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Editorial

Dear colleagues,

What is the long-term prognosis for patients with **potential celiac disease** – i.e. those in whom transglutaminase antibodies have been detected but without duodenal changes? According to a meta-analysis, one-third of these patients consuming a gluten-containing diet develop villous atrophy and manifest celiac disease, while another third experience normalization of serology despite this diet. Most symptomatic patients with potential celiac disease respond well to a gluten-free diet (Shiha et al., p. 3). Neoadjuvant chemotherapy is the standard approach for perioperative care of **gastric cancer**. However, in recent years, the significance of **neoadjuvant radiochemotherapy** has been a topic of debate. As part of the TOPGEAR phase 3 trial, the addition of radiation to preoperative chemotherapy did not demonstrate a survival benefit in the treatment of resectable gastric or gastroesophageal junction cancer compared to chemotherapy alone (Leong et al. p. 5).

In the ARTEMIS UC phase 2 trial, treatment with **tulisokibart**, an antibody targeting **tumor necrosis factor-like cytokine 1A** (TL1A), resulted in significantly higher remission rates during induction therapy for **ulcerative colitis** compared to placebo (Sands et al., p. 14). TL1A is a key pro-inflammatory cytokine with pro-fibrogenic properties, and its multifaceted mechanism of action may play an important role in the future treatment of inflammatory bowel disease. For this reason, several TL1A antibodies are currently being evaluated in phase 3 trials for the treatment of ulcerative colitis and Crohn's disease. Patients with **steroid-refractory acute severe ulcerative colitis** are often given **higher doses** of **infliximab** at shorter intervals in order to optimize the therapeutic response. Now, this strategy has been called into question by the Australian PREDICT-UC trial, which found that a double dose of infliximab with shortened dosing intervals had no impact on clinical response or colectomy rates (Choy et al., p. 15).

Computer-aided detection (CADe) of polyps has been promoted in recent years as a key innovation for endoscopic **colorectal screening**. However, a multicenter trial found that incorporating CADe into colorectal screening resulted in only a minimal increase in the adenoma detection rate and rarely affected the recommended follow-up intervals, likely diminishing its overall added benefit (Sinonquel et al., p. 21). The efficacy of treatment with **checkpoint inhibitors** has been demonstrated in multiple treatment settings for microsatellite-instability-high (MSI-H) or mismatch-repair-deficient (dMMR) metastatic **colorectal cancer**. In a phase 3 trial, **first-line therapy** with nivolumab plus ipilimumab in patients with **metastatic** disease significantly improved progression-free survival (72%) at 24 months compared to standard chemotherapy (14%) (Andre et al., p. 19).

Patients with **pancreatic cancer** continue to show poor responses to chemotherapy. A proof-of-concept trial investigated the use of **organoids** derived from pancreatic cancer biopsies to **predict chemotherapy response**. After cultivation of the organoids, potentially effective chemotherapy treatments were identified in 91% of patients. Targeted therapy resulted in better overall survival outcomes compared to standard therapy (Boilève et al., p. 29).

Progress has also been reported in liver cancer therapy. A French research group identified tumor DNA in the blood of individuals with hepatocellular carcinoma. Longitudinal analyses of mutations in the tumor material and the blood from the same individuals revealed that **tumor-specific mutations in the circulation closely matched those in tumor tissue** and the changes in mutation burden correlated with treatment response and disease stage (Campani et al., p. 43).

The clinical benefits of determining quantitative HBsAg in individuals with chronic hepatitis B virus infection are becoming increasingly evident. A Chinese study developed a predictive model that estimates the likelihood of **HBsAg loss** with high accuracy through biannual measurement of quantitative HBsAg in individuals undergoing nucleos(t)ide analogue therapy (Fan et al., p. 31).

The utility of transient elastography may also improve in the future. A European multicenter study involving more than 400 individuals with chronic liver disease found that **spleen stiffness measurement** combined with body mass index and platelet count identified **clinically significant portal hypertension** as efficiently as liver stiffness measurement. The combination of liver and spleen stiffness measurement with body mass index and platelet count even outperformed currently available diagnostic models (Jachs et al., p. 42).

We hope you find these articles, along with the other publications summarized in this issue, both stimulating and informative. We also aim for this selection to be valuable in your daily clinical practice and to address relevant questions.

Yours sincerely,

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ESOPHAGUS TO SMALL INTESTINE

Celiac Disease, Gluten Sensitivity and Food Allergy

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Long-term cost-effectiveness of case finding and mass screening for celiac disease in children

Background and aims: Celiac disease (CD) is a common yet underdiagnosed autoimmune disease with substantial long-term consequences. High-accuracy point-of-care tests for CD antibodies conducted at youth primary health care centers may enable earlier identification of CD, but evidence about the cost-effectiveness of such strategies is lacking. The authors estimated the long-term cost-effectiveness of active case finding and mass screening compared with clinical detection in the Netherlands.
Methods: A decision tree and Markov model were used to simulate a cohort of 3-year-old children with CD according to each strategy, taking into account their impact on long-term costs (from a societal perspective) and quality-adjusted life-years (QALYs). Model parameters incorporated data from the GLUTENSCREEN project, the Dutch Celiac Society, the Dutch Pediatric Surveillance Unit, and published sources. The primary outcome was the incremental cost-effectiveness ratio (ICER) between strategies.
Results: Mass screening produced 7.46 more QALYs and was € 28,635 more costly compared with current care (ICER: € 3841 per QALY), and case finding produced 4.33 more QALYs and was € 15,585 more costly compared with current care (ICER: € 3603 per QALY). At a willingness to pay of € 20,000 per QALY, both strategies were highly cost-effective compared with current care. Scenario analyses indicated that mass screening is likely the optimal strategy, unless no benefit in detecting asymptomatic cases is assumed.

Conclusions: An earlier identification of celiac disease through screening or case finding in children using a point-of-care test leads to improved health outcomes and is cost-effective in the long-term compared with current care. If the feasibility and acceptability of the proposed strategies are successful, implementation in Dutch regular care is needed.

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Clinical outcomes of potential coeliac disease: A systematic review and meta-analysis

Objective: Potential coeliac disease (PCD) is characterised by positive serological and genetic markers of coeliac disease with architecturally preserved duodenal mucosa. The clinical outcomes and rates of progression to overt coeliac disease in patients with PCD remain uncertain. In this systematic review and meta-analysis, the authors aimed to evaluate the clinical outcomes of patients with PCD.
Design: The authors searched Medline, Embase, Scopus and Cochrane Library from 1991 through May 2024 to identify studies evaluating the clinical outcomes of patients with PCD. The progression rates to villous atrophy, seroconversion and response to a gluten-free diet (GFD) were analysed. A random-effect meta-analysis was performed, and the results were reported as pooled proportions with 95% confidence intervals (CIs).
Results: 17 studies comprising 1010 patients with PCD were included in the final analyses. The pooled prevalence of PCD among patients with suspected coeliac disease was 16% (95% CI: 10–22%). The duration of follow-up in most of the studies was at least 1 year, with follow-up periods within individual studies ranging from 5 months to 13 years. During follow-up, 33% (95% CI: 18–48%; I^2 = 96.4%) of patients with PCD on a gluten-containing diet developed villous atrophy, and 33% (95% CI: 17–48%; I^2 = 93.0%) had normalisation of serology. Among those who adhered to a GFD, 88% (95% CI: 79–97%; I^2 = 93.2%) reported symptomatic improvement.

Conclusion: Almost a third of patients with potential coeliac disease (PCD) develop villous atrophy over time, whereas a similar proportion experience normalisation of serology despite a gluten-containing diet. Most symptomatic patients benefit from a gluten-free diet. These findings highlight the importance of structured follow-up and individualised management for patients with PCD.

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Reflux

Laine L, Spechler S, Yadlapati R, Schnoll-Sussman F, Smith N, Leifke E, Harris T, Hunt B, Fass R, Katz P

Vonoprazan is efficacious for treatment of heartburn in non-erosive reflux disease: A randomized trial

Background and aims: Potassium-competitive acid blockers have documented efficacy for erosive esophagi-

tis. The authors performed a randomized trial in United States subjects diagnosed with non-erosive reflux disease of vonoprazan vs. placebo for 4 weeks, followed by a 20-week active-treatment extension.

Methods: Adult subjects with heartburn ≥ 4 days/week during screening without erosive esophagitis on endoscopy were randomized to placebo, vonoprazan 10 mg, or vonoprazan 20 mg. After 4 weeks, subjects on placebo were re-randomized to vonoprazan 10 mg or 20 mg, and those already on vonoprazan continued at the same dose for 20 weeks. Electronic diaries were completed twice daily. The primary endpoint was percentage of days without daytime or nighttime heartburn (24-hour heartburn-free days).

Results: Among 772 randomized subjects, the percentage of 24-hour heartburn-free days was 27.7% for placebo vs. 44.8% for vonoprazan 10 mg (least squares mean difference, 17.1%; p < 0.0001) and 44.4% for vonoprazan 20 mg (least squares mean difference, 16.7%; p < 0.0001). Differences in percentage of subjects with a 24-hour heartburn-free day for vonoprazan 10 mg vs. placebo and vonoprazan 20 mg vs. placebo were 8.3% and 11.6% on day 1 and 18.1% and 23.2% on day 2. The mean/median percentages of 24-hour heartburn-free days over the extension period were similar across the 4 study arms: 61–63% / 76–79%.

Conclusions: Vonoprazan reduced heartburn symptoms in subjects diagnosed with non-erosive reflux disease, with the benefit appearing to begin as early as the first day of therapy. Treatment effect persisted after the initial 4-week placebo-controlled period throughout the 20-week extension period. The 2 vonoprazan doses (10 mg and 20 mg) were similar in efficacy.

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EoE

Strauss Starling A, Ren Y, Li H, Spergel JM, Muir AB, Lynch KL, Liacouras CA, Falk GW

Reducing eosinophil counts in eosinophilic esophagitis in children is associated with reduction in later stricture development

Introduction: There are limited longitudinal data on the impact of chronic therapy on the natural history of eosinophilic esophagitis (EoE), a chronic allergic disease of the esophagus. The purpose of this study was to evaluate if patients with well-controlled EoE were less likely to develop fibrostenotic complications.

Methods: Subjects were identified from a database of pediatric patients with EoE at the Children's Hospital of Philadelphia started in 2000. Patients were then searched in adult medical records to identify patients who transitioned care. All office visits, emergency department visits, and endoscopic, histologic, and imaging reports were reviewed for the primary outcome of strictures and the secondary outcomes of food

impactions and dysphagia. Cox proportional hazard regression was performed for outcomes.

Results: 105 patients were identified with the mean follow-up of 11.4 ± 4.9 years. 52.3% (n = 55) had a period of histologic disease control defined as ≥ 2 consecutive endoscopies with histologic remission. These patients were less likely to develop strictures compared with patients who did not have a period of histologic control (hazard ratio [HR] = 0.232; 95% confidence interval [CI]: 0.084–0.64, p = 0.005). Patients who were diagnosed at younger ages were less likely to develop strictures. Presentation with dysphagia or impaction was associated with higher rate of stricture development.

Discussion: In this cohort study with > 10 years of follow-up, children with eosinophilic esophagitis with a period of histologic disease control and diagnosed at younger ages were less likely to develop esophageal strictures. While this suggests histologic remission is associated with reduction of remodeling complications, additional prospective data with long-term follow-up are needed.

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Gastritis and Helicobacter pylori

Olmedo L, Calvet X, Gené E, Bordin DS, Voynovan I, Castro-Fernandez M, Pabón-Carrasco M, Keco-Huerga A, Perez-Aisa Á, Lucendo AJ, Rodrigo L, Sarsenbaeva AS, Khlinov IB, Fadieienko G, Zaytsev O, Lanas Á, Martínez-Domínguez SJ, Alfaro E, Jonaitis L, Núñez Ó, Pellicano R, Hernández L, Gridnyev O, Kupcinskas J, Gasbarrini A, Boltin D, Niv Y, Babayeva G, Marcos-Pinto R, Tepes B, Venerito M, Papp V, Lerang F, Leja M, Phull PS, Marlicz W, Doulberis M, Smith SM, Milivojevic V, Kunovsky L, Mestrovic A, Matysiak-Budnik T, Simsek H, Cano-Català A, Puig I, Moreira L, Parra P, Nyssen OP, Megraud F, O'Morain C, Gisbert JP; Hp-EuReg investigators

Evolution of the use, effectiveness and safety of bismuth-containing quadruple therapy for *Helicobacter pylori* infection between 2013 and 2021: Results from the European registry on *H. pylori* management (Hp-EuReg)

Background: Bismuth quadruple therapies (BQTs) including bismuth, a proton pump inhibitor (PPI) and 2 antibiotics have been shown to be highly effective for treating *Helicobacter pylori* infection even in areas of high bacterial antibiotic resistance.

Objective: To describe the time trends of use, effectiveness and safety of BQT in Europe using the European Registry on *Helicobacter pylori* Management (Hp-EuReg).

Design: Patients registered in the Hp-EuReg from 2013–2021 who had received BQT were included. The

regimens prescribed, the number of eradication attempts, effectiveness, adherence and safety were analysed. The effectiveness was assessed by modified intention to treat (mITT). Time-trend and multivariate analyses were performed to determine variables that predicted treatment success.

Results: Of the 49,690 patients included in the Hp-EuReg, 15,582 (31%) had received BQT. BQT use increased from 8.6% of all treatments in 2013 to 39% in 2021. Single-capsule BQT – containing bismuth, metronidazole and tetracycline – plus a PPI (single-capsule BQT, ScBQT) was the most frequent treatment mode (43%). Schemes that obtained an effectiveness above 90% were the 10-day ScBQT and 14-day BQT using tetracycline plus metronidazole, or amoxicillin plus either clarithromycin or metronidazole. Only ScBQT achieved above 90% cure rates in all the geographical areas studied. Using the ScBQT scheme, adherence, the use of standard or high-dose PPIs, 14-day prescriptions and the use of BQT as first-line treatment were significantly associated with higher mITT effectiveness.

Conclusion: The use of bismuth quadruple therapy (BQT) increased notably in Europe over the study period. A 10-day single-capsule BQT was the scheme that most consistently achieved optimal effectiveness.

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Screening for *Helicobacter pylori* to prevent gastric cancer: A pragmatic randomized clinical trial

Importance: Effects of screening for *Helicobacter pylori* on gastric cancer incidence and mortality are unknown.
Objective: To evaluate the effects of an invitation to screen for *H. pylori* on gastric cancer incidence and mortality.
Design, setting, and participants: A pragmatic randomized clinical trial of residents aged 50–69 years in Changhua County, Taiwan, eligible for biennial fecal immunochemical tests (FIT) for colon cancer screening. Participants were randomized to either an invitation for *H. pylori* stool antigen (HPSA) + FIT assessment or FIT alone. The study was conducted between January 1, 2014, and September 27, 2018. Final follow-up occurred December 31, 2020.
Intervention: Invitation for testing for *H. pylori* stool antigen.
Main outcomes and measures: The primary outcomes were gastric cancer incidence and gastric cancer mortality. All invited individuals were analyzed according to the groups to which they were randomized.
Results: Of 240,000 randomized adults (mean age, 58.1 years [standard deviation {SD}, 5.6]; 46.8% female),

63,508 were invited for HPSA + FIT, and 88,995 were invited for FIT alone. Of the 240,000 randomized, 38,792 who were unreachable and 48,705 who did not receive an invitation were excluded. Of those invited, screening participation rates were 49.6% (31,497/63,508) for HPSA + FIT and 35.7% (31,777/88,995) for FIT alone. Among 12,142 participants (38.5%) with positive HPSA results, 8664 (71.4%) received antibiotic treatment, and eradication occurred in 91.9%. Gastric cancer incidence rates were 0.032% in the HPSA + FIT group and 0.037% in the FIT-alone group (mean difference, -0.005% [95% confidence interval {CI}: -0.013–0.003%]; p = 0.23). Gastric cancer mortality rates were 0.015% in the HPSA + FIT group and 0.013% in the FIT-alone group (mean difference, 0.002% [95% CI: -0.004–0.007%]; p = 0.57). After adjusting for differences in screening participation, length of follow-up, and patient characteristics in post hoc analyses, an invitation for HPSA + FIT was associated with lower rates of gastric cancer (0.79 [95% CI: 0.63–0.98]) but not with gastric cancer mortality (1.02 [95% CI: 0.73–1.40]), compared with FIT alone. Among participants who received antibiotics, the most common adverse effects were abdominal pain or diarrhea (2.1%) and dyspepsia or poor appetite (0.8%).

Conclusions and relevance: Among residents of Taiwan, an invitation to test for *Helicobacter pylori* stool antigen (HPSA) combined with fecal immunochemical testing (FIT) did not reduce rates of gastric cancer or gastric cancer mortality, compared with an invitation for FIT alone. However, when differences in screening participation and length of follow-up were accounted for, gastric cancer incidence, but not gastric cancer mortality, was lower in the HPSA + FIT group, compared with FIT alone.

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Barrett's Esophagus, Esophageal and Gastric Cancer

Leong T, Smithers BM, Michael M, Haustermans K, Wong R, Gebski V, O'Connell RL, Zalcberg J, Boussioutas A, Findlay M, Willis D, Moore A, Murray WK, Lordick F, O'Callaghan C, Swallow C, Darling G, Miller D, Strickland A, Liberman M, Mineur L, Simes J; Australasian Gastro-Intestinal Trials Group, National Health and Medical Research Council Clinical Trials Centre, Trans-Tasman Radiation Oncology Group, European Organisation for Research and Treatment of Cancer, Canadian Cancer Trials Group

Preoperative chemoradiotherapy for resectable gastric cancer

Background: In Western countries, the current standard of care for resectable gastric cancer is perioperative chemotherapy. Preoperative chemoradiotherapy has been considered, but data are limited regarding this

treatment as compared with perioperative chemotherapy alone.

Methods: The authors conducted an international, phase 3 trial in which patients with resectable adenocarcinoma of the stomach or gastroesophageal junction were randomly assigned to receive preoperative chemoradiotherapy plus perioperative chemotherapy or perioperative chemotherapy alone (control). In both groups, patients received either epirubicin, cisplatin, and fluorouracil or fluorouracil, leucovorin, oxaliplatin, and docetaxel both before and after surgery; the preoperative-chemoradiotherapy group also received chemoradiotherapy (45 Gy in 25 fractions of radiation, plus fluorouracil infusion). The primary end point was overall survival, and secondary end points included progression-free survival, pathological complete response, toxic effects, and quality of life.

Results: A total of 574 patients underwent randomization at 70 sites in Australasia, Canada, and Europe: 286 to the preoperative-chemoradiotherapy group and 288 to the perioperative-chemotherapy group. A higher percentage of patients in the preoperative-chemoradiotherapy group than in the perioperative-chemotherapy group had a pathological complete response (17% vs. 8%) and greater tumor downstaging after resection. At a median follow-up of 67 months, no significant between-group differences in overall survival or progression-free survival were noted. The median overall survival was 46 months with preoperative chemoradiotherapy and 49 months with perioperative chemotherapy (hazard ratio for death = 1.05; 95% confidence interval: 0.83–1.31), and the median progression-free survival was 31 months and 32 months, respectively. Treatment-related toxic effects were similar in the two groups.

Conclusions: The addition of preoperative chemoradiotherapy to perioperative chemotherapy did not improve overall survival as compared with perioperative chemotherapy alone among patients with resectable gastric and gastroesophageal junction adenocarcinoma.

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EXPERT OPINION

Prof. Dr. Michael Quante

Chemotherapy or Chemoradiotherapy? The Current State of Neoadjuvant Therapy of the Gastroesophageal Junction and Gastric Cancer

Standard neoadjuvant therapy for gastric cancer is based on perioperative chemotherapy, which reduces tumor volume, treats micrometastases, and improves the R0 resection rate. However, the role of radiotherapy (RT) in the neoadjuvant treatment of resectable adenocarcinomas of the stomach and gastroesophageal junction (GEJ) remains controversial.

For GEJ carcinomas, the combination of neoadjuvant chemoradiotherapy (NACRT), surgical resection, and adjuvant chemotherapy has traditionally been applied. Recent studies, however, have questioned this approach. The Neo-AEGIS trial demonstrated equivalence between preoperative chemotherapy with ECF (epirubicin, cisplatin, and 5-FU) and preoperative chemoradiotherapy with carboplatin/paclitaxel. Additionally, the ESOPEC study showed the superiority of perioperative FLOT therapy (5-FU, leucovorin, oxaliplatin, and docetaxel) to preoperative chemoradiotherapy with carboplatin/paclitaxel.

