract cancer

Background and aims: The previous first-line standard of care for advanced biliary tract cancer (aBTC), gemcitabine/cisplatin, has modest efficacy. NUC-1031 is a phosphoramidate modification of gemcitabine. The authors report final analyses of the NuTide:121 study, designed to compare the efficacy of NUC-1031/cisplatin to gemcitabine/cisplatin in aBTC.
Methods: In this open-label, multicenter study, adult patients with treatment-naïve aBTC were randomized (1:1) to NUC-1031/cisplatin (n = 388) or gemcitabine/cisplatin (n = 385) on days 1 and 8 of 21-day cycles until disease progression or intolerance. Primary endpoints were overall survival (OS) and objective response rate (blinded independent central review). Three interim analyses (IA) and a final analysis were planned.
Results: Baseline characteristics were balanced; median age 65 years, 53% male, primary tumors: intrahepatic cholangiocarcinoma (CCA) (54%), extrahepatic CCA (21%), gallbladder cancer (21%) and ampullary cancer (5%). Enrollment stopped at IA1 as the OS futility boundary was crossed. At final data cut-off, median OS for NUC-1031/cisplatin versus gemcitabine/cisplatin was 9.2 months (95% CI: 8.3–10.4) versus 12.6 months (95% CI: 11.0–15.1) (HR = 1.79) and median PFS was 4.9 months (95% CI: 4.4–6.0) versus 6.4 months (95% CI: 6.1–7.4) (HR = 1.45). Objective response rate was higher for NUC-1031/cisplatin (18.7% vs. 12.4%; OR = 1.59; $p = 0.049$). The adverse event profile was similar between arms, except for hepatobiliary disorders (25% vs. 11%; higher with NUC-1031/cisplatin) and hematological events (48% vs. 65%; higher with gemcitabine/cisplatin). More patients met criteria for potential drug-induced liver injury (27% vs. 7%) and Hy's law (1.6% vs. 0.5%) with NUC-1031/cisplatin. Treatment exposure was lower for NUC-1031/cisplatin, likely due to early discontinuation for AEs (30% vs. 18%).

Conclusions: NuTide:121 was terminated early due to futility. NUC-1031/cisplatin did not set a new standard in first-line aBTC.

J.J. Knox, Princess Margaret Cancer Centre, Toronto, ON, Canada, e-mail: jennifer.knox@uhn.ca

DOI: 10.1016/j.jhep.2025.01.040 ■

Liver Transplantation

J Hepatol. 2025;83(3):729-737

Larson EL, Ellias SD, Blezek DJ, Klug J, Hartman RP, Ziller NF, Bamlet H, Mao SA, Perry DK, Nimma IR, Badurdeen D, Yang L, Leise MD, Watt KD, Diwan TS, Taner T, Rosen CD, Elli EF, Madura JA, Jadlowiec CC, Lizaola-Mayo B, Kellogg TA, Heimbach JK

Simultaneous liver transplant and sleeve gastrectomy provides durable weight loss, improves metabolic syndrome and reduces allograft steatosis

Background and aims: The prevalence of obesity and metabolic syndrome is rising among liver transplant (LT) candidates, many of whom have metabolic dysfunction-associated steatotic liver disease (MASLD). The authors aimed to determine the long-term impact of simultaneous LT and sleeve gastrectomy (LTSG) in patients with obesity transplanted for MASLD.
Methods: The authors analyzed patients undergoing LTSG using a single clinical protocol (n = 72), and patients with BMI > 30 who underwent LT alone for MASLD (n = 185) in a multicenter retrospective cohort study. Follow-up duration was 4–153 (median 41) months for LTSG and 12–161 (median 75) months for LT. Outcomes included mortality, graft loss, BMI, metabolic syndrome components, allograft steatosis and fibrosis.
Results: Mortality and graft loss were not significantly different between the LT and LTSG groups. The prevalence of diabetes was significantly lower in patients undergoing LTSG versus LT alone after 8 years of follow-up ($p < 0.05$), while hypertension decreased from 61.1% to 35.8% in the LTSG group ($p < 0.01$). Patients undergoing LTSG (average starting BMI of 45.5) experienced significant weight loss compared to baseline for > 9 years ($p < 0.001$), while no significant change was seen for the LT-alone group (average starting BMI 34.0). The incidence of allograft steatosis was significantly lower in the LTSG versus LT group ($p = 0.004$). The prevalence of fibrosis was reduced in the LTSG versus LT group 3–10 years postoperatively (relative risk ratio = 0.46; $p = 0.09$). One patient in the LTSG group had a gastric sleeve leak and one required hiatal hernia repair. Severe gastroesophageal reflux disease occurred in 11.1% of the LTSG group; risk factors included pre-existing diabetes and gastroesophageal reflux disease.