In the context of neoadjuvant therapy for gastric cancer, a meta-analysis of 7 randomized controlled trials (601 patients) comparing NACRT with NACT revealed significant advantages of NACRT: higher R0 resection rates, improved pathological complete response rates (pCR), and longer median survival – with comparable adverse effects and postoperative complications. These findings supported the notion that chemoradiotherapy plays an important role in the neoadjuvant treatment of gastric cancer.

The phase 3 TOPGEAR trial examined the benefit of NACRT in addition to perioperative chemotherapy compared to perioperative chemotherapy alone in 574 patients with resectable gastric (65%) or GEJ (35%) adenocarcinoma. Preoperative therapy consisted of either chemotherapy alone or a sequence of preoperative chemotherapy followed by chemoradiotherapy (4500 cGy with capecitabine or 5-FU). All patients received adjuvant chemotherapy after surgery. NACRT significantly increased the proportion of patients with pCR (17% vs. 8%) and tumor downstaging but did not lead to improved overall survival (46 months vs. 49 months; hazard ratio = 1.05; 95% confidence interval: 0.83–1.31) or progression-free survival (31 months vs. 32 months). Adverse effects and severe surgical complications (≥ grade 3) were comparable between the groups. The results of the TOPGEAR trial indicate that adding radiotherapy to preoperative chemotherapy in resectable gastric and GEJ carcinomas does not provide a survival benefit. Combined with the findings of the Neo-AEGIS and ESOPEC trials, perioperative chemotherapy, particularly with FLOT, is recommended as the standard treatment. The use of chemoradiotherapy should be limited to patients who cannot undergo surgery. Future analyses may identify specific subgroups that could benefit from NACRT. Advances in molecular tumor characterization, as well as in radiotherapy and surgical techniques, may also enable personalized approaches in the future. ■

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Comparison of EMR versus endoscopic submucosal dissection for Barrett's neoplasia and esophageal adenocarcinoma: A systematic review and meta-analysis

Background and aims: Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are both accepted resection strategies for Barrett's esophagus-related neoplasia and esophageal adenocarcinoma (EAC). However, a lack of consensus exists regarding which technique offers superior outcomes. This study aims to systematically review the evidence

comparing EMR versus ESD in treating Barrett's neoplasia and EAC.

Methods: The authors searched 3 databases (Embase, MEDLINE, Cochrane Central) through October 2023. They included studies comparing the efficacy of EMR and ESD for Barrett's neoplasia and EAC. Primary outcomes include en bloc, R0, and curative resection; complete remission of dysplasia (CRD), and local recurrence. Secondary outcomes encompass adverse events.

Results: The search identified 905 records. Eleven studies were included in the final analyses. Data showed significantly higher en bloc resection rates with ESD (odds ratio [OR] = 31.53; 95% confidence interval [CI]: 10.02–99.19; p < 0.01; 7 studies). R0 resection rates were significantly higher with ESD (OR = 5.92; 95% CI: 2.75–12.77; p < 0.01; 8 studies). Curative resection rates tended to be higher with ESD (OR = 3.49; 95% CI: 0.86–14.14; p = 0.080; 4 studies). There was no significant difference in CRD rates (OR = 0.92; 95% CI: 0.37–2.26; p = 0.86; 3 studies). Local recurrence rates tended to be lower with ESD (OR = 0.35; 95% CI: 0.11–1.04; p = 0.058; 10 studies). As for adverse events, there was no significant difference in bleeding, perforation, and postoperative stricture rates.

Conclusions: This systematic review and meta-analysis demonstrates that endoscopic submucosal dissection (ESD) achieves higher en bloc, R0, and curative resection rates, with a tendency toward lower recurrence rates. These results suggest that ESD may be a more effective option for managing Barrett's neoplasia and esophageal adenocarcinoma.

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Randon G, Lonardi S, Fassan M, Palermo F, Tamberi S, Giommoni E, Ceccon C, Di Donato S, Fornaro L, Brunetti O, De Vita F, Bittoni A, Chini C, Spallanzani A, Nappo F, Bethaz V, Strippoli A, Latiano T, Cardellino GG, Giuliani F, Morano F, Niger M, Raimondi A, Prisciandaro M, Pircher CC, Sciortino C, Marchesi S, Garattini SK, Airò G, Miceli R, Di Bartolomeo M, Pietrantonio F

Ramucirumab plus paclitaxel as switch maintenance versus continuation of first-line oxaliplatin-based chemotherapy in patients with advanced HER2-negative gastric or gastro-oesophageal junction cancer (ARMANI): A randomised, open-label, multicentre, phase 3 trial

Background: Paclitaxel plus ramucirumab is recommended as a second-line treatment regimen in patients with advanced HER2-negative gastric or gastro-oesophageal junction cancer. The authors aimed to assess whether switch maintenance or early second-line therapy with paclitaxel plus ramucirumab improved outcomes compared with continuation of oxaliplatin and fluoropyrimidine doublet chemotherapy as a first-line strategy.

Methods: ARMANI was a multicentre, open-label, randomised, phase 3 trial done in 31 hospitals in Italy. The authors enrolled patients aged 18 years or older with an Eastern Cooperative Oncology Group performance status of 0 or 1 and locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction cancer, who had disease control after 3 months of FOLFOX (leucovorin, fluorouracil, and oxaliplatin) or CAPOX (capecitabine and oxaliplatin). Patients were randomly assigned (1:1) to either paclitaxel 80 mg/m^2 on days 1, 8, and 15 plus ramucirumab at 8 mg/kg on days 1 and 15 every 28 days intravenously (switch maintenance group) or continuation of oxaliplatin-based doublet chemotherapy (FOLFOX or CAPOX) for an additional 12 weeks, followed by fluoropyrimidine monotherapy maintenance (control group). Randomisation was stratified by previous gastrectomy (no vs. yes), peritoneal carcinomatosis (yes vs. no), and primary tumour location (gastro-oesophageal junction vs. gastric). Treatment group allocation was done using a web-based system with a minimisation algorithm implementing a random component. The primary endpoint was progression-free survival, analysed on an intention-to-treat basis. The safety population included patients who received at least 1 dose of the study treatment.

Findings: Between January 1, 2017, and October 2, 2023, 280 patients were randomly assigned to receive paclitaxel plus ramucirumab (switch maintenance group; n = 144) or to continue FOLFOX or CAPOX (control group; n = 136). All patients were White. 180 (64%) of 280 patients were male and 100 (36%) were female. At a median follow-up of 43.7 months (interquartile range [IQR], 24.0–57.9), 253 (90%) of 280 patients had a progression-free survival event: 131 (91%) of 144 patients in the switch maintenance group and 122 (90%) of 136 patients in the control group. Median progression-free survival was 6.6 months (95% confidence interval [CI]: 5.9–7.8) in the switch maintenance group and 3.5 months (2.8–4.2) in the control group (hazard ratio [HR] = 0.61, 95% CI: 0.48–0.79; p = 0.0002). The assumption of proportional hazards was violated; in an analysis of 24-month restricted mean survival time, restricted mean progression-free survival was 8.8 months (95% CI: 7.7–9.9) in the switch maintenance group and 6.1 months (5.0–7.2) in the control group (p = 0.0010). The most frequent grade 3–4 treatment-related adverse events were neutropenia (37 [26%] patients in the switch maintenance group vs. 13 [10%] patients in the control group), peripheral neuropathy (8 [6%] vs. 9 [7%]) and arterial hypertension (9 [6%] vs. none). Serious adverse events occurred in 28 (20%) of 141 patients in the experimental group and 15 (11%) of 135 patients in the control group; these events were treatment-related in 2 (1%) patients in the switch maintenance group (pulmonary embolism) and 2 (1%) patients in the control group (mucositis and anaemia). No treatment-related deaths occurred.

Interpretation: Paclitaxel and ramucirumab switch maintenance could be a potential treatment strategy in patients with advanced HER2-negative gastric or gastro-oesophageal junction cancer who are not eligible for immunotherapy or targeted agents.

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Nutrition and Obesity

Li Y, Jia X, Li C, Sun H, Nie S, Giovannucci EL, Liu L

The global incident gastrointestinal cancers attributable to suboptimal diets from 1990 to 2018

Background and aims: The contribution of suboptimal diets to gastrointestinal (GI) cancer incidence globally remains unquantified, and this study aimed to evaluate it.
Methods: Comprehensive meta-analyses and rigorous evidence-grading assessment identified the associations between suboptimal diets and 6 GI cancers and their subtypes. A comparative risk assessment model was used to estimate the proportional attributable burden and attributable rate of GI cancers to suboptimal diets by using the corroborative association estimates. In addition, correlation assessments with the Socio-demographic Index were carried out.
Results: In 2018, 21.5% (95% uncertainty interval, 19.1–24.5%) of incident GI cancer cases globally were attributable to suboptimal diets, maintaining a relatively stable proportion since 1990 (22.4%; 19.7–25.6%), whereas the absolute diet-attributable cases doubled from 580,862 (510,658–664,076) in 1990 to 1,039,877 (923,482–1,187,244) in 2018. Excessive processed meat consumption (5.9%; 4.2–7.9%), insufficient fruit intake (4.8%; 3.8–5.9%), and insufficient whole grain intake (3.6%; 2.8–5.1%) were the most significant dietary risk factors in 2018, a shift from 1990 when the third major concern was insufficient nonstarchy vegetable intake. In addition, Central and Eastern Europe and Central Asia experienced the highest attributable burden across

regions in both 1990 (31.6%; 27.0–37.4%) and 2018 (31.6%; 27.3–36.5%), and a positive correlation (p < 0.001) between the Sociodemographic Index and the attributable GI cancer incidence was observed.

Conclusions: Although the proportional attributable gastrointestinal incidence remains relatively stable, the doubling of absolute cases from 1990 to 2018, along with the discrepancies among urbanicity and countries/regions, informs dietary priorities and more targeted preventive measures.

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Rodriguez PJ, Goodwin Cartwright BM, Gratzl S, Brar R, Baker C, Gluckman TJ, Stucky NL

Semaglutide versus tirzepatide for weight loss in adults with overweight or obesity

Importance: Although tirzepatide and semaglutide were shown to reduce weight in randomized clinical trials, data from head-to-head comparisons in populations with overweight or obesity are not yet available.
Objective: To compare on-treatment weight loss and rates of gastrointestinal adverse events (AEs) among adults with overweight or obesity receiving tirzepatide or semaglutide labeled for type 2 diabetes (T2D) in a clinical setting.
Design, setting, and participants: In this cohort study, adults with overweight or obesity receiving semaglutide or tirzepatide between May 2022 and September 2023 were identified using electronic health record (EHR) data linked to dispensing information from a collective of US health care systems. On-treatment weight outcomes through November 3, 2023, were assessed. Adults with overweight or obesity and regular care in the year before initiation, no prior glucagon-like peptide-1 receptor agonist use, a prescription within 60 days prior to initiation, and an available baseline weight were identified. The analysis was completed on April 3, 2024.
Exposures: Tirzepatide or semaglutide in formulations labeled for T2D, on or off label.
Main outcomes and measures: On-treatment weight change in a propensity score-matched population, assessed as hazard of achieving 5% or greater, 10% or greater, and 15% or greater weight loss, and percentage change in weight at 3, 6, and 12 months. Hazards of gastrointestinal AEs were compared.
Results: Among 41,222 adults meeting the study criteria (semaglutide, 32,029; tirzepatide, 9193), 18,386 remained after propensity score matching. The mean (standard deviation, SD) age was 52.0 (12.9) years, 12,970 were female (70.5%), 14,182 were White (77.1%), 2171 Black (11.8%), 354 Asian (1.9%), 1679 were of other or unknown race, and 9563 (52.0%) had T2D. The mean (SD) baseline weight was 110 (25.8) kg. Follow-up was ended by discontinuation for 5140 patients (55.9%) receiving tirzepatide and 4823 (52.5%) receiving semaglutide. Patients receiving tirzepatide were significantly more likely to achieve weight loss (≥ 5%; hazard ratio [HR] = 1.76, 95% confidence interval [CI]: 1.68–1.84; ≥ 10%; HR = 2.54; 95% CI: 2.37–2.73; and ≥ 15%; HR = 3.24; 95% CI: 2.91–3.61). On-treatment changes in weight were larger for patients receiving tirzepatide at 3 months (difference, -2.4%; 95% CI: -2.5% to -2.2%), 6 months (difference, -4.3%; 95% CI: -4.7% to -4.0%), and 12 months (difference, -6.9%; 95% CI: -7.9% to -5.8%). Rates of gastrointestinal AEs were similar between groups.

Conclusions and relevance: In this population of adults with overweight or obesity, use of tirzepatide was associated with significantly greater weight loss than semaglutide. Future study is needed to understand differences in other important outcomes.

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Upper and Middle Gastrointestinal Bleeding

El Hajj W, Nahon S, Fares E, Quentin V, Grasset D, Arpurt JP, Skinazi F, Vitte RL, Costes L, Remy AJ, Locher C, Macaigne G; ANGH for the SANGHRIA Study Group

Prophylactic proton pump inhibitors in upper gastrointestinal bleeding: Impact and underprescription in a French multicentric cohort

Background: Appropriate prescription of proton pump inhibitors (PPIs) remains an important concern amid the rising overuse. A gap exists in the literature regarding the benefit of PPI prophylaxis and the consequences of underprescription in patients at risk for upper gastrointestinal bleeding (UGIB).
Aims: This study aims to describe the characteristics of hemorrhage in relation to PPI use in patients experiencing UGIB, with a focus on high-risk individuals requiring gastroprotection.
Methods: Data from a French multicentric cohort of patients experiencing UGIB were analyzed. Patients using PPI were compared to those without PPI considering bleeding etiologies and outcomes of peptic ulcer disease (PUD)-related hemorrhage. The rate of PPI use and its effect on bleeding characteristics in high-risk populations, defined based on international guidelines, were also assessed.
Results: Among 2497 included patients, 31.1% were on PPI at bleeding onset. PPI users exhibited a significantly lower rate of PUD-related bleeding in comparison with those without PPI (24.7% vs. 40.8%, respectively, p < 0.0001). Similar difference was observed in high-risk populations, of whom only 40.3% had gastroprotection with PPI before bleeding onset. PPI prophylaxis, however, did not influence the severity of bleeding in the general study population or in high-risk groups. Multivariate analysis identified age, comorbidities, and having more than 2 anti-thrombotic agents as predictors of severe bleeding.

Conclusions: Proton pump inhibitor (PPI) users appear to have a lower rate of bleeding ulcers compared to non-users. However, underprescription in high-risk groups raises the need for standardized care to ensure appropriate PPI use.

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Endoscopy of the Upper GI Tract

Alkabbani W, Suissa K, Gu KD, Cromer SJ, Paik JM, Bykov K, Hobai I, Thompson CC, Wexler DJ, Patorno E

Glucagon-like peptide-1 receptor agonists before upper gastrointestinal endoscopy and risk of pulmonary aspiration or discontinuation of procedure: Cohort study

Objective: To assess whether use of glucagon-like peptide-1 (GLP-1) receptor agonists before upper gastrointestinal endoscopy is associated with increased risk of pulmonary aspiration or discontinuation of the procedure compared with sodium-glucose cotransporter-2 (SGLT-2) inhibitors.
Design: Cohort study.
Setting: Two deidentified US commercial healthcare databases.
Participants: 43,365 adults (≥ 18 years) with type 2 diabetes who used a GLP-1 receptor agonist or SGLT-2 inhibitor within 30 days before upper gastrointestinal endoscopy.
Main outcome measures: The primary outcome was pulmonary aspiration on the day of or the day after endoscopy, defined using diagnostic codes. The secondary outcome was discontinuation of endoscopy. Risk ratios and corresponding 95% confidence intervals (CIs) were estimated after fine stratification weighting based on propensity score.
Results: After weighting, 24,817 adults used a GLP-1 receptor agonist (mean age 59.9 years; 63.6% female) and 18,537 used an SGLT-2 inhibitor (59.8 years; 63.7% female). Among users of GLP-1 receptor agonists and SGLT-2 inhibitors, the weighted risk per 1000 people was, respectively, 4.15 and 4.26 for pulmonary aspiration and 9.79 and 4.91 for discontinuation of endoscopy. Compared with SGLT-2 inhibitor use, GLP-1 receptor agonist use was not associated with an increased risk of pulmonary aspiration (pooled risk ratio [RR] = 0.98, 95% confidence interval [CI]: 0.73–1.31), although it was associated with a higher risk for discontinuation of endoscopy (pooled RR = 1.99, 95% CI: 1.56–2.53).

Conclusions: In this comparative cohort study, no increased risk of pulmonary aspiration during upper gastrointestinal endoscopy was observed among adults with type 2 diabetes using glucagon-like peptide-1 (GLP-1) receptor agonists compared with sodium-glucose cotransporter-2 (SGLT-2) inhibitors within 30 days of the procedure; however, GLP-1 receptor agonists were associated with a higher risk of discontinuation of endoscopy, possibly owing to a higher risk of retained gastric content. In the absence of evidence from randomized trials, these findings could inform future practice recommendations on the preprocedural protocol for patients requiring endoscopy.

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Crohn's Disease

Alsoud D, Sabino J, Franchimont D, Cremer A, Busschaert J, D'Heygere F, Bossuyt P, Vijverman A, Vermeire S, Ferrante M

Real-world effectiveness and safety of risankizumab in patients with moderate to severe multirefractory Crohn's disease: A Belgian multicentric cohort study

Background: As real-world data on risankizumab in patients with moderate to severe Crohn's disease (CD) are scarce, the authors evaluated its effectiveness and safety in multirefractory Belgian patients.
Methods: Data from consecutive adult CD patients who started risankizumab before April 2023 were retrospectively collected at 6 Belgian centers. Clinical remission and response were defined using the 2-component patient-reported outcome. Endoscopic response was defined as a decrease in baseline Simple Endoscopic Score with ≥ 50%. Both effectiveness end points were evaluated at week 24 and/or 52, while surgery-free survival and safety were assessed throughout follow-up.
Results: A total of 69 patients (56.5% female, median age 37.2 years, 85.5% exposed to ≥ 4 different advanced therapies and 98.6% to ustekinumab, 14 with an ostomy) were included. At week 24, 61.8% (34/55) and 18.2% (10/55) of patients without an ostomy achieved steroid-free clinical response and remission, respectively. At week 52, these numbers were 58.2% (32/55) and 27.3% (15/55), respectively. Endoscopic data were available in 32 patients, of whom 50.0% (16/32) reached endoscopic response within the first 52 weeks. Results in patients with an ostomy were similar (steroid-free clinical response and remission, 42.9% and 14.3%, respectively). During a median follow-up of 68.3 weeks, 18.8% (13/69) of patients discontinued risankizumab, and 20.3% (14/69) of patients underwent CD-related intestinal resections. The estimated surgery-free survival at week 52 was 75.2%. No new safety issues were observed.

Conclusions: In this real-world cohort of multirefractory Crohn's disease patients, risankizumab was effective in inducing both clinical remission and endoscopic response. Risankizumab was well tolerated with no safety issues.

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Tyrode G, Lakkis Z, Vernerey D, Falcoz A, Clairet V, Alibert L, Koch S, Vuitton L

KONO-S anastomosis is not superior to conventional anastomosis for the reduction of postoperative endoscopic recurrence in Crohn's disease

Background: Surgical resection rates remain high in Crohn's disease (CD). Reducing postoperative recurrence (POR) is challenging. Besides drug therapy, the surgical anastomosis technique may reduce POR. The authors aimed to compare the endoscopic POR rate after Kono-S versus standard ileocolic anastomosis.

Methods: The study included all consecutive CD patients operated on for ileocolic resection with a Kono-S anastomosis between February 2020 and March 2022. These patients were prospectively followed, and colonoscopy was performed 6–12 months after surgery. Patients were compared with a historical cohort of patients operated on with a conventional anastomosis in the same center. The primary end point was endoscopic POR (Rutgeerts score ≥ i2). Factors associated with POR were assessed by univariate and multivariable analyses.

Results: A total of 85 patients were included, 30 in the Kono-S group and 55 in the control group. At baseline, there was no significant difference between the 2 groups regarding CD characteristics or known POR risk factors, including previous exposure to biologics. At 6–12 months, endoscopic POR rate did not differ significantly between groups (56.7% in the Kono-S group vs. 49.1% in the control group; $p = 0.50$), nor did endoscopic POR according to the modified Rutgeerts score ≥ i2b (46.7% in the Kono-S group vs. 40% in the control group; $p = 0.55$). Severe endoscopic POR rates were 23.3% and 18.2% in each group, respectively. Clinical recurrence rate was similar in both groups, and no recurrent surgery occurred. By multivariable analysis, the type of anastomosis was not associated with endoscopic POR (odds ratio [OR] = 1.229; 95% confidence interval [CI]: 0.461–3.274, $p = 0.68$); however, postoperative treatment with anti-TNF was (OR = 0.337; 95% CI: 0.131–0.865 $p = 0.02$).

Conclusions: Kono-S anastomosis was not associated with a reduced rate of endoscopic postoperative recurrence. These results warrant confirmation in prospective, randomized, multicenter studies.

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KNOWLEDGE DRIVES EVERYTHING

Falk Foundation – Scientific dialogue to advance therapeutic progress

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Symposium 241 | Oxford (United Kingdom)

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ALL ASPECTS OF FIBROSIS

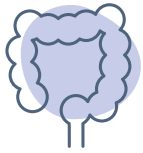Workshop | Berlin (Germany)

October 24–25, 2025

ADVANCES IN HEPATOLOGY – FROM MECHANISTIC INSIGHTS TO NOVEL THERAPEUTIC CONCEPTS

Symposium 242 | Berlin (Germany)

Ulcerative Colitis, Crohn's Colitis

Croft A, Okano S, Hartel G, Lord A, Walker G, Tambakis G, Radford-Smith G

A personalised algorithm predicting the risk of intravenous corticosteroid failure in acute ulcerative colitis

Background: An episode of acute ulcerative colitis (UC) represents an important watershed moment in a patient's disease course.
Aims: To derive a personalised algorithm for identifying patients at high risk of corticosteroid non-response from variables available at hospital presentation using a large prospectively collected acute UC patient database and machine learning-based techniques.
Methods: The authors analysed data from 682 consecutive presentations of acute UC. They used an Akaike information criterion-based elastic net model to select variables based on the 419 earliest presentations of acute UC (1996–2017). They constructed 2 risk-scoring algorithms, with and without utilising additional endoscopic variables, using logistic regression models. They validated these risk scores on separate cohorts of 181 (2018–2022) and 82 (2015–2022) acute UC presentations.
Results: The partial risk of rescue (ROR) score included the admission indices of oral corticosteroid treatment, bowel frequency ≥ 6/24 h, albumin, CRP ≥ 12 mg/mL and $\log_{10}$CRP. The full ROR score incorporates the same variables with the addition of the Mayo endoscopic subscore and disease extent. The AUCs in the main validation cohort were 0.76 (95% confidence interval [CI]: 0.69–0.83) and 0.78 (95% CI: 0.71–0.85) for the partial and full ROR scores, respectively.

Conclusions: These pragmatic personalised risk scores (available at www.severecolitis.com) have comparably strong performance characteristics and usability enabling the identification of individuals at high risk of corticosteroid non-response before or after endoscopic assessment. The risk of rescue scores have the potential to challenge conventional acute ulcerative colitis treatment paradigms by identifying patients who may benefit from early rescue therapy or participation in relevant clinical trials.

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Does surgery before pregnancy in women with inflammatory bowel disease increase the risk of adverse maternal and fetal outcomes? A Danish national cohort study

Introduction: Up to 15% of women with Crohn's disease (CD) or ulcerative colitis (UC) undergo bowel surgery before pregnancy, and there is little data on pregnancy outcomes in this population. The authors aimed to assess maternal/fetal outcomes in women with CD or UC who underwent surgeries before pregnancy.
Methods: In this nationwide study, the authors included all pregnancies in women with CD or UC from 1997 to 2022 and examined 6 categories of CD and UC surgeries before pregnancy. They used multilevel logistic regression to compute crude and adjusted odds ratios (aOR) with 95% confidence intervals (CI) for the risk of pregnancy and offspring complications in women who did, versus did not, undergo surgery before pregnancy.
Results: There were 833 UC and 3150 CD pregnancies with prior surgery and 12,883 UC and 6972 CD pregnancies without surgery. For UC, prior surgery was associated with Cesarian section (C-section) (ileoanal pouch: aOR = 20.03 [95% CI: 10.33–38.83]; functional ileostomy: aOR = 8.55 [6.10–11.98]; diverting ileostomy: aOR = 38.96 [17.05–89.01]) and preterm birth (aOR = 2.25 [1.48–3.75]; 3.25 [2.31–4.59]; and 2.17 [1.17–4.00]) respectively. For CD and prior intestinal surgery, the risks of C-section (aOR = 1.94 [1.66–2.27]), preterm birth (aOR = 1.30 [1.04–1.61]), and low 5-minute Apgar (aOR = 1.95 [95% CI: 1.07–3.54]) increased and premature rupture of membranes (aOR = 0.68 [0.52–0.89]) decreased. For CD with only prior perianal surgery, the risk of C-section (aOR = 3.02 [2.31–3.95]) increased and risk of gestational hypertension/preeclampsia/eclampsia (aOR = 0.52 [0.30–0.89]) decreased.

Discussion: Providers should be aware there is an increased likelihood of Cesarian section and certain perinatal complications in patients with Crohn's disease or ulcerative colitis surgery before pregnancy.

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The natural history after ileal pouch-anal anastomosis for ulcerative colitis: A population-based cohort study from the United States

Introduction: There are limited data regarding the natural history after ileal pouch-anal anastomosis (IPAA) for ulcerative colitis (UC). The principal objectives of

this study were to identify 4 key outcomes in the natural history after IPAA within 1, 3, 5, and 10 years: the incidence of pouchitis, Crohn's-like disease of the pouch, use of advanced therapies after IPAA, and pouch failure requiring excision in a network of electronic health records.

Methods: The authors performed a retrospective cohort study in TriNetX, a research network of electronic health records. In addition to evaluating incidence rates, they also sought to identify factors associated with pouchitis and advanced therapy use within 5 years of IPAA after 1:1 propensity score matching, expressed as adjusted hazard ratios (aHRs).

Results: Among 1331 patients who underwent colectomy with IPAA for UC, the incidence of pouchitis increased from 58% in the first year after IPAA to 72% at 10 years after IPAA. After propensity score matching, nicotine dependence (aHR = 1.61, 95% confidence interval [CI]: 1.19–2.18), anti-tumor necrosis factor therapy (aHR = 1.33, 95% CI: 1.13–1.56), and vedolizumab prior to colectomy (aHR = 1.44, 95% CI: 1.06–1.96) were associated with an increased risk of pouchitis in the first 5 years after IPAA. The incidence of Crohn's-like disease of the pouch increased to 10.3% within 10 years of IPAA while pouch failure increased to 4.1%. The incidence of advanced therapy use peaked at 14.4% at 10 years after IPAA.

Discussion: The incidence of inflammatory conditions of the pouch remains high in the current era, with 14% of patients requiring advanced therapies after ileal pouch-anal anastomosis.

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Gargallo-Puyuelo CJ, Ricart E, Iglesias E, de Francisco R, Gisbert JP, Taxonera C, Mañosa M, Aguas Peris M, Navarrete-Muñoz EM, Sanahuja A, Guardiola J, Mesonero F, Rivero Tirado M, Barrio J, Vera Mendoza I, de Castro Parga L, García-Planella E, Calvet X, Martín Arranz MD, García S, Sicilia B, Carpio D, Domenech E, Gomollón F; ENEIDA registry of GETECCU

Sex-related differences in the phenotype and course of inflammatory bowel disease: SEXEII study of ENEIDA

Background and aims: The impact of patient sex on the presentation of inflammatory bowel disease (IBD) has been poorly evaluated. The present study aimed to assess potential disparities in IBD phenotype and progression between sexes.

Methods: The authors performed an observational multicenter study that included patients with Crohn's disease (CD) or ulcerative colitis from the Spanish Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales registry. Data extraction was conducted in July 2021.

Results: A total of 51,595 patients with IBD were included, 52% were males and 25,947 had CD. The median follow-up period after diagnosis was 9 years in males and 10 years in females. In CD, female sex was an independent risk factor for medium disease onset (age, 17–40 y) (relative risk ratio [RR] = 1.45; 95% confidence interval [CI]: 1.31–1.62), later disease onset (age, > 40 y) (relative RR = 1.55; 95% CI: 1.38–1.73), exclusive colonic involvement (odds ratio [OR] = 1.24; 95% CI: 1.14–1.34), inflammatory behavior (OR = 1.14; 95% CI: 1.07–1.21), and extraintestinal manifestations (OR = 1.48; 95% CI: 1.38–1.59). However, female sex was a protective factor for upper gastrointestinal involvement (OR = 0.84; 95% CI: 0.79–0.90), penetrating behavior (OR = 0.76; 95% CI: 0.70–0.82), perianal disease (OR = 0.77; 95% CI: 0.71–0.82), and complications (OR = 0.73; 95% CI: 0.66–0.80). In ulcerative colitis, female sex was an independent risk factor for extraintestinal manifestations (OR = 1.48; 95% CI: 1.26–1.61). However, female sex was an independent protective factor for disease onset from age 40 onward (relative RR = 0.76; 95% CI: 0.66–0.87), left-sided colonic involvement (relative RR = 0.72; 95% CI: 0.67–0.78), extensive colonic involvement (relative RR = 0.59; 95% CI: 0.55–0.64), and abdominal surgery (OR = 0.78; 95% CI: 0.69–0.88).

Conclusions: There is sexual dimorphism in inflammatory bowel disease. The patient's sex should be taken into account in the clinical management of the disease.

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Sands BE, Feagan BG, Peyrin-Biroulet L, Danese S, Rubin DT, Laurent O, Luo A, Nguyen DD, Lu J, Yen M, Leszczyszyn J, Kempiński R, McGovern DPB, Ma C, Ritter TE, Targan S; ARTEMIS-UC Study Group

Phase 2 trial of anti-TL1A monoclonal antibody tulisokibart for ulcerative colitis

Background: Tulisokibart is a tumor necrosis factor-like cytokine 1A (TL1A) monoclonal antibody in development for the treatment of moderately to severely active ulcerative colitis. A genetic-based diagnostic test was designed to identify patients with an increased likelihood of response.

Methods: The authors randomly assigned patients with glucocorticoid dependence or failure of conventional or advanced therapies for ulcerative colitis to receive intravenous tulisokibart (1000 mg on day 1 and 500 mg at weeks 2, 6, and 10) or placebo. Cohort 1 included patients regardless of status with respect to the test for likelihood of response. Cohort 2 included only patients with a positive test for likelihood of response. The primary analysis was performed in cohort 1; the primary end point was clinical remission at week 12. Patients with a positive test for likelihood of response from cohorts 1 and 2 were combined in prespecified analyses.

Results: In cohort 1, a total of 135 patients underwent randomization. A significantly higher percentage of patients who received tulisokibart had clinical remission than those who received placebo (26% vs. 1%; difference, 25 percentage points; 95% confidence interval [CI]: 14–37; p < 0.001). In cohort 2, a total of 43 patients

underwent randomization. A total of 75 patients with a positive test for likelihood of response underwent randomization across both cohorts. Among patients with a positive test for likelihood of response (cohorts 1 and 2 combined), clinical remission occurred in a higher percentage of patients who received tulisokibart than in those who received placebo (32% vs. 11%; difference, 21 percentage points; 95% CI: 2–38; p = 0.02). Among all the enrolled patients, the incidence of adverse events was similar in the tulisokibart and placebo groups; most adverse events were mild to moderate in severity.

Conclusions: In this short-term trial, tulisokibart was more effective than placebo in inducing clinical remission in patients with moderately to severely active ulcerative colitis.

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EXPERT OPINION

Prof. Dr. Peter Hasselblatt

TL1A – A Novel Therapeutic Target for IBD

Innovative therapies for the treatment of inflammatory bowel disease (IBD) primarily focus on the inhibition of pro-inflammatory cytokines, lymphocyte trafficking, or lymphocyte activation. Inhibiting the pro-inflammatory cytokine tumor necrosis factor (TNF)-like ligand 1a (TL1A) represents a novel and particularly promising approach. The cytokine TL1A belongs to the TNF superfamily and exerts its effect by binding to death receptor 3 (DR3). TL1A is expressed in the inflamed intestine, where it activates the innate immune system in synergy with IL-23 and stimulates the adaptive immune system. This activation leads to the release of TNF and IFN-γ by T lymphocytes. Additionally, TL1A has pro-fibrogenic functions. Several monoclonal antibodies against TL1A are currently being investigated in clinical trials for IBD therapy. Two phase 2 trials with the TL1A antibody RVT-3101 have demonstrated good efficacy and tolerability during induction therapy for ulcerative colitis (UC, TUSCANY studies). The efficacy of RVT-3101 is currently under investigation in phase 3 trials for the treatment of UC and Crohn's disease. In contrast, the ARTEMIS-UC study presented here investigated the efficacy of the monoclonal TL1A antibody tulisokibart (PRA23) to treat UC in a phase 2 trial. The current publication reports results of the induction therapy after 12 weeks. Of the patients treated with tulisokibart, 26% achieved clinical remission with very good tolerability compared to (a notable) 1% with placebo during this period. Unfortunately, this report does not include data on maintenance therapy, leaving the long-term efficacy uncertain. It also raises the question of whether TL1A inhibition is useful and effective even after failure of TNF antibody treatment. In the ARTEMIS-UC trial, only approximately half of the patients had been pre-treated with biologics, making it difficult to draw conclusions on this issue due to the small number of cases. Interest-ingly, however, an exploratory biomarker was incorporated into the study program to identify patients with a higher probability of responding to TL1A inhibition. In this subgroup, too, the remission rates were higher with tulisokibart than with placebo. However, it remains unclear whether this biomarker is suitable for identifying patients with an increased probability of a clinical response. Despite these uncertainties, integrating personalized medicine approaches into early clinical trials is highly commendable and could influence future therapeutic algorithms. With ongoing trials, we can look forward to additional results on the potential of TL1A inhibition for treating IBD in the future. ■

Choy MC, Li Wai Suen CFD, Con D, Boyd K, Pena R, Burrell K, Rosella O, Proud D, Brouwer R, Gorelik A, Liew D, Connell WR, Wright EK, Taylor KM, Pudipeddi A, Sawers M, Christensen B, Ng W, Begun J, Radford-Smith G, Garg M, Martin N, van Langenberg DR, Ding NS, Beswick L, Leong RW, Sparrow MP, De Cruz P

Intensified versus standard dose infliximab induction therapy for steroid-refractory acute severe ulcerative colitis (PREDICT-UC): An open-label, multicentre, randomised controlled trial

Background: The optimal dosing strategy for infliximab in steroid-refractory acute severe ulcerative colitis (ASUC) is unknown. The authors compared intensified and standard dose infliximab rescue strategies and explored maintenance therapies following infliximab induction in ASUC.

Methods: In this open-label, multicentre, randomised controlled trial, patients aged 18 years or older from 13 Australian tertiary hospitals with intravenous steroid-refractory ASUC were randomly assigned (1:2) to receive a first dose of 10 mg/kg infliximab or 5 mg/kg infliximab (randomisation 1). Block randomisation was used and stratified by history of thiopurine exposure and study site, with allocation concealment maintained via computer-generated randomisation. Patients in the 10 mg/kg group (intensified induction strategy [IIS]) received a second dose at day 7 or earlier at the time of non-response; all patients in the 5 mg/kg group were re-randomised between day 3 and day 7 (1:1; randomisation 2) to a standard induction strategy (SIS) or accelerated induction strategy (AIS), resulting in 3 induction groups. Patients in the SIS group received 5 mg/kg infliximab at weeks 0, 2, and 6, with an extra 5 mg/kg dose between day 3 and day 7 if no response. Patients in the AIS group received 5 mg/kg infliximab at weeks 0, 1, and 3, with the week 1 dose increased to 10 mg/kg and given between day 3 and day 7 if no response. The primary outcome was clinical response by day 7 (reduction in Lichtiger score to < 10 with a decrease of ≥ 3 points from baseline, improvement in rectal bleeding, and decreased stool frequency to ≤ 4 per day). Secondary end points assessed outcomes to day 7 and exploratory outcomes compared induction regimens until month 3. From month 3, maintenance therapy was selected based on treatment experience, with use of thiopurine monotherapy, combination infliximab and thiopurine, or infliximab monotherapy, with follow-up as a cohort study up to month 12. Analysis was by intention to treat.

Findings: Between July 20, 2016, and September 24, 2021, 138 patients were randomly assigned (63 female [46%] and 75 male [54%]); 46 received a first dose of 10 mg/kg infliximab and 92 received 5 mg/kg infliximab. After randomisation 1, the authors observed no significant difference in the proportion of patients who had a clinical response by day 7 between the 10 mg/kg and 5 mg/kg groups (30/46 [65%] vs. 56/92 [61%], p = 0.62; risk ratio adjusted for thiopurine treatment history = 1.06 [95% confidence interval: 0.94–1.20], p = 0.32). The authors found no significant differences in secondary end points including time to clinical response or change in Lichtiger score from baseline to day 7. Two patients who received 10 mg/kg infliximab underwent colectomy in the first 7 days compared with no patients in the 5 mg/kg group (p = 0.21). Three serious adverse events occurred in 3 patients in both the 10 mg/kg group and 5 mg/kg group. After randomisation 2, the proportions of patients with clinical response at day 14 (34/46 [74%] in the IIS group, 35/48 [73%] in the AIS group, and 30/44 [68%] in the SIS group, p = 0.81), clinical remission at month 3 (23 [50%], 25 [52%], 21 [48%], p = 0.92), steroid-free remission at month 3 (19 [41%], 20 [42%], 18 [41%], p = 1.0), endoscopic remission at month 3 (21 [46%], 22 [46%], 21 [48%], p = 0.98), and colectomy at month 3 (3/45 [7%], 9/47 [19%], 5/43 [12%], p = 0.20) were not significantly different between groups. Between day 8 and month 3, the proportion of patients with at least 1 infectious adverse event possibly related to infliximab was 2 of 46 (4%) in the IIS group, 8 of 48 (17%) in the AIS group, and 8 of 44 (18%) in the SIS group (p = 0.082). No deaths occurred in the study.

Interpretation: Infliximab is a safe and effective rescue therapy in acute severe ulcerative colitis (ASUC). In steroid-refractory ASUC, a first dose of 10 mg/kg infliximab was not superior to 5 mg/kg infliximab in achieving clinical response by day 7. Intensified, accelerated, and standard induction regimens did not result in a significant difference in clinical response by day 14 or in remission or colectomy rates by month 3.

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Comparative risk of serious infection with vedolizumab versus anti-tumor necrosis factor in inflammatory bowel disease: Results from nationwide Swedish registers

Introduction: The authors aimed to assess the risk of serious infection in patients with inflammatory bowel disease (IBD) treated with vedolizumab compared with those treated with anti-tumor necrosis factors (TNF) and the general population.
Methods: In this Swedish cohort study, treatment episodes were identified from nationwide health registers. The authors used Cox regression with propensity score-matched cohorts to estimate hazard ratios (HRs) for incident serious infections, defined as infections requiring hospital admission.
Results: During 1376 treatment episodes in Crohn's disease, the rate of serious infections per 100 person-years (PY) was 5.18 (95% confidence interval [CI]: 3.98–6.63) with vedolizumab versus 3.54 (95% CI: 2.50–4.85) with anti-TNF; HR = 1.72 (95% CI: 1.12–2.65), partly explained by more gastrointestinal infections. Compared with the rate of 0.75/100 PY (95% CI: 0.59–0.92) in a matched general population cohort, vedolizumab demonstrated higher risk (HR = 7.00; 95% CI: 5.04–9.72). During 1294 treatment episodes in ulcerative colitis, the corresponding rates were 3.74/100 PY (95% CI: 2.66–5.11) with vedolizumab versus 3.42/100 PY (95% CI: 2.31–4.89) with anti-TNF; HR = 0.80 (95% CI: 0.47–1.36) during the initial 1.1 years and HR = 2.03 (95% CI: 0.65–6.32) after 1.1 years (truncated due to non-proportional hazards). Pneumonia accounted for 40% of all infections among anti-TNF, whereas no case was observed among vedolizumab episodes. Compared with the rate of 0.69/100 PY (95% CI: 0.53–0.87) in a matched general population cohort, vedolizumab showed an HR of 5.45 (95% CI: 3.67–8.11).

Discussion: Vedolizumab was associated with increased risks of serious infections compared with anti-tumor necrosis factor in Crohn's disease but not in ulcerative colitis. Nonetheless, the panorama of serious infections seemed to differ between the drugs. The findings underscore the importance of clinical awareness of infections and the safety profile of the 2 therapies.