Conclusions: LTSG results in sustained weight loss, resolution of diabetes and hypertension, and reduced recurrence of steatosis and possibly fibrosis compared to LT alone. It confers no increase in mortality or graft loss.

J.K. Heimbach, William Von Liebig Center for Transplantation Mayo Clinic College of Medicine Rochester MN, USA, e-mail: heimbach.julie@mayo.edu

DOI: 10.1016/j.jhep.2025.02.030 ■

Hepatology. 2025;82(3):612-625

Xu E, Tabrizian P, Gutierrez J, Hoteit M, Ghaziani T, Zhou K, Parikh N, Ajmera V, Aby E, Shui A, Marino R, Martin A, Wong C, Kao K, Dave S, Florman S, Yao F, Mehta N

Downstaging of hepatocellular carcinoma before liver transplantation: Results from a national multicenter prospective cohort study

Background and aims: Patients with HCC meeting United Network for Organ Sharing (UNOS)-downstaging (DS) criteria have excellent post-liver transplantation (LT) outcomes. Studies on HCC beyond UNOS-DS criteria ("All-Comers" [AC]) have been limited by small sample size and short follow-up time, prompting this analysis.
Approach and results: 326 patients meeting UNOS-DS and 190 meeting AC criteria from 9 LT centers across 5 UNOS regions were enrolled from 2015 to 2023 and prospectively followed. Competing risk analysis and Kaplan-Meier method were used to evaluate DS and LT outcomes, and Fine-and-Gray and Cox models were used to identify predictors of outcomes. AC and UNOS-DS had similar median alpha-fetoprotein (15 vs. 12 ng/mL; $p = 0.08$), MELD (9 vs. 9; $p = 0.52$), and Child-Pugh (A vs. A; $p = 0.30$). Two years after the first local regional therapy, 82% of UNOS-DS and 66% of AC were successfully downstaged ($p < 0.001$). In AC, DS rates were 72% for tumor number plus diameter of largest lesion < 10, 51% for sum 10–12, and 39% for sum > 12 ($p = 0.01$). Yttrium-90 achieved higher DS success than transarterial chemoembolization in AC (74% vs. 65%; $p < 0.001$). 48% of UNOS-DS and 40% of AC underwent LT ($p = 0.10$). Five-year post-LT survival was similar between UNOS-DS and AC (74% vs. 72%; $p = 0.77$), although 5-year post-LT recurrence was higher in AC (30% vs. 14%; $p = 0.02$).

Conclusions: Despite higher HCC recurrence and lower intention-to-treat survival in AC, post-LT survival was comparable between UNOS-DS and AC. Yttrium-90 attained higher DS success than transarterial chemoembolization in AC. LT after DS is feasible in AC, though defining an upper limit in tumor burden may be necessary.

N. Mehta, Department of Medicine, University of California, San Francisco, San Francisco, CA, USA, e-mail: neil.mehta@ucsf.edu

DOI: 10.1097/hep.0000000000001231

TRANSLATIONAL SCIENCE CORNER

Liver

Nature. 2025;645(8080):507-517

Gautam J, Wu J, Lally JSV, McNicol JD, Fayyazi R, Ahmadi E, Oniciu DC, Heaton S, Newton RS, Rehal S, Bhattacharya D, Di Pastena F, Nguyen B, Valvano CM, Townsend LK, Banskota S, Batchuluun B, Jabile MJT, Payne A, Lu J, Desjardins EM, Kubota N, Tsakiridis EE, Mistry B, Aganostopoulos A, Houde V, Dansercoer A, Verschueren KHG, Savvides SN, Hammill JA, Bezverbnaya K, Muti P, Tsakiridis T, Dai W, Jiang L, Hoshida Y, Larché M, Bramson JL, Friedman SL, Verstraete K, Wang D, Steinberg GR