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Preterm birth and in utero exposure to corticosteroids are associated with increased infection risk in children of mothers with IBD

Background: Corticosteroids, thiopurines, and biologics may come into play during pregnancy in women with inflammatory bowel disease and potentially impact the developing fetal immune system. The authors aimed to assess the risk of serious infections in children stratified by in utero exposure to biologics and immunomodulators or concomitant treatment with corticosteroids.
Methods: All singleton inflammatory bowel disease (IBD) pregnancies between 2008 and 2022 at a tertiary IBD center in Denmark were included. Maternal and offspring demographics, maternal disease activity, antenatal medical treatment, and infant infections resulting in hospital admission were recorded after review of medical records.
Results: In 602 live births (99.0%), the authors registered exposure to antenatal treatment as follows: biological monotherapy (n = 61, 10.2%), thiopurines (n = 110, 17.9%), biologics and concomitant thiopurines (n = 63, 10.3%),

and controls (i.e., no treatment with biological and/or thiopurines; n = 369, 60.6%). Preterm delivery (< 37 gestational weeks) and systemic steroid administration during the third trimester were associated with an increased risk of serious infection in the offspring immediately after birth (relative risk = 17.5; 95% confidence interval: 7.8–39.8; p < 0.001, and relative risk = 4.8; 95% confidence interval: 1.5–12.7; p = 0.003, respectively). Intra-uterine exposure to biologics or combination treatment were not associated with a statistically significant higher risk of serious infections compared with controls; however, combination treatment showed an inclination towards an increased risk across analyses.

Conclusion: Preterm birth and systemic corticosteroid administration late in pregnancy are significant risk factors for serious infections in the offspring of mothers with inflammatory bowel disease.

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Extended induction and prognostic indicators of response in patients treated with mirikizumab with moderately to severely active ulcerative colitis in the LUCENT trials

Background: Efficacy and safety of mirikizumab, a p19-targeted anti-interleukin-23 monoclonal antibody, for moderately to severely active ulcerative colitis was demonstrated previously. The authors evaluated clinical response, baseline characteristics, and clinical status in patients not responding by 12 weeks (W) of induction who then received extended induction treatment.
Method: Patients unresponsive to 300 mg of intravenous (IV) mirikizumab every 4 weeks by W12 received 3 additional 300 mg IV doses every 4 weeks. W4 responders received 200 mg mirikizumab every 4 weeks subcutaneously until W52. Patients responding by W12 but subsequently losing response received rescue therapy with 300 mg IV for 3 doses every 4 weeks. Logistic regression modelling was performed for patients not achieving W12 clinical response to assess baseline characteristics and W12 efficacy parameters and potential prognostic factors of clinical response at W24.
Results: Of patients not achieving clinical response during induction, 53.7% achieved response following extended induction. After W52, 72.2%, 43.1%, and 36.1% of patients achieved clinical response, endoscopic, and clinical remission, respectively. Of induction responders who subsequently lost response, 63.2% and 36.8% achieved symptomatic response and remission, respectively, after receiving rescue therapy. No prior biologic or tofacitinib treatment, no immunomodulators at baseline, age older than 40 years, and W12 modified Mayo Score improvement were positively associated with a response to extended induction. The safety profile was similar to initial induction, with 38.3% treatment emergent adverse events, mostly mild.

Conclusion: With "extended induction," total of 80.3% mirikizumab-treated patients achieved clinical response by week 24. Potential prognostic factors determining response include disease severity, disease phenotype, C-reactive protein, and previous biologic therapy.

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IBS, Functional and Motility Disorders

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A multicenter randomized controlled trial of microbiome-based artificial intelligence-assisted personalized diet versus low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet: A novel approach for the management of irritable bowel syndrome

Introduction: Personalized management strategies are pivotal in addressing irritable bowel syndrome (IBS). This multicenter randomized controlled trial focuses on comparing the efficacy of a microbiome-based artificial intelligence-assisted personalized diet (PD) with a low-fermentable oligosaccharides, disaccharides, mono-saccharides, and polyols diet (FODMAP) for IBS management.
Methods: 121 patients participated, with 70 assigned to the PD group and 51 to the FODMAP diet group. IBS subtypes, demographics, symptom severity (IBS-SSS), anxiety, depression, and quality of life (IBS-QOL) were evaluated. Both interventions spanned 6 weeks. The trial's primary outcome was the within-individual difference in IBS-SSS compared between intervention groups.
Results: For the primary outcome, there was a change in IBS-SSS of -112.7 for those in the PD group versus -99.9 for those in the FODMAP diet group (p = 0.29). Significant improvement occurred in IBS-SSS scores (p < 0.001), frequency (p < 0.001), abdominal distension (p < 0.001), and life interference (p < 0.001) in both groups. In addition, there were significant improvements in anxiety levels and IBS-QOL scores for both groups (p < 0.001). Importantly, PD was effective in reducing IBS-SSS scores across all IBS subtypes IBS-constipation (IBS-C; p < 0.001), IBS-diarrhea (IBS-D; p = 0.01), and IBS-mixed (IBS-M; p < 0.001) while FODMAP diet exhibited comparable improvements in IBS-C (p = 0.004) and IBS-M (p < 0.001). PD intervention significantly improved IBS-QOL scores for all subtypes (IBS-C [p < 0.001], IBS-D [p < 0.001], and IBS-M [p = 0.008]) while the FODMAP diet did so for the IBS-C (p = 0.004) and IBS-D (p = 0.022). Notably, PD intervention led to signif-

icant microbiome diversity shifts (p < 0.05) and taxa alterations compared with FODMAP diet.

Discussion: The artificial intelligence-assisted personalized diet (PD) emerges as a promising approach for comprehensive irritable bowel syndrome (IBS) management. With its ability to address individual variation, the PD approach demonstrates significant symptom relief, enhanced quality of life, and notable diversity shifts in the gut microbiome, making it a valuable strategy in the evolving landscape of IBS care.

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Clinical trial: Effects of treatment with a vibrating capsule in patients with severe chronic constipation

Background: There is little information on the effectiveness of therapies for severe chronic constipation. In a phase 3 trial, the authors previously demonstrated that a vibrating capsule was significantly more efficacious than a placebo in chronic constipation.
Aim: To examine the effects of a vibrating capsule and placebo on symptoms and health-related quality of life (HRQoL) in patients with severe chronic constipation.
Methods: The authors performed a post hoc analysis of phase 3, multicentre, randomised, double-blind, and placebo-controlled 8-week clinical trial of a vibrating capsule to specifically assess outcomes among subjects who reported 0 complete spontaneous bowel movements (CSBMs) during the 2-week baseline period. They assessed effects of treatment on bowel symptoms, patient satisfaction, and HRQoL. CSBM responders were defined as subjects with increases of ≥ 1 or ≥ 2 or ≥ 3 weekly CSBMs (CSBM1 or CSBM2, CSBM3, respectively) over baseline for ≥ 6 out of 8 weeks of treatment.
Results: The severe chronic constipation subgroup comprised 175 (56%) of the 312 subjects. Significantly more subjects with severe chronic constipation who received the vibrating capsule than those who received the placebo were CSBM1 (44.9% vs. 20.9%, p = 0.007), CSBM2 (29.2% vs. 11.6%, p = 0.004), and CSBM3 (19.10% vs. 6.98%, p = 0.017) responders. Straining effort, stool consistency, patient satisfaction, and HRQoL significantly improved in the severe chronic constipation subgroup. A mild vibrating sensation was reported in 10%.

Conclusion: The vibrating capsule significantly improved constipation-related symptoms and health-related quality of life in patients with severe constipation, affirming its efficacy and safety across the spectrum of chronic constipation.

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The efficacy of tradipitant in patients with diabetic and idiopathic gastroparesis in a phase 3 randomized placebo-controlled clinical trial

Background: Neurokinin receptor 1 antagonists are effective in reducing nausea and vomiting in chemotherapy-induced emesis. The authors investigated the safety and efficacy of tradipitant, a neurokinin receptor 1 antagonist, in patients with idiopathic and diabetic gastroparesis.
Methods: A total of 201 adults with gastroparesis were randomly assigned to oral tradipitant 85 mg (n = 102) or placebo (n = 99) twice daily for 12 weeks. Symptoms were assessed by a daily symptom diary, Gastroparesis Cardinal Symptom Index scores, and other patient-reported questionnaires. Blood levels were monitored for an exposure-response analysis. The primary outcome was change from baseline to week 12 in average nausea severity, measured by daily symptom diary.
Results: The intention-to-treat (ITT) population did not meet the prespecified primary endpoint at week 12 (difference in nausea severity change drug vs. placebo; p = 0.741) or prespecified secondary endpoints. Post hoc analyses were performed to control for drug exposure, rescue medications, and baseline severity inflation. Subjects with high blood levels of tradipitant significantly improved average nausea severity beginning at early time points (weeks 2–4). In post hoc sensitivity analyses, tradipitant treatment demonstrated strengthened effects, with statistically significant improvements in nausea at week 12.

Conclusions: Although tradipitant did not reach significance in the intention-to-treat population, a pharmacokinetic exposure-response analysis demonstrated significant effects with adequate tradipitant exposure. When accounting for confounding factors such as baseline severity inflation and rescue medication, a statistically significant effect was also observed. These findings suggest that tradipitant has potential as a treatment for the symptom of nausea in gastroparesis.

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A minority of childhood disorders of gut-brain interaction persist into adulthood: A risk-factor analysis

Introduction: Disorders of gut-brain interaction (DGBIs) may originate in childhood. There are currently limited data on persistence of DGBI into adulthood and risk

factors for persistence. Furthermore, there are no data on this question from general practice, where the majority of DGBIs are diagnosed and managed. This study documents the proportion of childhood-diagnosed DGBIs that persisted into adulthood and what factors were associated with persistence.

Methods: General practice records were obtained for more than 60,000 patients whose medical record spanned both childhood and adulthood years. Patients with diagnosed organic gastrointestinal disorder were excluded. Medical records were also interrogated for potential risk factors.

Results: 11% of patients with irritable bowel syndrome (IBS) and 20% of patients with functional dyspepsia (FD) diagnosed in childhood had repeat diagnoses of the same condition in adulthood. Female sex (odds ratio [OR] = 2.02) was associated with persistence for IBS, while a childhood diagnosis of gastritis (OR = 0.46) was risk-protective. Childhood non-steroidal anti-inflammatory drug use (OR = 1.31, 95% confidence interval [CI]: 1.09–1.56) was a risk factor for persistence in IBS. For FD, a childhood diagnosis of asthma (OR = 1.30, 95% CI: 1.00–1.70) was a risk factor, as was anxiety for both IBS (OR = 1.24, 95% CI: 1.00–1.54) and FD (OR = 1.48, 95% CI: 1.11–1.97) with a similar finding for depression for IBS (OR = 1.34, 95% CI: 1.11–1.62) and FD (OR = 1.88, 95% CI: 1.47–2.42).

Discussion: Childhood disorders of gut-brain interaction persist into adulthood in 10–20% of patients, suggesting that management monitoring should continue into adulthood. Those diagnosed with anxiety or mood disorders in childhood should receive particular attention, and prescription of non-steroidal anti-inflammatory drugs in children should be made judiciously.

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Colorectal Cancer

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Nivolumab plus ipilimumab in microsatellite-instability-high metastatic colorectal cancer

Background: Patients with microsatellite-instability-high (MSI-H) or mismatch-repair-deficient (dMMR) metastatic colorectal cancer have poor outcomes with standard chemotherapy with or without targeted therapies. Nivolumab plus ipilimumab has shown clinical benefit in non-randomized studies of MSI-H or dMMR metastatic colorectal cancer.

Methods: In this phase 3 open-label trial, the authors randomly assigned patients with unresectable or metastatic colorectal cancer and MSI-H or dMMR status according to local testing to receive, in a 2:2:1 ratio, nivolumab plus ipilimumab, nivolumab alone, or chemotherapy with or without targeted therapies. The dual primary end points, assessed in patients with centrally confirmed MSI-H or dMMR status, were progression-free survival with nivolumab plus ipilimumab as compared with chemotherapy as first-line therapy and progression-free survival with nivolumab plus ipilimumab as compared with nivolumab alone in patients regardless of previous systemic treatment for metastatic disease. At this prespecified interim analysis, the first primary end point (involving nivolumab plus ipilimumab vs. chemotherapy) was assessed.

Results: A total of 303 patients who had not previously received systemic treatment for metastatic disease were randomly assigned to receive nivolumab plus ipilimumab or chemotherapy; 255 patients had centrally confirmed MSI-H or dMMR tumors. At a median follow-up of 31.5 months (range, 6.1–48.4), progression-free survival outcomes (the primary analysis) were significantly better with nivolumab plus ipilimumab than with chemotherapy (p < 0.001 for the between-group difference in progression-free survival, calculated with the use of a 2-sided stratified log-rank test); 24-month progression-free survival was 72% (95% confidence interval [CI]: 64–79) with nivolumab plus ipilimumab as compared with 14% (95% CI: 6–25) with chemotherapy. At 24 months, the restricted mean survival time was 10.6 months (95% CI: 8.4–12.9) longer with nivolumab plus ipilimumab than with chemotherapy, a finding consistent with the primary analysis of progression-free survival. Grade 3 or 4 treatment-related adverse events occurred in 23% of the patients in the nivolumab-plus-ipilimumab group and in 48% of the patients in the chemotherapy group.

Conclusions: Progression-free survival was longer with nivolumab plus ipilimumab than with chemotherapy among patients who had not previously received systemic treatment for microsatellite-instability-high (MSI-H) or mismatch-repair-deficient (dMMR) metastatic colorectal cancer.

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Oxaliplatin added to fluoropyrimidine/bevacizumab as initial therapy for unresectable metastatic colorectal cancer in older patients: A multicenter, randomized, open-label phase 3 trial (JCOG1018)

Purpose: Doublet chemotherapy with fluoropyrimidine (FP) and oxaliplatin (OX) plus bevacizumab (BEV) is a standard regimen for unresectable metastatic colorectal

cancer (MCRC). However, the efficacy of adding OX to FP plus BEV (FP + BEV) remains unclear for older patients, a population for whom FP + BEV is standard. The authors aimed to confirm the superiority of adding OX to FP + BEV for this population.

Methods: This open-label, randomized, phase 3 trial was conducted at 42 institutions in Japan. Patients with unresectable MCRC age 70–74 years with Eastern Cooperative Oncology Group performance status (ECOG-PS) 2 and those 75 years and older with ECOG-PS 0–2 were randomly assigned (1:1) to an FP + BEV arm or an OX addition (FP + BEV + OX) arm. Fluorouracil plus levofolinate calcium or capecitabine was declared before enrollment. The primary end point was progression-free survival (PFS).

Results: Between September 2012 and March 2019, 251 patients were randomly assigned to the FP + BEV arm (n = 125) and the FP + BEV + OX arm (n = 126). The median age was 80 and 79 years in the respective arm. The median PFS was 9.4 months (95% confidence interval [CI]: 8.3–10.3) in the FP + BEV arm and 10.0 months (9.0–11.2) in the FP + BEV + OX arm (hazard ratio [HR] = 0.84 [90.5% CI: 0.67–1.04]; 1-sided p = 0.086). The median overall survival was 21.3 months (18.7–24.3) in the FP + BEV arm and 19.7 months (15.5–25.5) in the FP + BEV + OX arm (HR = 1.05 [0.81–1.37]). The proportion of any grade ≥ 3 adverse events was higher in the FP + BEV + OX arm (52% vs. 69%). There was 1 treatment-related death in the FP + BEV arm and 3 in the FP + BEV + OX arm.

Conclusion: No benefit of adding oxaliplatin (OX) to fluoropyrimidine (FP) plus bevacizumab (BEV) as first-line treatment was demonstrated in older patients with metastatic colorectal cancer. FP + BEV is recommended for this population.

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Colorectal Cancer Screening/ Endoscopy

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Impact of bowel preparation quality on colonoscopy findings and colorectal cancer deaths in a nation-wide colorectal cancer screening program

Introduction: Adequate bowel preparation is paramount for a high-quality screening colonoscopy. Despite the importance of adequate bowel preparation, there is a lack of large studies that associated the degree of bowel preparation with long-term colorectal cancer outcomes in screening patients.

Methods: In a large population-based screening program database in Austria, quality of bowel preparation was estimated according to the Aronchick Scale by the endoscopist (excellent, good, fair, poor, and inadequate bowel preparation). The authors used logistic regression to assess the influence of bowel preparation on the detection of different polyp types and the interphysician variation in bowel preparation scoring. Time-to-event analyses were performed to investigate the association of bowel preparation with postcolonoscopy colorectal cancer (PCCRC) death.

Results: A total of 335,466 colonoscopies between January 2012 and follow-up until December 2022 were eligible for the analyses. As compared with excellent bowel preparation, adenoma detection was not significantly lower for good bowel preparation (odds ratio [OR] = 1.01, 95% confidence interval [CI]: 0.9971–1.0329, p = 0.1023); however, adenoma detection was significantly lower in fair bowel preparation (OR = 0.97, 95% CI: 0.9408–0.9939, p = 0.0166). Individuals who had fair or lower bowel preparation at screening colonoscopy had significantly higher hazards for PCCRC death (hazard ratio for fair bowel preparation = 2.56, 95% CI: 1.67–3.94, p < 0.001).

Discussion: Fair bowel preparation on the Aronchick Scale was not only associated with a lower adenoma detection probability but also with increased risk of postcolonoscopy colorectal cancer death. Efforts should be made to increase bowel cleansing above fair scores.

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Cold versus hot snare endoscopic mucosal resection for large (≥ 15 mm) flat non-pedunculated colorectal polyps: A randomised controlled trial

Background and aims: Conventional hot snare endoscopic mucosal resection (H-EMR) is effective for the management of large (≥ 20 mm) non-pedunculated colon polyps (LNPCPs) however, electrocautery-related complications may incur significant morbidity. With a superior safety profile, cold snare EMR (C-EMR) of LNPCPs is an attractive alternative however evidence is lacking. The authors conducted a randomised trial to compare the efficacy and safety of C-EMR to H-EMR.

Methods: Flat, 15–50 mm adenomatous LNPCPs were prospectively enrolled and randomly assigned to C-EMR or H-EMR with margin thermal ablation at a single tertiary centre. The primary outcome was endoscopically visible and/or histologically confirmed recurrence at 6 months surveillance colonoscopy. Secondary outcomes were clinically significant post-EMR bleeding (CSPEB), delayed perforation and technical success.

Results: 177 LNPCPs in 177 patients were randomised to C-EMR arm (n = 87) or H-EMR (n = 90). Treatment

groups were equivalent for technical success (C-EMR 86/87 [98.9%] vs. H-EMR 90/90 [100%]; p = 0.31). Recurrence was significantly greater in C-EMR (16/87, 18.4% vs. 1/90, 1.1%; relative risk [RR] = 16.6, 95% confidence interval [CI]: 2.24–122; p < 0.001). Delayed perforation (1/90 [1.1%] vs. 0; p = 0.32) only occurred in the H-EMR group. CSPEB was significantly greater in the H-EMR arm (7/90 [7.8%] vs. 1/87 [1.1%]; RR = 6.77, 95% CI: 0.85–53.9; p = 0.034).

Conclusion: Compared with hot snare endoscopic mucosal resection, cold snare endoscopic mucosal resection for flat, adenomatous large (≥ 20 mm) non-pedunculated colon polyps, demonstrates superior safety with equivalent technical success. However, endoscopic recurrence is significantly greater for cold snare resection and is currently a limitation of the technique.

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Impact of margin thermal ablation after endoscopic mucosal resection of large (≥ 20 mm) non-pedunculated colonic polyps on long-term recurrence

Background and aims: The efficacy of colorectal endoscopic mucosal resection (EMR) is limited by recurrence and the necessity for conservative surveillance. Margin thermal ablation (MTA) after EMR has reduced the incidence of recurrence at the first surveillance colonoscopy at 6 months (SC1). Whether this effect is durable to second surveillance colonoscopy (SC2) is unknown. The authors evaluated long-term surveillance outcomes in a cohort of large non-pedunculated colonic polyps (LNPCPs) that have undergone MTA.
Methods: LNPCPs undergoing EMR and MTA from 4 academic endoscopy centres were prospectively recruited. EMR scars were evaluated at SC1 and in the absence of recurrence, SC2 colonoscopy was conducted in a further 12 months. A historical control arm was generated from LNPCPs that underwent EMR without MTA. The primary outcome was recurrence at SC2 in all LNPCPs with a recurrence-free scar at SC1.
Results: 1152 LNPCPs underwent EMR with complete MTA over 90 months until October 2022. 854 LNPCPs underwent SC1 with 29 of 854 (3.4%) LNPCPs demonstrating recurrence. 472 LNPCPs free of recurrence at SC1 underwent SC2. 260 LNPCPs with complete SC2 follow-up formed the control arm from January 2012 to May 2016. Recurrence at SC2 was significantly less in the MTA arm versus controls (1/472 [0.2%] vs. 9/260 [3.5%]; p < 0.001).