ACLY inhibition promotes tumour immunity and suppresses liver cancer

Immunosuppressive tumour microenvironments are common in cancers such as metabolic dysfunction-associated steatohepatitis (MASH)-driven hepatocellular carcinoma (HCC) (MASH-HCC). Although immune cell metabolism influences effector function, the effect of tumour metabolism on immunogenicity is less understood. ATP citrate lyase (ACLY) links substrate availability and mitochondrial metabolism with lipid biosynthesis and gene regulation. Although ACLY inhibition shows antiproliferative effects in various tumours, clinical translation has been limited by challenges in inhibitor development and compensatory metabolic pathways. Here, using a mouse model of MASH-HCC that mirrors human disease, genetic inhibition of ACLY in hepatocytes and tumours reduced neoplastic lesions by over 70%. To evaluate the therapeutic potential of this pathway, a novel small-molecule ACLY inhibitor, EVT0185 (6-[4-(5-carboxy-5-methyl-hexyl)-phenyl]-2,2-dimethylhexanoic acid), was identified via phenotypic screening. EVT0185 is converted to a CoA thioester in the liver by SLC27A2 and structural analysis by cryo-electron microscopy reveals that EVT0185-CoA directly interacts with the CoA-binding site of ACLY. Oral delivery of EVT0185 in three mouse models of MASH-HCC dramatically reduces tumour burden as monotherapy and enhances efficacy of current standards of care including tyrosine kinase inhibitors and immunotherapies. Transcriptomic and spatial profiling in mice and humans linked reduced tumour ACLY with increases in the chemokine CXCL13, tumour-infiltrating B cells and tertiary lymphoid structures. The depletion of B cells blocked the antitumour effects of ACLY inhibition.

Conclusion: Together, these findings illustrate how targeting tumour metabolism can rewire immune function and suppress cancer progression in MASH-HCC.

G.R. Steinberg, Centre for Metabolism, Obesity and Diabetes Research, Department of Medicine, McMaster University, Hamilton, ON, Canada,
e-mail: gsteinberg@mcmaster.ca

DOI: 10.1038/s41586-025-09297-0

EXPERT OPINION

Prof. Dr. Dr. Bertram Bengsch

Targeting ACLY-mediated lipogenesis in MASH-HCC enhances B cell-mediated antitumor immunity

The incidence of metabolic dysfunction-associated steatohepatitis (MASH)-driven hepatocellular carcinoma (HCC) is rising worldwide, driven by lifestyle-related cardiometabolic risk factors. There is clear evidence from mouse models of MASH-HCC that the etiology of HCC can shape the antitumor immune response and influence the results from checkpoint therapy regimen (DOI: 10.1038/s41586-021-03362-0). While precise definitions for MASH-HCC are lacking in published prospective clinical trials of checkpoint therapy, patients with viral etiology tend to have better responses than non-viral etiology patients, which includes patients with MASH-HCC (DOI: 10.1158/1078-0432.ccr-21-1258). However, the mechanisms linking metabolism, carcinogenesis, and antitumor immune responses remain poorly understood. A recently published study by Gautam et al. sheds light on the role of lipogenesis in HCC. The authors focused on ATP-citrate lyase (ACLY), a key metabolic enzyme that supports lipogenesis through its role in the citrate shuttle for the generation of cytosolic acetyl-CoA. The authors used a murine model combining chemical carcinogenesis (using diethylnitrosamine [DEN]) and high-fat, high-fructose "Western" diet (WD-DEN) to mimic human MASH-HCC. Control models included DEN alone and DEN-CCl4. The authors observed broad *ACLY* expression and the major histological hallmarks of MASH-HCC, such as macrovesicular and microvesicular steatosis, ballooning, Mallery-Denk bodies, and lymphocytic infiltration. In hepatocyte-targeted *Acly* knockout mice, the authors observed a marked reduction in ACLY expression, fatty acid levels, and tumor numbers, consistent with prior findings.
The authors performed a phenotypic screen in primary mouse hepatocytes. This led to the discovery of EVT0185, a small-molecule prodrug converted by SLC27A2-expressing cells (expressed in hepatocytes but not significantly in immune cells) into the active EVT0185-CoA thioester, which inhibits ACLY. EVT0185 effectively suppressed MASH-HCC development in the murine model and synergized with checkpoint blockade therapy (anti-PD-L1 and anti-VEGFR).
Multiplexed imaging analysis and single-cell and spatial transcriptomics revealed that ACLY inhibition induced the chemokine CXCL13 and promoted B-cell, particularly plasma cell, enrichment within the tumor microenvironment. Depletion studies demonstrated that B cells were essential for mediating tumor suppression. Indeed, *Acly*-deficient cancer cells proliferated unrestrained in immunodeficient hosts, indicating that the antitumor

effect of ACLY arises from the recruitment of B cell-mediated responses rather than direct inhibition of cancer growth or cytotoxicity.
The study highlights a metabolic link between lipogenesis in HCC cells and immunoregulation. This pathway is associated with MASH-HCC models and resembles features observed in human MASH-HCC. However, the study is inconclusive with respect to whether the mechanism is specific to MASH-HCC. Indeed, ACLY is also expressed in non-MASH HCC, suggesting that it may represent a broader therapeutic target across HCC etiologies. Indeed, previous Acly-focused studies in non-MASH HCC models have implicated ACLY inhibition in modulating resistance to tyrosine kinase inhibitor (TKI) therapy (e.g., DOI: 10.7150/jca.52778).
Targeting metabolic enzymes that are central to all human cells carries the risk of significant off-target effects. In particular, ACLY plays a critical role in supporting T-cell effector responses (DOI: 10.1084/jem.20231820). The development of a small-molecule ACLY inhibitor that, as a prodrug, is selectively activated in hepatocytes —but not in immune cells—via SLC27A2-dependent conversion offers a promising strategy for reducing off-target toxicity. The study also puts B cells into focus as potential mediators of antitumor activity in HCC. Interestingly, despite the observed synergy with T-cell dependent checkpoint therapy, the authors did not report a prominent role for T-cell responses following ACLY inhibition in their model. Of note, B cells have been identified as components of immune architecture neighborhoods enriched with CD8+ T cells, which are associated with improved responses to checkpoint therapy in patients (DOI: 10.1136/gutjnl-2024-332837). They are also found within tertiary lymphoid structures associated with therapeutic response in HCC (DOI: 10.1101/2023.10.16.562104). The authors did not investigate the contribution of B-cell interactions with T cells or other immune cells in further detail. It thus remains unclear how B cells mechanistically contribute to antitumor effects downstream of ACLY inhibition. The observed enrichment of plasma cells raises the possibility that local immunoglobulin production may be involved. Further studies are warranted to delineate the mediators of the immunosensitizing effect. Collectively, the findings reveal a cancer cell metabolism–immune crosstalk in MASH-HCC—that may be exploited to enhance tumor responsiveness to immunotherapy. ■

Gastrointestinal Oncology

Nature. 2025;644(8076):527-536

Dai Y, Aizenbud L, Qin K, Austin M, Jaycox JR, Cunningham J, Wang EY, Zhang L, Fischer S, Carroll SM, van Aggelen H, Kluger Y, Herold KC, Furchtgott L, Kluger HM, Ring AM

Humoral determinants of checkpoint immunotherapy

Although the role of cellular immunity in checkpoint immunotherapy (CPI) for cancer is well established, the effect of antibody-mediated humoral immunity is comparably underexplored. Here we used rapid extracellular antigen profiling to map the autoantibody reactome within a cohort of 374 patients with cancer treated with CPIs and 131 healthy control participants for autoantibodies to 6,172 extracellular and secreted proteins (the 'exoproteome'). Globally, patients with cancer treated with CPIs had diverse autoreactivities that were elevated relative to control individuals but changed minimally with treatment. Autoantibody signatures in patients treated with CPI strikingly distinguished them from healthy individuals. Although associations of specific autoantibodies with immune-related adverse events were sparse, we detected numerous individual autoantibodies that were associated with greatly altered odds ratios for response to therapy. These included autoantibodies to immunomodulatory proteins, such as cytokines, growth factors and immunoreceptors, as well as tumour surface proteins. Functional evaluation of several autoantibody responses indicated that they neutralized the activity of their target proteins, which included type I interferons (IFN-I), IL-6, OSM, TL1A, and BMPR1A and BMPR2. Modelling the effects of autoantibodies to IFN-I and TL1A in preclinical mouse tumour models resulted in enhanced CPI efficacy, consistent with their effects in patients.

In conclusion, these findings indicate that autoantibodies to the exoproteome modify CPI responses and highlight therapeutically actionable pathways that can be exploited to augment immunotherapy.

L. Furchtgott, Seranova Bio, South San Francisco, CA, USA, e-mail: leon@seranovabio.com

or

H.M. Kluger, Yale Cancer Center, New Haven, CT, USA, e-mail: harriet.kluger@yale.edu

or

A.M. Ring, Division of Translational Science and Therapeutics, Fred Hutchinson Cancer Center, Seattle, WA, USA, e-mail: aaronring@fredhutch.org

DOI: 10.1038/s41586-025-09188-4 ■

Congresses 2026

January 16–17, 2026, Frankfurt am Main + online
IBD D-A-CH Kongress
E-Mail: veranstaltungen@ced-service.de
E-Mail: office@ibd-dach.com
https://www.ibd-dach.com

January 19–21, 2026, Paris, France
First Annual Paris International Liver Meeting
E-Mail: contact@parislivermeeting.com
https://www.parislivermeeting.com/

January 22–24, 2026, Edinburgh, United Kingdom
EASL Liver Cancer Summit 2026
E-Mail: easloffice@easloffice.eu
https://www.easl.eu
https://easl.eu/event/liver-cancer-summit-2026/