Conclusion: Large non-pedunculated colonic polyps that have undergone successful endoscopic mucosal resection with margin thermal ablation and are free of recurrence at the first surveillance colonoscopy at 6 months are unlikely to develop recurrence in subsequent surveillance out to 2 years. Provided the colon is cleared of synchronous neoplasia, the next surveillance can be potentially extended to 3–5 years. Such an approach would reduce costs and enhance patient compliance.

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Clinical consequences of computer-aided colorectal polyp detection

Background and aim: Randomised trials show improved polyp detection with computer-aided detection (CADe), mostly of small lesions. However, operator and selection bias may affect CADe's true benefit. Clinical outcomes of increased detection have not yet been fully elucidated.
Methods: In this multicentre trial, CADe combining convolutional and recurrent neural networks was used for polyp detection. Blinded endoscopists were monitored in real time by a second observer with CADe access. CADe detections prompted reinspection. Adenoma detection rates (ADR) and polyp detection rates were measured prestudy and poststudy. Histological assessments were done by independent histopathologists. The primary outcome compared polyp detection between endoscopists and CADe.
Results: In 946 patients (51.9% male, mean age 64), a total of 2141 polyps were identified, including 989 adenomas. CADe was not superior to human polyp detection (sensitivity 94.6% vs. 96.0%) but outperformed them when restricted to adenomas. Unblinding led to an additional yield of 86 true positive polyp detections (1.1% ADR increase per patient; 73.8% were < 5 mm). CADe also increased non-neoplastic polyp detection by an absolute value of 4.9% of the cases (1.8% increase of entire polyp load). Procedure time increased with 6.6 ± 6.5 min (+42.6%). In 22 of 946 patients, the additional detection of adenomas changed surveillance intervals (2.3%), mostly by increasing the number of small adenomas beyond the cut-off.

Conclusion: Even if computer-aided detection (CADe) appears to be slightly more sensitive than human endoscopists, the additional gain in adenoma detection rate was minimal and follow-up intervals rarely changed. Additional inspection of non-neoplastic lesions was increased, adding to the inspection and/or polypectomy workload.

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PD Dr. Armin Küllmer

AI in Colorectal Polyp Detection: Hype or Help?

The use of artificial intelligence (AI) in colorectal screening has been a major focus of endoscopy research for several years, with numerous randomized controlled trials (RCTs) conducted to evaluate its effectiveness. Typically, these studies compare colonoscopies with and without AI assistance for polyp detection. Tandem studies, where the same patient undergoes 2 consecutive colonoscopies, one with and one without AI, have also been used. However, both study designs have inherent biases. In this European RCT, a novel study design was used: the endoscopist conducted the procedure without AI assistance, while a second observer in the same room used computer-aided detection in real time to assess its diagnostic performance. This approach allowed for better comparability, as AI's performance was evaluated on the same patient during the same examination in real time. The study yielded findings consistent with previous research on computer-aided detection. First, using AI improved adenoma detection rates (significantly, although this was not the case for overall polyp detection). Second, inexperienced examiners benefited more than experienced examiners. The third and most notable outcome is that the improvements were moderate, primarily involving the detection of small, low-risk polyps. The computer-aided detection influenced follow-up recommendations in only 2.3% of patients.
These results suggest that the initial expectation that AI would revolutionize colorectal screening to the same extent it has impacted other industries has not (yet) been realized. While its impact should not be overestimated, even small absolute improvements could be highly significant given the large number of patients undergoing screening, however. Furthermore, AI does not appear to negatively affect colonoscopy, such as by increasing complications or extending procedure times. Therefore, unlike autonomous driving, AI will not replace the human performing the endoscopy. Instead, the best outcomes will likely come from effective collaboration between humans and machines. ■

Guo R, Wang J, Min L, Dong N, Zhang L, Song R, Zhang Y, Zhang Q, Zhai H, Li P, Zhang S

Improved adenoma detection rate using a novel colonoscopic distal attachment: A multicenter randomized controlled trial

Introduction: To evaluate the effect of Embrella, a novel-designed colonoscopic distal attachment, on adenoma detection rate (ADR) and adenoma per colonoscopy (APC), compared with standard colonoscopy in routine practice.
Methods: All consecutive participants who underwent routine colonoscopic examinations at 3 endoscopy centers in China were enrolled. Participants were randomly assigned in a 1:1 ratio to the Embrella-assisted colonoscopy (EAC) or standard colonoscopy (SC) groups. ADR, APC, inspection time, pain scores, and adverse events were recorded.
Results: Overall, 1179 participants were randomized into the EAC (n = 593) and SC groups (n = 586). EAC increased the overall ADR from 24.6% to 34.2% (p < 0.001) and improved APC from 0.44 to 0.64 (p = 0.002). Subgroup analyses indicated that EAC significantly improved ADR for adenomas < 10 mm (13.8% vs. 8.5%, p = 0.004 for 5–9 mm and 27.0% vs. 17.2%, p < 0.001 for < 5 mm), non-pedunculated adenomas (26.6% vs. 18.8%, p < 0.001), and adenomas in the transverse (10.8% vs. 6.1%, p = 0.004) and left colon (21.6% vs. 13.7%, p < 0.001). APC in the subgroup analyses was consistent with ADR. The mean inspection time was shorter with EAC (6.52 vs. 6.68 minutes, p = 0.046), with no significant impact on participants' pain scores (p = 0.377). Moreover, no EAC-related adverse events occurred.

Discussion: Embrella-assisted colonoscopy significantly increased adenoma detection rate and adenoma per colonoscopy compared with standard colonoscopy, particularly for adenomas < 10 mm, non-pedunculated adenomas, and adenomas in the transverse and left colon.

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A computer-aided detection system in the everyday setting of diagnostic, screening, and surveillance colonoscopy: An international, randomized trial

Background: Computer-aided detection (CADe) has been developed to improve detection during colonoscopy. After initial reports of high efficacy, there has been an increasing recognition of variability in the effectiveness of CADe systems. The aim of this study was to evaluate a CADe system in a varied colonoscopy population.
Methods: A multicenter, randomized trial was conducted at 7 hospitals (both university and non-university) in Europe and Canada. Participants referred for diagnostic, non-immunochemical fecal occult blood test (iFOBT) screening, or surveillance colonoscopy were randomized (1:1) to undergo CADe-assisted or conventional colonoscopy by experienced endoscopists. Participants with insufficient bowel preparation were excluded from the analysis. The primary outcome was adenoma detection rate (ADR). Secondary outcomes included adenomas

per colonoscopy (APC) and sessile serrated lesions (SSLs) per colonoscopy.

Results: 581 participants were enrolled, of whom 497 were included in the final analysis: 250 in the CADe arm and 247 in the conventional colonoscopy arm. The indication was surveillance in 202 of 497 colonoscopies (40.6%), diagnostic in 199 of 497 (40.0%), and non-iFOBT screening in 96 of 497 (19.3%). Overall, ADR (38.4% vs. 37.7%; p = 0.43) and APC (0.66 vs. 0.66; p = 0.97) were similar between CADe and conventional colonoscopy. SSLs per colonoscopy was increased (0.30 vs. 0.19; p = 0.049) in the CADe arm versus the conventional colonoscopy arm.

Conclusions: In this study conducted by experienced endoscopists, computer-aided detection (CADe) did not result in a statistically significant increase in adenoma detection rate (ADR). However, the ADR of the control group substantially surpassed the sample size assumptions, increasing the risk of an underpowered trial.

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Gastrointestinal Infections, Diverticular Disease, Other Inflammation

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Risk of cancer in patients with diverticular disease: A population-based cohort study

Background and aims: Several studies have investigated the association between diverticular disease (DD) and colorectal cancer. However, whether there is an association between DD and malignancies other than those in the colorectum remains uncertain.
Methods: For the 1978–2019 period, the authors conducted a nationwide, population-based cohort study using national Danish health care data. They followed patients with DD for up to 20 years, beginning 1 year after the date of DD diagnosis until the first occurrence of incident cancer, emigration, death, 20 years of follow-up, or December 31, 2019. They calculated cumulative incidence proportions of cancer and standardized incidence ratios (SIRs) comparing cancer incidence among patients with DD with that in the general population.
Results: The authors identified 200,639 patients with DD, of whom 20,498 were diagnosed with cancer during the 1–20 years after their DD diagnosis. The SIRs were increased for most cancer sites except for those in the colorectum (SIR = 0.75; 95% confidence interval [CI]: 0.72–0.78). The highest SIRs were observed for cancers of the lung, bronchi, and trachea (SIR = 1.20; 95% CI: 1.15–1.24) and kidney (SIR = 1.27; 95% CI: 1.16–1.39).

Conclusions: The findings show an increased long-term relative risk of cancer following a diagnosis of diver- ticular disease (DD). These findings are likely caused by prevalence of numerous risk factors in patients with DD that confer an increased risk of cancer. The decreased relative risk of colorectal cancer might be explained by an increased likelihood of patients with DD undergoing colonoscopy with polypectomy.

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Microscopic Colitis

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Psychiatric disorders among 5800 patients with microscopic colitis: A nationwide population-based matched cohort study

Introduction: Microscopic colitis (MC) is an inflammatory condition of the large intestine. Primarily diagnosed in middle-aged and older adults, the incidence of the disease has increased markedly during the past few decades. While MC is associated with a reduced quality of life, large-scale studies on the association with future psychiatric disorders are lacking.
Methods: The authors conducted a nationwide matched cohort study in Sweden from 2006 to 2021. Through a nationwide histopathology database (the Epidemiology Strengthened by histoPathology Reports in Sweden study), they identified 5816 patients with a colorectal biopsy consistent with MC. These patients were matched with 21,509 reference individuals from the general population all of whom with no previous record of psychiatric disorders.
Results: From 2006 to 2021, 519 patients with MC (median age 64.4 years [interquartile range, 49.5–73.3]) and 1313 reference individuals were diagnosed with psychiatric disorders (9.9 vs. 6.5 events per 1000 person-years), corresponding to 1 extra case of psychiatric disorder in 29 patients with MC over 10 years. After adjustments, the hazard ratio for psychiatric disorders was 1.57 (95% confidence interval: 1.42–1.74). The authors found significantly elevated estimates up to 10 years after MC diagnosis and a trend toward higher risk with increasing age. Specifically, they observed increased risks for unipolar depression, anxiety disorders, stress-related disorders, substance abuse, and suicide attempts. In sibling-controlled analysis, the adjusted hazard ratio was 1.76 (95% confidence interval: 1.44–2.15).

Discussion: Patients with microscopic colitis are at increased risk of incident psychiatric disorders compared with the general population.

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Effectiveness of bile acid sequestrants in microscopic colitis and utility of bile acid testing: A systematic review and meta-analysis

Introduction: Bile acid sequestrants (BAS) are an option for microscopic colitis (MC) refractory or intolerant to budesonide. There are inconsistent data on the prevalence of bile acid malabsorption (BAM) and utility of bile acid testing in MC. The aim of this systematic review and meta-analysis was to evaluate these outcomes.
Methods: A systematic search of randomized control trials and observational studies of adults with MC treated with BAS was conducted using MEDLINE, Embase, Cochrane, and Scopus from inception to January 22, 2024. Data were extracted on (i) prevalence of BAM, (ii) clinical response and adverse events, and (iii) recurrence after BAS discontinuation. Data were pooled using random-effects models to determine weighted pooled estimates and 95% confidence intervals (CIs).
Results: The authors included 23 studies (1 randomized control trial, 22 observational), with 1011 patients with MC assessed for BAM and 771 treated with BAS. The pooled prevalence of BAM was 34% (95% CI: 0.26–0.42, $I^2 = 81\%$). The pooled response rate with BAS induction for all patients with MC, irrespective of BAM, was 62% (95% CI: 0.55–0.70, $I^2 = 71\%$). There was a higher pooled response rate in patients with BAM compared with those without BAM ($p < 0.0001$). The pooled rate of BAS-related adverse effects was 9% (95% CI: 0.05–0.14, $I^2 = 58\%$).

Discussion: One-third of patients with microscopic colitis (MC) had bile acid malabsorption (BAM), and almost two-thirds of all patients responded to bile acid sequestrants (BAS) with limited side effects. Patients with MC and BAM were more likely to respond to therapy, supporting the value of bile acid testing.

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Immuno-Mediated Diseases of the GI Tract: Where Do We Stand?

Interview with Prof. Dr. Axel Dignass, Frankfurt am Main (Germany)

Networking and a holistic view bring us gastroenterologists together

by Dr. Corinna Kolac, Medical Journalist, eickhoff kommunikation GmbH

Prof. Dr. Axel Dignass is the Head of the Department of Medicine I at the Agaplesion Markus Hospital in Frankfurt am Main (Germany). He has a special interest in inflammatory bowel disease and is also interested in the use of artificial intelligence in the field of gastroenterology. Dignass is well known as the author of guidelines and is the chairperson of various national and international professional and medical associations.

Prof. Dignass, you helped plan the Symposium 238 "Immuno-Mediated Diseases of the GI Tract: Where Do We Stand?" in Florence. What is your personal event highlight?

Prof. Dignass: For me, the highlight is not one particular outstanding aspect of the symposium, but rather the entire event. We succeeded in linking four different conditions in such a way that each session featured one presentation on each of the four conditions, so that we could contribute to the discussion on EoE, celiac disease, IBD, and microscopic colitis. In other settings, we typically meet up with the experts on one specific topic and discuss the latest developments. This symposium was quite different. All participants had the opportunity to listen to experts working in various areas and compare similarities and differences. We covered all areas, from epidemiology to pathophysiology, medical and surgical management as well as diet. We covered the management of simple cases and also complicated and refractory patients. The format offered a great opportunity for seeing what is happening in other fields and for benefiting from other specialists. But for me there was another highlight. Our guests included leading experts from all over the world, Prof. Detlef Schuppan, to name just one. He is responsible for discovering the autoantibody for celiac disease and participated in developing many of the treatments. I am also pleased that Prof. Silvio Danese from Milan (Italy) participated. He is a world leader in IBD research. I would also like to touch on the very underrated topic of microscopic colitis. We received input from the European working group on MC (Microscopic Colitis).

An entire session was dedicated to dietary therapy and the patients' perspective. What role do these topics play in practice?

Prof. Dignass: Dietary therapy and the patients' perspective are two extremely important topics and are underrepresented in clinical practice. From my point of view, there is a huge need for education. Our goal is to continue to advance the concept of shared decision-making, which can help us improve adherence to clinical management including better adherence to medical management. Currently, only around 40% of patients with EoE adhere to therapy. Many people with celiac disease take a day off from their therapy every week, which has long-term consequences. What health care professionals (HCPs) may consider to be burdensome symptoms is often different than what patients experience. For patients, for instance, urgency is a critical factor. And yet only 1 out of 3 doctors considers urgency to be an important therapy objective. Doctors often describe undesired effects to be less relevant than our patients do. These are good reasons to focus more closely on this topic, as well as on dietary therapy.

The different preferences for therapy objectives are an interesting topic. Patients often prioritize relief from their symptoms, while physicians typically focus on achieving histological remission. Why is it so hard to align these two objectives?

Prof. Dignass: It's true that for example for Crohn's disease the CDAI score often does not correlate with the endoscopic findings. But that has to do with the fact that the symptoms not only correlate with current inflammation, but often have to be attributed to previous damage resulting in strictures, fistula or scarring. Inflammation promotes tissue scarring. Motility may be disturbed even though the mucosa is currently in histological remission. But patients only notice the symptoms. That's why for inflammatory disorders of the GI tract, it is important to take a holistic view of the situation. In this perspective, symptoms play a role, as do endoscopic, histological, and ultrasound findings.

You have a special interest in inflammatory bowel disease. Where do you see some unsolved mysteries?

Prof. Dignass: Inflammatory bowel diseases like ulcerative colitis and Crohn's disease have been studied for

many years, and we have learned a lot about them. But there are always topics that require more investigation. From my point of view, one such topic is time-dependent treatment of IBDs. In many cases, we fail to keep this in mind. It should be clear to everyone involved in the therapy that patient-related outcomes need to be achieved in a timely manner. However, subjective, patient-reported improvement of symptoms needs to be confirmed by more objective tests like biochemical blood and stool tests such as calprotectin and CRP. Ultimately, we aim to achieve mucosal healing assessed by endoscopic assessment as a long-term goal. And last but not least, the therapeutic ceiling is very important to me. We have to find new ways to improve the long-term outcomes of our patients beyond our current success rate. Efficacy has to increase, for instance, with new drugs or through intelligent combinations of biological drugs, earlier initiation of effective treatments and regular monitoring of treatment success.

There is no lack of pharmacologic options for IBD, is there?

Prof. Dignass: Compared to other disorders, like celiac disease, that is true. We have a number of biologics available. But we still too often fail to achieve the treatment objective of long-lasting remission. I am hoping that we will have solutions created with the help of artificial intelligence to improve diagnosis and, in particular, improve our treatment algorithms. We have a lot of medications, but we struggle with how to use our options in the most optimal way: sequential or combination therapy, which sequences and which combinations? With AI, we can evaluate our findings more quickly and hopefully answer the unanswered questions better. To address these questions, we are also still missing biomarkers. So far, all our attempts to identify them have failed. But there is a lot of research in this area, and I am sure that we will find a solution to this problem in the near future. Although we already have a lot of drugs available, in the near future we might be in the favorable position of being able to address additional mechanisms of IBD. For now, we can improve patient outcomes by treating

patients according to medical guidelines and evidence-based recommendations for the use of the currently available drugs. Implementing a therapy currently requires a significant amount of specialized knowledge. I hope and wish that AI will help us create a tailored treatment that each and every colleague can implement based on clear guidance. So you see, there is still a lot to do when it comes to IBD.

What do you like about the international symposia like this one, and about the Falk Foundation symposia in particular?

Prof. Dignass: This is not the first symposium I have helped organize for the Falk Foundation. I always enjoy becoming involved, because the organizers have complete freedom to design the program and to select the speakers. The topics and formats are geared to the pressing issues of today and not to what is in a company pipeline. That does not go unnoticed by the many participants from all over the world. The events also attract experts who do not hold a presentation but come because they are interested. They all value the interactive exchange and the high quality of the events.

Professor Dignass, thank you very much for taking the time to talk to us.

PANCREAS

Acute/Chronic Pancreatitis

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Biflanged metal stents versus plastic stents for endoscopic ultrasound-guided drainage of walled-off necrosis: A randomized controlled trial

Background: Endoscopic ultrasound (EUS)-guided drainage of walled-off necrosis (WON) using either plastic or metal stents is the mainstay of WON management. This single-center randomized controlled trial aimed to evaluate the efficacy of biflanged metal stents (BFMSs) and plastic stents for WON drainage.
Methods: Patients with symptomatic WON amenable to EUS-guided drainage were randomized to receive either BFMSs or plastic stents. The primary outcome was re-intervention-free clinical success at 4 weeks. Secondary outcomes were: overall clinical success (complete resolution of symptoms and significant reduction in size of WON [< 50% of original size and < 5 cm in largest diameter at 4-week follow-up]); number of reinterventions; adverse events (AEs); hospital stay for first admission; and medium-term outcomes at 6 months (recurrence, disconnected pancreatic duct, chronic pancreatitis, and new-onset diabetes mellitus).
Results: 92 patients were randomized: 46 in each arm. The reintervention-free clinical success rate was significantly higher in the BFMS group on intention-to-treat analysis (67.4% vs. 43.5%; p = 0.02). Overall clinical success at 1 month was similar in both groups. There were significantly fewer reinterventions (median 0 [interquartile range, 0–1] vs. 1 [0–2]; p = 0.03) and shorter hospital stays in the BFMS group (7.0 [standard deviation, 3.4] vs. 9.1 [5.5] days; p = 0.04). There were no differences in procedure-related AEs, mortality, or medium-term outcomes.

Conclusions: Biflanged metal stents provide better reintervention-free clinical success at 4 weeks, with shorter hospital stay and without increased risks of adverse events, compared with plastic stents for endoscopic ultrasound-guided drainage of walled-off necrosis. Medium-term outcomes are however similar for both stent types.

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Tailored hydration with lactated Ringer's solution for postendoscopic retrograde cholangiopancreatography pancreatitis prevention: A randomized controlled trial

Introduction: Aggressive hydration using lactated Ringer's solution prevents postendoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP). Concerns of this strategy are large volume and lengthy hydration. This study aimed to evaluate the efficacy of tailored aggressive hydration (TAH) for PEP prevention.
Methods: In this prospective, multicenter, double-blinded, randomized trial conducted across 3 tertiary Korean hospitals, patients who underwent ERCP for the first time were randomly assigned (1:1) to the tailored standard hydration (TSH) and TAH groups. The TSH group received 1.5 ml/kg/h lactated Ringer's solution during and after ERCP, whereas the TAH group was administered a 20 ml/kg bolus post-ERCP and 3 ml/kg/h during and after the procedure. Both groups were assessed for elevated serum amylase levels and pain 4–6 hours after ERCP. If both were absent, hydration was discontinued. If either was present, hydration was continued at the original rate until 8 hours. The primary end point was PEP development and was analyzed on an intention-to-treat analysis.
Results: A total of 344 patients were randomly assigned to treatment groups (171 to the TSH group and 172 to the TAH group). PEP was observed in 9.4% (16/171) in the TSH group and 3.5% (6/172) in the TAH group (relative risk = 0.37, 95% confidence interval: 0.15–0.93, p = 0.03). No difference was identified between the 2 groups in PEP severity (p = 0.80) and complications related to volume overload (p = 0.32).

Discussion: Tailored aggressive hydration according to the presence of abdominal pain or elevated serum amylase levels at 4–6 hours after endoscopic retrograde cholangiopancreatography (ERCP) is safe and prevents post-ERCP pancreatitis (PEP) development.

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Acute venous thromboembolism is common following acute necrotizing pancreatitis and is associated with worse clinical outcomes

Objectives: Although splanchnic vein thrombosis (SVT) is a well-known local complication of acute pancreatitis, extrasplanchnic venous thromboembolism (ESVT) is inadequately studied. Here, the authors aim to explore the incidence of venous thromboembolism (VTE) in

acute necrotizing pancreatitis (ANP) and the associated mortality.

Methods: Adults with a diagnosis of ANP from January 2017 to December 2022 were identified using appropriate International Classification of Diseases, 10th Revision, Clinical Modification codes. The primary outcome was development of acute ESVT within 1 month of ANP. Secondary outcomes were 90-day mortality, 30-day rehospitalization, and oral anticoagulant (OAC) use in patients with ESVT. Propensity score matching (1:1) was performed for baseline characteristics and common comorbidities.

Results: During the study period, 17,942 (7.11%) patients were diagnosed with ANP, and about 10% (1737) of them had a diagnosis of ESVT. Of all VTEs, 61% were ESVT with or without SVT, and 63% (n = 1799) were SVT. Ninety-day mortality (16.3% vs. 5.7%; risk ratio [RR] = 2.86; 95% confidence interval [CI]: 2.29–3.56) and 30-day rehospitalization (31% vs. 19%; RR = 1.63; 95% CI: 1.49–1.79) were higher in patients with ESVT compared with non-VTE patients. Sixty percent of patients with ESVT were on OAC, and OAC use was associated with lower 90-day mortality (8.9% vs. 19.4%; RR = 0.46) without increased risk of adverse events (acute gastrointestinal bleeding, intracranial bleeding, or need for transfusion).

Conclusions: Systemic venous thromboembolism (VTE) is common in patients with acute necrotizing pancreatitis (ANP) and may contribute to increased mortality and risk of readmissions. Prospective studies can confirm these findings and explore the role of aggressive VTE prophylaxis in patients with ANP during hospital stay and in the immediate ambulatory period.

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Sphincterotomy for biliary sphincter of Oddi disorder and idiopathic acute recurrent pancreatitis: The RESPOnD longitudinal cohort

Objective: Sphincter of Oddi disorders (SOD) are contentious conditions in patients whose abdominal pain, idiopathic acute pancreatitis (iAP) might arise from pressurisation at the sphincter of Oddi. The present study aimed to measure the benefit of sphincterotomy for suspected SOD.

Design: Prospective cohort conducted at 14 US centres with 12 months follow-up. Patients undergoing first-time endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy for suspected SOD were eligible: pancreatobiliary-type pain with or without iAP. The primary outcome was defined as the composite of improvement by Patient Global Impression of Change (PGIC), no new or increased opioids and no repeat intervention. Missing data were addressed by hierarchal, multiple imputation scheme.

Results: Of 316 screened, 213 were enrolled with 190 (89.2%) of these having a dilated bile duct, abnormal labs, iAP or some combination. By imputation, an average of 122 of 213 (57.4% [95% confidence interval: 50.4–64.4%]) improved; response rate was similar for those with complete follow-up (99/161, 61.5% [54.0–69.0%]); of these, 118 (73.3%) improved by PGIC alone. Duct size, elevated labs and patient characteristics were not associated with response. AP occurred in 37 of 213 (17.4%) at a median of 6 months post ERCP and was more likely in those with a history of AP (30.9% vs. 2.9%, p < 0.0001).

Conclusion: Nearly 60% of patients undergoing endoscopic retrograde cholangiopancreatography for suspected sphincter of Oddi disorders improve, although the contribution of a placebo response is unknown. Contrary to prevailing belief, duct size and labs are poor response predictors. Acute pancreatitis (AP) recurrence was common and like observations from prior non-intervention cohorts, suggesting no benefit of sphincterotomy in mitigating future AP episodes.

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Pancreatic Tumors

Boilève A, Cartry J, Goudarzi N, Bedja S, Mathieu JRR, Bani MA, Nicolle R, Mouawia A, Bouyakoub R, Nicotra C, Ngo-Camus M, Job B, Lipson K, Boige V, Valéry M, Tarabay A, Dartigues P, Tselikas L, de Baere T, Italiano A, Cosconea S, Gelli M, Fernandez-de-Sevilla E, Annereau M, Malka D, Smolenschi C, Ducreux M, Hollebecque A, Jaulin F

Organoids for functional precision medicine in advanced pancreatic cancer

Background and aims: Patient-derived organoids (PDOs) are promising tumor avatars that could enable ex vivo drug tests to personalize patients' treatments in the frame of functional precision oncology. However, clinical evidence remains scarce. This study aims to evaluate whether PDOs can be implemented in clinical practice to benefit patients with advanced refractory pancreatic ductal adenocarcinoma (PDAC).

Methods: During 2021 to 2022, 87 patients were prospectively enrolled in an institutional review board-approved protocol. Inclusion criteria were histologically confirmed PDAC with the tumor site accessible. A panel of 25 approved antitumor therapies (chemogram) was tested and compared to patient responses to assess PDO predictive values and map the drug sensitivity landscape in PDAC.

Results: 54 PDOs were generated from 87 pretreated patients (take-on rate, 62%). The main PDO mutations were KRAS (96%), TP53 (88%), and CDKN2A/B (22%), with a 91% concordance rate with their tumor of origin. The mean turnaround time to chemogram was 6.8 weeks. In 91% of cases, ≥ 1 hit was identified (gemcitabine

[n = 20/54], docetaxel [n = 18/54], and vinorelbine [n = 17/54]), with a median of 3 hits/patient (range, 0–12). This cohort included 34 evaluable patients with full clinical follow-up. A chemogram sensitivity of 83.3% and specificity of 92.9% were reported. The overall response rate and progression-free survival were higher when patients received a hit treatment as compared to patients who received a non-hit drug (as part of routine management). Finally, the authors leveraged this PDO collection as a platform for drug validation and combo identification. They tested anti-KRAS^{G12D} (MRTX1133), alone or combined, and identified a specific synergy with anti-EGFR therapies in KRAS^{G12D} variants.

Conclusions: The authors report the largest prospective study aiming at implementing functional precision oncology based on patient-derived organoids (PDOs) and identify very robust predictive values in this clinical setting. In a clinically relevant turnaround time, they identify putative hits for 91% of patients, providing unexpected potential survival benefits in this very aggressive indication. Although this remains to be confirmed in interventional precision oncology trials, PDO collection already provides powerful opportunities for drugs and combinatorial treatment development.

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prognostic factors from unadjusted data and 38 (OR) and 30 (HR) prognostic factors from adjusted data, respectively. On the basis of frequency counts of adjusted data, preoperative carbohydrate antigen 19-9, N status, non-delivery of adjuvant therapy, grading, and tumor size based on imaging were identified as key prognostic factors for early recurrence.

Conclusions: Reported prognostic factors of early recurrence vary considerably. Identified key prognostic factors could aid in the development of a risk stratification framework for early recurrence. However, prospective validation is necessary.

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Prognostic factors for early recurrence after resection of pancreatic cancer: A systematic review and meta-analysis

Background and aims: More than half of pancreatic ductal adenocarcinomas (PDACs) recur within 12 months after curative-intent resection. This systematic review and meta-analysis was conducted to identify all reported prognostic factors for early recurrence in resected PDACs.
Methods: After a systematic literature search, a meta-analysis was conducted using a random-effects model. Separate analyses were performed for adjusted versus unadjusted effect estimates as well as reported odds ratios (ORs) and hazard ratios (HRs). Risk of bias was assessed using the Quality in Prognostic Studies tool, and evidence was rated according to Grading of Recommendations Assessment, Development and Evaluation recommendations.
Results: After 2903 abstracts were screened, 65 studies were included. Of these, 28 studies (43.1%) defined early recurrence as evidence of recurrence within 6 months, whereas 34 (52.3%) defined it as evidence of recurrence within 12 months after surgery. Other definitions were uncommon. Analysis of unadjusted ORs and HRs revealed 41 and 5 prognostic factors for early recurrence within 6 months, respectively. When exclusively considering adjusted data, the authors identified 25 and 10 prognostic factors based on OR and HR, respectively. Using a 12-month definition, they identified 38 (OR) and 15 (HR)

LIVER AND BILE

Viral Hepatitis

Fan R, Zhao S, Niu J, Ma H, Xie Q, Yang S, Xie J, Dou X, Shang J, Rao H, Xia Q, Liu Y, Yang Y, Gao H, Sun A, Liang X, Yin X, Jiang Y, Yu Y, Sun J, Naoumov NV, Hou J; Chronic Hepatitis B Study Consortium

High accuracy model for HBsAg loss based on longitudinal trajectories of serum qHBsAg throughout long-term antiviral therapy

Objective: Hepatitis B surface antigen (HBsAg) loss is the optimal outcome for patients with chronic hepatitis B (CHB) but this rarely occurs with currently approved therapies. The authors aimed to develop and validate a prognostic model for HBsAg loss on treatment using longitudinal data from a large, prospectively followed, nationwide cohort.
Design: CHB patients receiving nucleos(t)ide analogues as antiviral treatment were enrolled from 50 centres in China. Quantitative HBsAg (qHBsAg) testing was prospectively performed biannually per protocol. Longitudinal discriminant analysis algorithm was used to estimate the incidence of HBsAg loss, by integrating clinical data of each patient collected during follow-up.
Results: In total, 6792 CHB patients who had initiated antiviral treatment 41.3 (interquartile range [IQR], 7.6–107.6) months before enrolment and had median qHBsAg 2.9 (IQR, 2.3–3.3) $\log_{10}$ IU/mL at entry were analysed. With a median follow-up of 65.6 (IQR, 51.5–84.7) months, the 5-year cumulative incidence of HBsAg loss was 2.4%. A prediction model integrating all qHBsAg values of each patient during follow-up, designated GOLDEN model, was developed and validated. The AUCs of GOLDEN model were 0.981 (95% confidence interval [CI]: 0.974–0.987) and 0.979 (95% CI: 0.974–0.983) in the training and external validation sets, respectively, and were significantly better than those of a single qHBsAg measurement. GOLDEN model identified 8.5–10.4% of patients with a high probability of HBsAg loss (5-year cumulative incidence: 17.0–29.1%) and was able to exclude 89.6–91.5% of patients whose incidence of HBsAg loss is 0. Moreover, the GOLDEN model consistently showed excellent performance among various subgroups.

Conclusion: The novel GOLDEN model, based on longitudinal quantitative Hepatitis B surface antigen (qHBsAg) data, accurately predicts HBsAg clearance, provides reliable estimates of functional hepatitis B virus (HBV) cure and may have the potential to stratify different subsets of patients for novel anti-HBV therapies.

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Clinical outcomes of untreated adults living with chronic hepatitis B in The Gambia: An analysis of data from the prospective PROLIFICA cohort study

Background: Expanding antiviral therapy to people with chronic hepatitis B virus (HBV) infection who are ineligible to receive treatment under current international criteria has been increasingly debated. Evidence to support this approach is scarce, especially in Africa. The authors aimed to address this knowledge gap by analysing the clinical outcomes of people with chronic hepatitis B in The Gambia who were untreated and ineligible for antiviral therapy at diagnosis.
Methods: Between December 7, 2011, and January 24, 2014, the authors implemented the prospective PROLIFICA cohort study in The Gambia. Participants with chronic hepatitis B aged 16 years or older were recruited after large-scale, community-based HBV screening; blood bank-based HBV screening in Edward Francis Small Teaching Hospital, Banjul; and prospective follow-up of HBsAg-positive individuals via historical, population-based HBsAg serosurveys in 2 rural villages (Keneba and Manduar). Participants underwent HBV serology and other laboratory tests, fasting FibroScan, and abdominal ultrasound. Survival data were collected between December 7, 2011, and August 17, 2021. Between October 9, 2018, and August 17, 2021, all HBsAg-positive participants enrolled in the 2011–2014 cohort were invited for a reassessment. For this analysis, the authors included HBsAg-positive people and excluded all participants who were eligible for treatment according to the 2012 European Association for the Study of the Liver (EASL) criteria at baseline and those who were treated irrespective of treatment eligibility. The primary outcome was all-cause mortality, assessed in all treatment-ineligible and treatment-naive participants with follow-up data. The secondary outcome, analysed in those who were reassessed, was disease progression, defined as becoming eligible for antivirals per 2017 EASL criteria; having an increase in liver fibrosis of at least 1 stage; or having a clinical diagnosis of hepatic decompensation or hepatocellular carcinoma.
Findings: 943 HBsAg-positive people with chronic hepatitis B were recruited to the PROLIFICA study. Of these 943, 58 (6%) fulfilled 2012 EASL treatment eligibility criteria at baseline, 35 (4%) were ineligible for treatment but received antiviral therapy, and 44 (5%) were immediately lost to follow-up. Thus, 806 (85%) participants were analysed for the primary outcome (486 [60%] were male and 320 [40%] were female).

After a median follow-up of 6.11 years (interquartile range, 5.34–6.80), 708 (88%) participants were confirmed to be alive at last surveillance, 71 (9%) were lost to follow-up and were censored, and 27 (3%) died, giving an all-cause mortality rate of 582 per 100,000 person-years (95% confidence interval [CI]: 399–849). Of the 27 people who died, 5 (19%) had liver-related deaths. Of 708 participants confirmed to be alive, 544 (77%) attended follow-up and were assessed for the secondary outcome. Disease progression occurred in 36 (7%) participants: 5 (1%) became newly eligible for antiviral therapy per EASL 2017 criteria without liver fibrosis progression; 18 (3%) had liver fibrosis progression alone; 13 (2%) had liver fibrosis progression and newly fulfilled the treatment criteria; and none had hepatic decompensation or developed hepatocellular carcinoma. In multivariable analysis adjusted for sex and age, only a baseline HBV DNA of 20,000 IU/mL or more, compared with the baseline HBV DNA of 2000 IU/mL or lower as the reference, was significantly associated with liver disease progression (odds ratio = 5.39, 95% CI: 1.37–21.23).

Interpretation: Among people with chronic hepatitis B who were ineligible for antiviral therapy in The Gambia, all-cause mortality and liver disease progression were low. The clinical benefit of expanding antiviral therapy in this subgroup of patients remains uncertain.

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EXPERT OPINION

Prof. Dr. Tobias Böttler

Natural Course of Hepatitis B Virus Infections without Antiviral Therapy in The Gambia – Implications for the New WHO Guidelines?

The indication for initiating antiviral therapy in individuals with chronic hepatitis B virus (HBV) infection is based on the assessment of the extent of liver damage, inflammatory activity, and viral load. This requires regular specialist consultations with appropriate diagnostic procedures. However, despite the resource-intensive nature of this diagnostic approach, "gray areas" remain in which available guidelines provide inconsistent recommendations. The situation is even more complex in developing countries, where resources are often limited and HBV incidence tends to be very high. To address this, the World Health Organization (WHO) recently published new guidelines on hepatitis B, which simplified the criteria for initiating antiviral therapy. These changes significantly expand the number of individuals eligible for treatment. Within this context, the present study is highly significant. The authors investigated the natural course of chronic HBV infection in individuals in The Gambia who did not qualify for antiviral therapy according to the European Association for the Study of the Liver (EASL) criteria. The study, which followed a cohort

of initially over 800 individuals for nearly 7 years, showed that 5 liver-related deaths occurred during this period. Out of 544 people who were followed up with full liver assessment, only 18 individuals (3%) became newly eligible for antiviral treatment according to the current guidelines. 18 additional individuals (3%) had fibrosis progression without meeting the criteria for antiviral therapy. Meanwhile, the majority of participants maintained a stable infection without any progression of liver disease. The question is whether the relatively low number of individuals with a progressive course of the disease justifies expanding treatment indications. Although antiviral therapy is generally well tolerated and can be administered with minimal hesitation, maintaining strict treatment adherence is crucial. Interruptions in treatment often result in severe viral flares and potentially lead to liver failure. Whether expanding treatment indications in resource-limited countries could lead to an increase in such dramatic disease courses remains to be seen. In any case, the results of this study are highly significant in advancing our understanding of the natural course of uncomplicated and untreated HBV infection. ∎

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Recompensation of chronic hepatitis C-related decompensated cirrhosis following direct-acting antiviral therapy: Prospective cohort study from a hepatitis C virus elimination program

Background and aims: Chronic hepatitis C-related decompensated cirrhosis is associated with lower sustained virological response (SVR)-12 rates and variable regression of disease severity after direct-acting antiviral agents. The authors assessed rates of SVR-12, recompensation (Baveno VII criteria), and survival in such patients.
Methods: Between July 2018 and July 2023, patients with decompensated chronic hepatitis C-related cirrhosis after direct-acting antiviral agents treatment were evaluated for SVR-12 and then had 6-monthly follow-up.
Results: Of 6516 patients with cirrhosis, 1152 with decompensated cirrhosis (age 53.2 ± 11.5 years; 63% men; Model for End-stage Liver Disease-Sodium [MELD-Na]: 16.5 ± 4.6; 87% genotype 3) were enrolled. SVR-12 was 81.8% after 1 course; ultimately SVR was 90.8% after additional treatment. Decompensation events included ascites (1098; 95.3%), hepatic encephalopathy (191; 16.6%), and variceal bleeding (284; 24.7%). Ascites resolved in 86% (diuretic withdrawal achieved in 24% patients). Recompensation occurred in 284 (24.7%) at a median time of 16.5 (interquartile range, 14.5–20.5) months. On multivariable Cox proportional hazards analysis, low bilirubin (adjusted hazard ratio [aHR] = 0.6; 95% confidence interval [CI]: 0.5–0.8; p < 0.001), international normalized ratio (aHR = 0.2; 95% CI: 0.1–0.3; p < 0.001), absence of large esophageal varices (aHR = 0.4; 95% CI: 0.2–0.9; p = 0.048), or gastric varices (aHR = 0.5; 95% CI: 0.3–0.7; p = 0.022) predicted recompensation. Portal hypertension progressed in 158 (13.7%) patients, with rebleed in 4%. Prior decompensation with

variceal bleeding (aHR = 1.6; 95% CI: 1.2–2.8; p = 0.042), and presence of large varices (aHR = 2.9; 95% CI: 1.3–6.5; p < 0.001) were associated with portal hypertension progression. Further decompensation was seen in 221 (19%); 145 patients died and 6 underwent liver transplantation. A decrease in MELD-Na of ≥ 3 was seen in 409 (35.5%) and a final MELD-Na score of < 10 was seen in 335 (29%), but 2.9% developed hepatocellular carcinoma despite SVR-12.

Conclusions: Sustained virological response (SVR)-12 in hepatitis C virus-related decompensated cirrhosis in a predominant genotype 3 population led to recompensation in 24.7% of patients over a follow-up of 4 years in a public health setting. Despite SVR-12, new hepatic decompensation evolved in 19% and hepatocellular carcinoma developed in 2.9% of patients.

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Phase 1b/2a randomized study of heterologous ChAdOx1-HBV/MVA-HBV therapeutic vaccination (VTP-300) as monotherapy and combined with low-dose nivolumab in virally suppressed patients with CHB

Background and aims: The induction of effective CD8+ T cells is thought to play a critical role in the functional cure of chronic hepatitis B (CHB). Additionally, the use of checkpoint inhibitors is being evaluated to overcome T-cell dysfunction during CHB.
Methods: A chimpanzee adenoviral vector (ChAdOx1-HBV) and a modified vaccinia Ankara boost (MVA-HBV) encoding the inactivated polymerase, core, and S region from a consensus genotype C hepatitis B virus (HBV) were studied. 55 patients with virally suppressed CHB and hepatitis B surface antigen (HBsAg) < 4000 IU/ml were enrolled. Group 1 received MVA-HBV intramuscularly on day 0 and 28, group 2 received ChAdOx1-HBV on day 0 and MVA-HBV on day 28 (VTP-300), group 3 received VTP-300 + low-dose nivolumab (LDN) on day 28, and group 4 received VTP-300 plus LDN with both injections.
Results: VTP-300 alone and in combination with LDN was well tolerated with no treatment-related serious adverse events. Reductions of HBsAg were demonstrated in group 2: 3 of 18 patients with starting HBsAg < 50 IU/ml had durable $\log_{10}$ declines of > 0.7 $\log_{10}$ at 2 months after the last dose. Group 3 (n = 18) had mean reductions in HBsAg of 0.76 $\log_{10}$ and 0.80 $\log_{10}$ (p < 0.001) at 2 and 7 months after the last dose. Two patients developed persistent non-detectable HBsAg levels. CD4+ and CD8+ antigen-specific T-cell responses were generated and there was a correlation between interferon-γ ELISpot response and HBsAg decline in group 2.