January 22–24, 2026, Las Vegas, CA, USA
2026 Crohn's & Colitis Congress
Revolutionizing IBD Care
E-Mail: info@crohnscolitiscongress.org
Website: http://www.crohnscolitiscongress.org

February 4–8, 2026, Madonna Di Campiglio, Italy
Alpine Liver and Pancreatic Surgery Meeting (ALPS)
E-Mail: registration@alpshpbmeeting.org
http://www.alpshpbmeeting.org

February 5–6, 2026, Freiburg, Germany
Symposium
Next Gen Liver Immunology:
Bridging Basic Science and Clinical Practice
E-Mail: meeting@falkfoundation.org
https://falkfoundation.org

February 5–7, 2026, Düsseldorf, Germany
28th International Endoscopy Symposium
E-Mail: iesd@cocs.de
https://endo-duesseldorf.com

February 6–7, 2026, Freiburg, Germany
Annual Meeting 2026
42nd Annual Conference of the German Association for the Study of the Liver (GASL)
E-Mail: events@uhhmg.de
https://www.gasl.de
https://www.gasl.de/annual-meeting-2026/

February 11–13, 2026, Antwerp, Belgium
38th Belgian Week of Gastroenterology
E-Mail: info@bwge.be
http://www.bwge.be

February 18–21, 2026, Stockholm, Sweden
21st Congress of ECCO
Holistic IBD Care
E-Mail: ecco-congress@ecco-ibd.eu
https://www.ecco-ibd.eu
https://www.ecco-ibd.eu/ecco26

February 20–22, 2026, Freising, Germany
33rd Annual Meeting of the German Society for Neurogastroenterology and Motility
E-Mail: info@neurogastro.de
https://www.neurogastro.de

February 22–24, 2026, Edinburgh, United Kingdom
EASL Liver Cancer Summit 2026
E-Mail: easlsummit@easloffice.eu
http://www.easl.eu
https://easl.eu/event/liver-cancer-summit-2026/

February 26–28, 2026, Budapest, Hungary
EASL SLD Summit 2026
E-Mail: easloffice@easloffice.eu
https://www.easl.eu
Website: https://easl.eu/event/easl-sld-summit-2026/

February 27 – March 1, 2026, Toronto, ON, Canada
Joint CDDWTM-CLM Conference 2026
E-Mail: cddw-clm@mci-agency.com
https://www.cddw-clm.ca/

March 5–7, 2026, Freiburg, Germany
45th Annual Meeting of the German Pancreatic Club (DPC)
E-Mail: patrick.schreiber@conventus.de
https://dpc-conference.de/

March 14–15, 2026, Porto, Portugal
World Summit 2026
14th Annual Gut Microbiota for Health (GMFH)
E-Mail: gmfh@gastro.org
https://www.gutmicrobiotaforhealth.com/summit/

March 19–22, 2026, Miami, FL, USA
AHPBA 2026 Annual Meeting
E-Mail: ahpba@lp-etc.com
https://www.ahpba.org/future-meetings/

March 26–28, 2026, Incheon, Korea
HBP Surgery Week 2026
64th Annual Congress of the Korean Association of HBP Surgery
E-Mail: hbps@hbpsurgery.org
https://hbpsurgery.org

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:
Prof. Dr. Peter Hasselblatt, Deputy Director Department of Internal Medicine II
Prof. Dr. Tobias Böttler, Head of Gerok Liver Center

University Medical Center Freiburg, Hugstetter Str. 55, 79106 Freiburg, Germany

Scientific Collaboration:
Prof. Dr. Dr. Bertram Bengsch, Section Head for Translational Systems Immunology in Hepatogastroenterology
PD Dr. Armin Küllmer, Head of Endoscopy
Dr. Lena Sophie Mayer, Specialist Internal Medicine
Prof. Dr. Michael Quante, Head of Gastrointestinal Oncology
PD Dr. Michael Schultheiß, Head of the Interdisciplinary Ultrasound Center and Clinical Head of the TIPS Section

University Medical Center Freiburg, Department of Internal Medicine II, Hugstetter Str. 55, 79106 Freiburg, Germany

FSC www.fsc.org
MIX
Paper | Supporting responsible forestry
FSC® C084513

KNOWLEDGE DRIVES EVERYTHING

Falk Foundation – Scientific dialogue to advance therapeutic progress

Together we know more. Together we do more.

Falk Foundation e.V. | Leinenweberstr. 5 | 79108 Freiburg | Germany
www.falkfoundation.org | info@falkfoundation.org

FGRE126 1-11/2025 HOF