Conclusions: VTP-300 induced CD4+ and CD8+ T cells and lowered hepatitis B surface antigen in a subset of patients with baseline values below 100 IU/ml. The addition of low-dose nivolumab resulted in significant reduction in surface antigen. VTP-300 is a promising immunotherapeutic that warrants further development alone or in combination therapies.

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Porcine-derived pancreatic enzyme replacement therapy may be linked to chronic hepatitis E virus infection in cystic fibrosis lung transplant recipients

Objectives: In high-income countries hepatitis E virus (HEV) is an uncommonly diagnosed porcine-derived zoonosis. After identifying disproportionate chronic HEV infections in persons with cystic fibrosis (pwCF) postlung transplant, the authors sought to understand its epidemiology and potential drivers.
Design: All pwCF post-transplant attending the regional CF centre were screened for HEV. HEV prevalence was compared against non-transplanted pwCF and with all persons screened for suspected HEV infection from 2016 to 2022 in Alberta, Canada. Those with chronic HEV infection underwent genomic sequencing and phylogenetic analysis. Owing to their swine derivation, independently sourced pancreatic enzyme replacement therapy (PERT) capsules were screened for HEV.
Results: HEV seropositivity was similar between transplanted and non-transplanted pwCF (6/29 [21%] vs. 16/83 [19%]; p = 0.89). Relative to all other Albertans investigated for HEV as a cause of hepatitis (n = 115/1079, 10.7%), pwCF had a 2-fold higher seropositivity relative risk and this was 4 times higher than the Canadian average. Only 3 chronic HEV infection cases were identified in all of Alberta, all in CF lung transplant recipients (n = 3/29, 10.3%). Phylogenetics confirmed cases were unrelated porcine-derived HEV genotype 3a. 91% of pwCF were taking PERT (median 8760 capsules/person/year). HEV RNA was detected by RT-qPCR in 44% (47/107) of PERT capsules, and sequences clustered with chronic HEV cases.

Conclusion: Persons with cystic fibrosis (pwCF) had disproportionate rates of hepatitis E virus (HEV) seropositivity, regardless of transplant status. Chronic HEV infection was evident only in CF transplant recipients. HEV may represent a significant risk for pwCF, particularly post-transplant. Studies to assess HEV incidence and prevalence in pwCF, and potential role of pancreatic enzyme replacement therapy are required.

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VIR-2218 (elebsiran) plus pegylated interferon-alfa-2a in participants with chronic hepatitis B virus infection: A phase 2 study

Background: Chronic hepatitis B virus (HBV) remains a global concern, with current treatments achieving low rates of hepatitis B surface antigen (HBsAg) seroclearance. VIR-2218 (elebsiran), a small interfering RNA agent against HBV transcripts, reduces HBsAg concentrations. The authors aimed to evaluate the safety and antiviral activity of VIR-2218 with and without pegylated interferon-alfa-2a treatment in participants with chronic HBV.

Methods: This open-label, phase 2 study was conducted at 23 sites in 6 countries (New Zealand, Australia, Hong Kong, Thailand, South Korea, and Malaysia). Adults (aged 18–65 years) with chronic HBV infection without cirrhosis and with HBsAg more than 50 IU/ml and HBV DNA less than 90 IU/ml who were on continued nucleoside or nucleotide reverse transcriptase inhibitor (NRTI) therapy for 2 months or longer were eligible. Participants were enrolled into 1 of 6 cohorts to receive VIR-2218 200 mg subcutaneously every 4 weeks, with or without 180 µg subcutaneous pegylated interferon-alfa-2a once per week. Cohort 1 received 6 doses of VIR-2218 (total 20 weeks); cohort 2 received 6 doses of VIR-2218 starting at day 1, plus 12 doses of pegylated interferon-alfa-2a starting at week 12 (total 24 weeks); cohort 3 received 6 doses of VIR-2218 and 24 doses of pegylated interferon-alfa-2a (total 24 weeks); cohort 4 received 6 doses of VIR-2218 and up to 48 doses of pegylated interferon-alfa-2a (total 48 weeks); cohort 5 received up to 13 doses of VIR-2218 and up to 44 doses of pegylated interferon-alfa-2a (total 48 weeks); and cohort 6 received 3 doses of VIR-2218 and 12 doses of pegylated interferon-alfa-2a (total 12 weeks). The primary endpoints were the incidence of adverse events and clinical assessments (including results of laboratory tests). Secondary endpoints were the mean maximum reduction of serum HBsAg at any timepoint; the proportion of participants with serum HBsAg seroclearance at any timepoint and for more than 6 months after the end of treatment; and the proportion of participants with anti-HBs seroconversion at any timepoint. For patients who were hepatitis B e antigen (HBeAg)-positive, the authors also assessed the proportion with HBeAg seroclearance or anti-HBe seroconversion at any timepoint.

Findings: Between July 2, 2020, and November 2, 2021, 124 individuals were screened for eligibility, 84 of whom were enrolled (15 in cohort 1, 15 in cohort 2, 18 in cohort 3, 18 in cohort 4, 13 in cohort 5, and 5 in cohort 6). Participants were predominantly HBeAg-negative, Asian, and male (66 [79%] participants were male and 18 [21%] were female). Most treatment-emergent adverse events were grades 1–2. Three (20%) participants in cohort 1, 4 (27%) in cohort 2, 8 (44%) in cohort 3, 7 (39%) in cohort 4, 6 (46%) in cohort 5, and 2 (40%) in cohort 6 reported treatment-emergent adverse events related to VIR-2218. 12 (80%) participants in cohort 2, 12 (67%) in cohort 3, 14 (78%) in cohort 4, 13 (100%) in cohort 5, and 3 (60%) in cohort 6 reported treatment-emergent adverse events related to pegylated interferon-alfa-2a.

Two (13%) participants in cohort 1 had elevations in alanine aminotransferase, compared with 13 (87%) participants in cohort 2, 15 (83%) in cohort 3, 17 (94%) in cohort 4, 11 (85%) in cohort 5, and 3 (60%) in cohort 6. The mean maximum change from baseline at any timepoint in HBsAg concentration was -2.0 $\log_{10}$ IU/ml (95% confidence interval: -2.1 to -1.8) in cohort 1, -2.2 $\log_{10}$ IU/ml (-2.5 to -1.8) in cohort 2, -2.5 $\log_{10}$ IU/ml (-2.8 to -2.1) in cohort 3, -2.4 $\log_{10}$ IU/ml (-3.1 to -1.8) in cohort 4, -3.0 $\log_{10}$ IU/ml (-3.7 to -2.3) in cohort 5, and -1.7 $\log_{10}$ IU/ml (-2.1 to -1.4) in cohort 6. 11 participants (1 in cohort 2, 1 in cohort 3, 5 in cohort 4, and 4 in cohort 5) receiving VIR-2218 plus pegylated interferon-alfa-2a had HBsAg seroclearance at any timepoint. Of these, 10 (91%; 1 in cohort 2, 5 in cohort 4, and 4 in cohort 5) had anti-HBs seropositivity. Six participants (1 in cohort 2, 3 in cohort 4, and 2 in cohort 5) had sustained HBsAg seroclearance through to 24 weeks after the end of treatment. No participants receiving VIR-2218 monotherapy (cohort 1) or VIR-2218 plus pegylated interferon-alfa-2a 12-week regimen (cohort 6) had HBsAg seroclearance. 12 (42%) of 26 participants (1 of 4 in cohort 1, 2 of 6 in cohort 2, 4 of 7 in cohort 3, 4 of 6 in cohort 4, and 1 of 3 in cohort 5) who were HBeAg-positive at baseline had HBeAg seroclearance or anti-HBe seroconversion.

Interpretation: The results of this phase 2 study support further development of VIR-2218 as a potential therapy for patients with chronic hepatitis B virus infection. Additional clinical trials of VIR-2218 with and without pegylated interferon-alfa-2a in combination with a hepatitis B surface antigen-targeting monoclonal antibody are ongoing.

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Bulevirtide monotherapy in patients with chronic HDV: Efficacy and safety results through week 96 from a phase 3 randomized trial

Background and aims: Bulevirtide (BLV), a first-in-class entry inhibitor, is approved in Europe for the treatment of chronic hepatitis delta (CHD). BLV monotherapy was superior to delayed treatment at week (W) 48, the primary efficacy endpoint, in the MYR301 study. Here, the authors assessed if continued BLV therapy until W96 would improve virologic and biochemical response rates, particularly among patients who did not achieve virologic response at W24.

Methods: In this ongoing, open-label, randomized phase 3 study, patients with CHD (n = 150) were rand-

omized (1:1:1) to treatment with BLV 2 mg/day (n = 49) or 10 mg/day (n = 50), each for 144 weeks, or to delayed treatment for 48 weeks followed by BLV 10 mg/day for 96 weeks (n = 51). Combined response was defined as undetectable hepatitis delta virus (HDV) RNA or a decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/ml from baseline and alanine aminotransferase (ALT) normalization. Other endpoints included virologic response, ALT normalization, and change in HDV RNA.

Results: Of 150 patients, 143 (95%) completed 96 weeks of the study. Efficacy responses were maintained and/or improved between W48 and W96, with similar combined, virologic, and biochemical response rates between BLV 2 and 10 mg. Of the patients with a suboptimal early virologic response at W24, 43% of non-responders and 82% of partial responders achieved virologic response at W96. Biochemical improvement often occurred independently of virologic response. Adverse events were mostly mild, with no serious adverse events related to BLV.

Conclusions: Virologic and biochemical responses were maintained and/or increased with longer term bulevirtide (BLV) therapy, including in those with suboptimal early virologic response. BLV monotherapy for chronic hepatitis delta was safe and well tolerated through week 96.

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Steatotic Liver Disease incl. MASLD*

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

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Effects of empagliflozin on liver fat in patients with metabolic dysfunction-associated steatotic liver disease without diabetes mellitus: A randomized, double-blind, placebo-controlled trial

Background and aims: The authors investigated whether empagliflozin reduces hepatic steatosis in patients with metabolic dysfunction-associated steatotic liver disease without diabetes mellitus.
Approach and results: This was an investigator-initiated, double-blind, randomized, placebo-controlled trial recruiting adult subjects from the community. Eligible subjects without diabetes mellitus (fasting plasma glucose < 7 mmol/L and HbA1c < 6.5%) who had magnetic resonance imaging-proton density fat fraction (MRI-PDFF) ≥ 5% were randomly allocated to receive empagliflozin 10 mg daily or placebo (1:1 ratio) for 52 weeks (end of treatment, EOT). MRI-PDFF was conducted at baseline and EOT. The primary outcome was the difference in change of MRI-PDFF between the 2 groups at EOT. Secondary outcomes were hepatic steatosis resolution (MRI-PDFF < 5%), alanine aminotransferase drop ≥ 17 U/L, MRI-PDFF decline ≥ 30%, a combination of both, and changes of anthropometric and laboratory parameters at EOT. All outcomes were based on intention-to-treat analysis. Of 98 recruited subjects (median age: 55.7 years [interquartile range, 49.5–63.4]; male: 54 [55.1%]), 97 (empagliflozin: 49, placebo: 48; median MRI-PDFF: 9.7% vs. 9.0%) had MRI-PDFF repeated at EOT. The empagliflozin group had a greater reduction in median MRI-PDFF compared to the placebo group (-2.49% vs. -1.43%; p = 0.025), with a nonsignificant trend of resolution of hepatic steatosis (44.9% vs. 28.6%; p = 0.094). There was no significant difference in alanine aminotransferase drop ≥ 17 U/L (16.3% vs. 12.2%; p = 0.564), MRI-PDFF drop ≥ 30% (49.0% vs. 40.8%; p = 0.417), and composite outcome (8.2% vs. 8.2%; p = 1.000). The empagliflozin group had a greater drop in body weight (-2.7 vs. -0.2 kg), waist circumference (-2.0 vs. 0 cm), fasting glucose (-0.3 vs. 0 mmol/L), and ferritin (-126 vs. -22 pmol/L) (all p < 0.05).

Conclusions: Empagliflozin for 52 weeks reduces hepatic fat content in subjects with non-diabetic metabolic dysfunction-associated steatotic liver disease.

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Synergistic association of sodium-glucose cotransporter-2 inhibitor and metformin on liver and non-liver complications in patients with type 2 diabetes mellitus and metabolic dysfunction-associated steatotic liver disease

Objective: Type 2 diabetes mellitus and metabolic dysfunction-associated steatotic liver disease (diabetic MASLD) frequently coexist and worsen liver and non-liver outcomes, but effective pharmacological therapies are limited. The authors aimed to evaluate the long-term effect of sodium-glucose cotransporter-2 inhibitor (SGLT-2i) on liver and non-liver outcomes among patients with diabetic MASLD.
Design: This population-based cohort study retrieved patients with diabetic MASLD from Merative Marketscan Research Databases (April 2013 and December 2021). The active comparator was other glucose-lowering drugs (oGLDs). Primary outcomes were liver complications including hepatocellular carcinoma (HCC) and liver cirrho-

sis, as well as non-liver complications including cardio-vascular disease (CVD), chronic kidney disease (CKD) and non-liver cancer. Propensity score matching was applied and Cox regression models were conducted.
Results: Compared with oGLD, SGLT-2i users had significantly lower risk of HCC (hazard ratio [HR] = 0.76, 95% confidence interval [CI]: 0.62–0.93), liver cirrhosis (HR = 0.80, 95% CI: 0.76–0.84), CVD (HR = 0.82, 95% CI: 0.79–0.85) and CKD (HR = 0.66, 95% CI: 0.62–0.70), non-liver cancer (HR = 0.81, 95% CI: 0.76–0.86). Compared with patients without metformin and SGLT-2i, a stepwise decreasing risk was observed in users of either metformin or SGLT-2i (HRs = 0.76–0.97) and in users of both medications (HRs = 0.58–0.79). The lower risk also was shown in liver decompensation, compensated cirrhosis, major CVD, end-stage renal disease and specific common cancers (HRs = 0.61–0.84).

Conclusion: In a nationwide cohort, sodium-glucose cotransporter-2 inhibitor users were associated with a substantially lower risk of liver and non-liver complications than other glucose-lowering drug users among patients with diabetic metabolic dysfunction-associated steatotic liver disease. The risk was further reduced with concomitant metformin use.

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EXPERT OPINION

Dr. Dr. Natascha Röhlen

Benefits of SGLT-2 Inhibitors in Diabetes Therapy for Patients with MASLD

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease in Western industrialized nations, affecting around 30% of the population worldwide. Both liver-specific and cardiovascular complications are responsible for the increased mortality of patients with MASLD. Coexistence of type 2 diabetes particularly increases the risk of hepatocellular carcinoma (HCC) and cardiovascular events in patients with MASLD. In their population-based retrospective cohort study recently published in *Gut*, Mao et al. investigated the influence of diabetes therapy with sodium-glucose cotransporter-2 (SGLT-2) inhibitors on hepatological and non-hepatological complications of MASLD. Using a US-wide database and documented health data from 2007 to 2021, the study included 399,126 patients with MASLD and type 2 diabetes (54.3% female, mean age: 54.4 years). Patients in the SGLT-2 inhibitor group (1 or more prescriptions for an SGLT-2 inhibitor alone or in combination with other glucose-lowering drugs [oGLDs], 15.7% of all included patients) were more frequently overweight and had diabetic complications at study inclusion compared to the group of patients taking oGLDs (oGLD group, taking 1 or more of the following glucose-lowering drugs: metformin, insulin, sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors,

glucagon-like peptide-1 agonists, meglitinides). After propensity score matching to balance baseline characteristics, between 39,822 and 53,628 patients per treatment group were analyzed regarding the respective outcomes. Interestingly, patients with documented use of an SGLT-2 inhibitor showed a reduced incidence of liver cirrhosis and HCC, as well as cardiovascular disease, chronic kidney disease, and specific common cancers compared to the oGLD group. The greatest risk reduction was observed for chronic kidney disease (hazard ratio [HR] = 0.66; p < 0.001) and the incidence of HCC (HR = 0.76; p < 0.001). A lower risk of hepatic decompensation (HR = 0.79; p < 0.001), myocardial infarction, stroke, or heart failure (HR = 0.66; p < 0.001), and end-stage renal disease (HR = 0.61; p < 0.001) was also observed. The risk reduction was also consistent in the subgroups stratified according to gender, age, diabetic secondary diseases, and duration of diabetic medication. Remarkably, the combined use of metformin and SGLT-2 inhibitors showed a synergistic protective effect on all primary outcomes compared to the use of the individual substances.

In summary, these data underline the need for interdisciplinary hepatologic and diabetologic treatment of patients with MASLD and type 2 diabetes. While the current study underpins the protective effects of SGLT-2 inhibitors and metformin with regard to liver-specific complications but also other associated conditions, other more recent studies have demonstrated the protective effects of GLP-1 receptor agonists on hepatological outcomes in patients with MASLD (Engström A et al., Hepatology. 2024; Simon TG et al., Clin Gastroenterol Hepatol. 2022). Thus, within the corresponding indication and approval restrictions, SGLT-2 inhibitors, GLP-1 analogues and metformin should be preferred for the treatment of type 2 diabetes in MASLD patients. The observed protective effects on the incidence of HCC and other malignancies are also noteworthy. Due to the retrospective design of this study, the dependence of these protective effects on blood glucose control as well as the molecular mechanisms of the described tumor-preventive effects are still unclear. Future prospective studies are needed to answer these questions. ■

Vitellius C, Desjonqueres E, Lequoy M, Amaddeo G, Fouchard I, N'Kontchou G, Canivet CM, Ziol M, Regnault H, Lannes A, Oberti F, Boursier J, Ganne-Carrie N

MASLD-related HCC: Multicenter study comparing patients with and without cirrhosis

Background and aims: Despite its growing incidence, hepatocellular carcinoma (HCC) related to metabolic dysfunction-associated steatotic liver disease (MASLD) in non-cirrhotic livers remains poorly characterized. The authors compared the characteristics, management, survival, and trends of MASLD-related HCC in patients with or without underlying cirrhosis in a large multicenter cohort.
Methods: A total of 354 cases of MASLD-related HCC presented at the liver tumor meetings of 4 French university hospitals between 2007 and 2018 were included in the study. Data were extracted from the meetings' databases and from the French Birth and Death Registry.

Results: Of HCC cases, 35% occurred in the absence of cirrhosis. HCC was diagnosed through screening in 60% of patients with cirrhosis, and incidentally in 72% of patients without it. Patients without cirrhosis were older, had a greater tumor burden, but also better liver function than patients with cirrhosis. Patients without cirrhosis showed better overall survival than those with cirrhosis (p = 0.043). However, cirrhosis was not independently associated with overall survival, the independent predictors were age, liver function, tumor burden and BCLC classification. Patients without cirrhosis underwent surgery more frequently than patients with cirrhosis (41% vs. 11%, p < 0.001), even in cases where the largest tumors were ≥ 5 cm (42% vs. 14%, p = 0.002) or there were 4 or more lesions (19% vs. 2%, p = 0.024). Among the patients (with/without cirrhosis) who underwent surgery, survival was not significantly different. The cirrhosis/no cirrhosis ratio remained stable over the study period.

Conclusions: In metabolic dysfunction-associated steatotic liver disease-related hepatocellular carcinoma, patients without cirrhosis account for 35% of cases and have poor prognostic factors (higher age and larger tumors) but also better liver function, resulting in more aggressive management of advanced tumors and better survival compared to patients with cirrhosis.

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Low-to-moderate alcohol consumption is associated with increased fibrosis in individuals with metabolic dysfunction-associated steatotic liver disease

Background and aims: Both metabolic dysfunction and alcohol consumption cause steatotic liver disease (SLD). The distinction between metabolic dysfunction-associated SLD (MASLD) and metabolic dysfunction-associated and alcohol-associated liver disease (MetALD) categories is based on arbitrary thresholds of alcohol intake. Thus, the authors assessed the impact of different levels of alcohol consumption on SLD severity and their interaction with metabolic comorbidities.
Methods: The authors performed a population-based study with transient elastography data from participants in Spain (derivation cohort) and the US (validation cohort). A controlled attenuation parameter ≥ 275 dB/m was used to define SLD. At least one cardiometabolic risk factor was required to define MASLD. Among patients with MASLD, low alcohol consumption was defined as an average of 5–9 drinks/week, moderate consumption as 10–13 drinks/week for females and 10–20 drinks/week for males, and increased alcohol intake (MetALD) as 14–35 drinks/week for females and 21–42 drinks/week

for males. Significant fibrosis was defined as a liver stiffness measurement ≥ 8 kPa and at-risk metabolic dysfunction-associated steatohepatitis (MASH) as a FAST score ≥ 0.35.
Results: The derivation cohort included 2227 individuals with MASLD (9% reported low, 14% moderate alcohol consumption) and 76 cases with MetALD. Overall prevalences of significant fibrosis and at-risk MASH were 7.6% and 14.8%, respectively. In the multivariable analysis, alcohol consumption was independently associated with significant fibrosis and at-risk MASH. A dose-dependent increase in the prevalence of significant fibrosis and at-risk MASH was observed between the number of drinks/week and the number of cardiometabolic factors. The validation cohort included 1732 participants with MASLD, of whom 17% had significant fibrosis and 13% at-risk MASH. This cohort validated the association between moderate intake and MASLD at risk of progression (odds ratio = 1.69, 95% confidence interval: 1.06–2.71).

Conclusions: Moderate alcohol intake is commonly seen in metabolic dysfunction-associated steatotic liver disease (MASLD) and increases the risk of advanced disease to a level similar to that observed in metabolic dysfunction-associated and alcohol-associated liver disease (MetALD).

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Denifanstat for the treatment of metabolic dysfunction-associated steatohepatitis: A multicentre, double-blind, randomised, placebo-controlled, phase 2b trial

Background: Denifanstat, an oral fatty acid synthase (FASN) inhibitor, blocks de-novo lipogenesis, a key pathway driving progressive lipotoxicity, inflammation, and fibrosis in metabolic dysfunction-associated steatohepatitis (MASH). This study aimed to examine the safety and efficacy of denifanstat for improving liver histology in individuals with MASH and moderate to advanced fibrosis.
Methods: This multicentre, double-blind, randomised, placebo-controlled, phase 2b trial was conducted at 100 clinical sites in the USA, Canada, and Poland. After a screening period of up to 90 days, participants aged 18 years and older with biopsy-confirmed MASH and stage F2 or F3 fibrosis were randomly assigned (2:1) to receive either 50 mg oral denifanstat or placebo once per day for 52 weeks. Participants were dynamically allocated to treatment groups via a centrally adminis-

tered interactive web-based response system and stratified by type 2 diabetes, region, and fibrosis stage. Investigators, patients, and the sponsor were masked to group allocation until database lock. The primary efficacy endpoints were a 2-point or greater improvement in non-alcoholic fatty liver disease activity score (NAS) without a worsening of fibrosis or MASH resolution with a 2-point or greater improvement in NAS without a worsening of fibrosis at week 52, assessed by intention to treat (ITT). Safety was assessed in all participants who received at least 1 dose of study drug. **Findings:** Of the 1087 individuals screened between June 2, 2021, and June 28, 2022, 168 eligible participants were randomly assigned to receive a dose of 50 mg denifanstat once per day (n = 112) or placebo (n = 56). All 168 participants (100 female, 68 male) received at least 1 dose of study treatment. In the ITT population, 42 (38%) of 112 participants in the denifanstat group had a 2-point or greater improvement in NAS without a worsening of fibrosis versus 9 (16%) of 56 participants in the placebo group (common risk difference, 21.0%, 95% confidence interval [CI]: 8.1–33.9; p = 0.0035). 29 (26%) of 112 participants in the denifanstat group showed MASH resolution with a 2-point or greater improvement in NAS without a worsening of fibrosis compared with 6 (11%) of 56 participants in the placebo group (common risk difference, 13.0%, 95% CI: 0.7–25.3; p = 0.0173). The most common treatment-emergent adverse events were COVID-19 (19/112 [17%] in the denifanstat group vs. 6/56 [11%] in the placebo group), dry eye symptoms (10/112 [9%] vs. 8/56 [14%]), and alopecia (21/112 [19%] vs. 2/56 [4%]). All adverse events considered to be related to the study drug were of grade 1 or grade 2. None of the serious adverse events (13/112 [12%] participants in the denifanstat group vs. 3/56 [5%] in the placebo group) were considered drug-related.

Interpretation: Treatment with denifanstat resulted in statistically significant and clinically meaningful improvements in disease activity, metabolic dysfunction-associated steatohepatitis resolution, and fibrosis. The results of this phase 2b trial support the advancement of denifanstat to phase 3 development.

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AIH/PBC/PSC

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Optimizing thiopurine therapy in autoimmune hepatitis: A multicenter study on monitoring metabolite profiles and co-therapy with allopurinol

Background and aims: In autoimmune hepatitis, achieving complete biochemical remission (CBR) with current weight-based thiopurine dosing is challenging. The authors investigated whether patients could be stratified regarding CBR according to a target range of thiopurine metabolites. Moreover, they explored the effects of azathioprine dosage increases and co-therapy of allopurinol with low-dose thiopurines on metabolite profiles and treatment response.

Approach and results: The relation between metabolites and treatment response was assessed in 337 individuals from 4 European centers. In a global, cross-sectional analysis, active metabolites 6-thioguanine nucleotides (6TGN) were similar in those with and without CBR. However, analyzing patients with sequential measurements over 4 years (n = 146) revealed higher average 6TGN levels in those with stable CBR (260 pmol/0.2 ml) compared to those failing to maintain CBR (181 pmol/0.2 ml; p = 0.0014) or never achieving CBR (153 pmol/0.2 ml; p < 0.0001), with an optimal 6TGN cutoff of ≥ 223 pmol/0.2 ml (sensitivity: 76% and specificity: 78%). Only 42% exhibited 6TGN ≥ 223 pmol/0.2 ml following weight-based dosing, as doses weakly correlated with 6TGN but with 6-methylmercaptopurine (6MMP), a metabolite associated with toxicity. Azathioprine dose increases led to preferential 6MMP formation (+127% vs. 6TGN +34%; p < 0.0001). Conversely, adding allopurinol to thiopurines in difficult-to-treat patients (n = 36) raised 6TGN (168→321 pmol/0.2 ml; p < 0.0001) and lowered 6MMP (2125→184 pmol/0.2 ml; p < 0.0001), resulting in improved transaminases in all patients and long-term CBR in 75%.

Conclusions: Maintaining complete biochemical remission (CBR) in autoimmune hepatitis was associated with 6-thioguanine nucleotides (6TGN) ≥ 223 pmol/0.2 mL. For patients who fail to achieve CBR and therapeutic 6TGN levels despite thiopurine dose increase due to preferential 6-methylmercaptopurine formation, comedication of allopurinol alongside low-dose thiopurines represents an efficient alternative.

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Gut pathobiont-derived outer membrane vesicles drive liver inflammation and fibrosis in primary sclerosing cholangitis-associated inflammatory bowel disease

Background and aims: Primary sclerosing cholangitis (PSC), often associated with inflammatory bowel disease (IBD), presents a multifactorial etiology involving genetic, immunologic, and environmental factors. Gut dysbiosis

and bacterial translocation have been implicated in PSC-IBD, yet the precise mechanisms underlying their pathogenesis remain elusive. Here, the authors describe the role of gut pathobionts in promoting liver inflammation and fibrosis due to the release of bacterial outer membrane vesicles (OMVs).

Methods: Preclinical mouse models in addition to ductal organoids were used to acquire mechanistic data. A proof-of-concept study including serum and liver biopsies of a patient cohort of PSC (n = 22), PSC-IBD (n = 45), and control individuals (n = 27) was performed to detect OMVs in the systemic circulation and liver.

Results: In both preclinical model systems and in patients with PSC-IBD, the translocation of OMVs to the liver correlated with enhanced bacterial sensing and accumulation of the NLRP3 inflammasome. Using ductal organoids, the authors were able to precisely attribute the pro-inflammatory and pro-fibrogenic properties of OMVs to signaling pathways dependent on Toll-like receptor 4 and NLRP3-gasdermin-D. The immunostimulatory potential of OMVs could be confirmed in macrophages and hepatic stellate cells. Furthermore, when gut pathobiont-derived OMVs were administered to Mdr2$^{-/-}$ mice, the authors observed a significant enhancement in liver inflammation and fibrosis. In a translational approach, they substantiated the presence of OMVs in the systemic circulation and hepatic regions of severe fibrosis using a PSC-IBD patient cohort.

Conclusions: This study demonstrates the contribution of gut pathobionts in releasing outer membrane vesicles (OMVs) that traverse the mucosal barrier and, thus, promote liver inflammation and fibrosis in primary sclerosing cholangitis associated with inflammatory bowel disease. OMVs might represent a critical new environmental factor that interacts with other disease factors to cause inflammation and thus define potential new targets for fibrosis therapy.

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A genome-wide association study identified PTPN2 as a population-specific susceptibility gene locus for primary biliary cholangitis

Background and aims: Previous genome-wide association studies (GWAS) have indicated the involvement of shared (population-non-specific) and non-shared (population-specific) susceptibility genes in the pathogenesis of primary biliary cholangitis (PBC) among European and East-Asian populations. Although a meta-analysis of these distinct populations has recently identified more than 20 novel PBC susceptibility loci, analyses of population-specific genetic architecture are still needed for a more comprehensive search for genetic factors in PBC.

Approach and results: Protein tyrosine phosphatase non-receptor type 2 (PTPN2) was identified as a novel PBC susceptibility gene locus through GWAS and subsequent genome-wide meta-analysis involving 2181 cases and 2699 controls from the Japanese population (GWAS-lead variant: rs8098858, p = 2.6 × 10^{-8}). In silico and in vitro functional analyses indicated that the risk allele of rs2292758, which is a primary functional variant, decreases PTPN2 expression by disrupting Sp1 binding to the PTPN2 promoter in T follicular helper cells and plasmacytoid dendritic cells. Infiltration of PTPN2-positive T-cells and plasmacytoid dendritic cells was confirmed in the portal area of the PBC liver by immunohistochemistry. Furthermore, transcriptomic analysis of PBC-liver samples indicated the presence of a compromised negative feedback loop in vivo between PTPN2 and IFNG in patients carrying the risk allele of rs2292758.

Conclusions: Protein tyrosine phosphatase non-receptor type 2 (PTPN2), a novel susceptibility gene for primary biliary cholangitis (PBC) in the Japanese population, may be involved in the pathogenesis of PBC through an insufficient negative feedback loop caused by the risk allele of rs2292758 in IFN-γ signaling. This suggests that PTPN2 could be a potential molecular target for PBC treatment.

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Inherited Liver Disease

Clark VC, Strange C, Strnad P, Sanchez AJ, Kwo P, Pereira VM, van Hoek B, Barjaktarevic I, Corsico AG, Pons M, Goldklang M, Gray M, Kuhn B, Vargas HE, Vierling JM, Vuppalanchi R, Brantly M, Kappe N, Chang T, Schluep T, Zhou R, Hamilton J, San Martin J, Loomba R

Fazirsiran for adults with alpha-1 antitrypsin deficiency liver disease: A phase 2 placebo controlled trial (SEQUOIA)

Background and aims: Homozygous ZZ alpha-1 antitrypsin (AAT) deficiency produces mutant AAT (Z-AAT)

proteins in hepatocytes, leading to progressive liver fibrosis. The authors evaluated the safety and efficacy of an investigational RNA interference therapeutic, fazirsiran, that degrades Z-AAT messenger RNA, reducing deleterious protein synthesis.

Methods: This ongoing, phase 2 study randomized 40 patients to subcutaneous placebo or fazirsiran 25, 100, or 200 mg. The primary endpoint was percent change in serum Z-AAT concentration from baseline to week 16. Patients with fibrosis on baseline liver biopsy received treatment on day 1, at week 4, and then every 12 weeks and had a second liver biopsy at or after weeks 48, 72, or 96. Patients without fibrosis received 2 doses on day 1 and at week 4.

Results: At week 16, least-squares mean percent declines in serum Z-AAT concentration were -61%, -83%, and -94% with fazirsiran 25 mg, 100 mg and 200 mg, respectively, versus placebo (all p < 0.0001). Efficacy was sustained through week 52. At postdose liver biopsy, fazirsiran reduced median liver Z-AAT concentration by 93% compared with an increase of 26% with placebo. All fazirsiran-treated patients had histologic reduction from baseline in hepatic globule burden. Portal inflammation improved in 5 of 12 and 0 of 8 patients with a baseline score of > 0 in the fazirsiran and placebo groups, respectively. Histologic meta-analysis of histologic data in viral hepatitis score improved by > 1 point in 7 of 14 and 3 of 8 patients with fibrosis of > F0 at baseline in the fazirsiran and placebo groups, respectively. No adverse events led to discontinuation, and pulmonary function tests remained stable.

Conclusions: Fazirsiran reduced serum and liver concentrations of mutant Z alpha-1 antitrypsin in a dose-dependent manner and reduced hepatic globule burden.

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Clinical Hepatology/Epidemiology

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Impact of SARS-CoV-2 vaccination in patients with vascular liver diseases: Observations from a VALDIG multicenter study

Background and aims: Patients with vascular liver diseases (VLD) are at higher risk of both severe courses of COVID-19 disease and thromboembolic events. The impact of SARS-CoV-2 vaccination in patients with VLD has not been described and represents the aim of this study.

Methods: International, multicenter, prospective observational study in patients with VLD analyzing the incidence of COVID-19 infection after vaccination, severity of side effects, occurrence of thromboembolic events and hepatic decompensation. In a subgroup of patients, the humoral and cellular responses to vaccination were also analyzed.

Results: A total of 898 patients from 14 European centers – part of the VALDIG network – were included, 872 (97.1%) patients received 2 vaccine doses (fully vaccinated), and 674 (75.1%) 3 doses. Of the total cohort, 151 of 898 had a COVID-19 infection prior to vaccination, of whom 9 of 151 (5.9%) were re-infected. Of the 747 of 898 patients who were not previously infected, 11.2% (84/747) were diagnosed with a COVID-19 infection during the study period. Two infected patients required intensive care unit admission and infection was fatal in 2 fully vaccinated patients. Adverse effects were reported in around 40% of patients, with local side effects being the most frequent. During the study period, 31 (3.5%) patients had thromboembolic events and 21 (2.3%) hepatic decompensations. No cases of vaccine-induced thrombocytopenia were reported. Vaccine immunogenicity was assessed in 36 patients; seroconversion reached 100% and IFNγ T-cell responses significantly increased post 2 mRNA-1273 vaccine doses.

Conclusion: Patients with vascular liver diseases (VLD) seem to have a preserved immune response to SARS-CoV-2 vaccination, which appears to be safe and effective in preventing severe COVID-19 infection. This study cannot definitively establish a direct link between vaccination and thrombotic events, though the contribution of vaccination as a cofactor in VLD remains to be elucidated.

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EXPERT OPINION

PD Dr. Michael Schultheiß

SARS-CoV-2 Vaccination for Vascular Liver Disease: A Sure Thing?!

The VALDIG ("vascular liver disease group") network connects scientists from all over the world to conduct multicenter studies on rare vascular liver diseases. The present international, multicenter, prospective observational study on the effect of SARS-CoV-2 vaccination in patients with vascular liver diseases was conducted to advance this objective. The authors examined the efficacy and safety of the vaccination with mRNA vaccines (87%) and adenoviral vector-based vaccines (13%) in 898 patients – 524 with non-cirrhotic portal vein thrombosis (NCPVT), 234 with porto-sinusoidal vascular disease (PSVD), and 140 with Budd-Chiari syndrome (BCS) – and conducted a follow-up for at least 6 months. The rate and severity of adverse effects of

the vaccination (asthenia, fever) and the immunological protective effect of the vaccination – evidenced by the low incidence of SARS-CoV-2 infections – were broadly comparable with available data. A particular focus was placed on the incidence of hepatic decompensation and thromboembolic events. Hepatic decompensation occurred in 21 patients (2.3%), manifesting as portal-hypertensive bleeding, ascites, or hepatic encephalopathy, mostly within the first week after vaccination. Thromboembolic events were observed in 31 patients (3.5%), with the majority (27/31 = 87%) occurring in the splanchnic venous system. However, most thromboembolic events occurred long after vaccination (18/31 thromboses > 30 days after vaccination; mean time 11 weeks after vaccination). Nearly all splanchnic thromboses were re-thromboses (23/27 patients with re-thrombosis). Among the 4 patients with new splanchnic thrombosis, all developed these events despite therapeutic anticoagulation.

Although the SARS-CoV-2 pandemic began several years ago, the main criticisms of the vaccines approved through fast-track procedures remain fresh in our memory. One serious adverse effect associated with adenoviral vector-based vaccines was thrombosis in the sinus veins and splenic vein, first observed in early 2021. This was later identified as vaccine-induced immune thrombotic thrombocytopenia. Although this immunological effect did not occur in any of the patients in the present trial the study provides valuable insights into the effectiveness and, more importantly, the safety of the SARS-CoV-2 vaccination in a "vulnerable" patient cohort. However, the study's strength is also its weakness. On the one hand, the combination of patients with NCPVT plus PSVD plus BCS alone introduces significant heterogeneity, while on the other hand, the underlying etiologies in these 3 groups are extremely diverse. For assessing thrombosis risk, patients with an underlying hematological/hemostaseological disorder would naturally be of special interest as a distinct subgroup. Finally, the data from this study provides strong support for vaccinators advising patients with vascular liver diseases. ■

Liver Cirrhosis

Pompili E, Zaccherini G, Piano S, Toniutto P, Lombardo A, Gioia S, Iannone G, De Venuto C, Tonon M, Gagliardi R, Baldassarre M, Tedesco G, Bedogni G, Domenicali M, Di Marco V, Nardelli S, Calvaruso V, Bitetto D, Angeli P, Caraceni P

Real-world experience with long-term albumin in patients with cirrhosis and ascites

Background and aims: Long-term albumin (LTA) is currently standard of care for patients with decompensated cirrhosis in many Italian hepatology centres. In this real-life study, the authors aimed to describe patient, logistical and treatment-related characteristics in daily clinical practice and to identify predictors of response.
Methods: The authors performed a multicentre, retrospective, observational study in patients with cirrhosis and ascites receiving LTA between 01/2016 and 02/2022 and followed until death, TIPS (transjugular intrahepatic portosystemic shunt) placement, transplantation or 02/2023.
Results: A total of 312 patients, the majority with alcohol-related cirrhosis, were included. At baseline, median Child-Pugh, MELD, and MELD-Na were 8, 15, and 18, respectively. Ascites was grade 2 in 55% of patients, grade 3 in 35% and refractory in 27%, while 47% had received large volume paracentesis in the previous 6 months. Median LTA was 10 months with a median dose of 40 g/week. Ascites resolved to grade 0–1 in 34% of patients within the first 3 months and 56% by the end of treatment. Predictors of ascites resolution were age (p = 0.007), baseline grade of ascites (p = 0.007), no paracentesis in the previous 6 months (p = 0.001), aetiological treatment in the past 12 months or during LTA (p = 0.005), weekly albumin dose (p = 0.014) and serum albumin concentration of 40 g/L after 1 month of treatment (p = 0.017). Of the 83 patients with refractory ascites at inclusion, 26% had grade 0–1 ascites at the last observation. No severe albumin-related side-effects were reported and only 1% discontinued for logistical reasons.

Conclusions: Long-term albumin (LTA) is feasible as an outpatient treatment for the management of ascites. In the current study, ascites resolved in more than half of patients receiving LTA on top of diuretics, including in some with refractory ascites. Predictors of response to LTA provide useful information for tailoring treatment.

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Zhou XD, Kim SU, Yip TC, Petta S, Nakajima A, Tsochatzis E, Boursier J, Bugianesi E, Hagström H, Chan WK, Romero-Gomez M, Calleja JL, de Lédinghen V, Castéra L, Sanyal AJ, Goh GB, Newsome PN, Fan J, Lai M, Fournier-Poizat C, Lee HW, Wong GL, Armandi A, Shang Y, Pennisi G, Llop E, Yoneda M, Saint-Loup M, Canivet CM, Lara-Romero C, Gallego-Duràn R, Asgharpour A, Teh KK, Mahgoub S, Chan MS, Lin H, Liu WY, Targher G, Byrne CD, Wong VW, Zheng MH; VCTE-Prognosis Study Group

Long-term liver-related outcomes and liver stiffness progression of statin usage in steatotic liver disease

Background: Statins have multiple benefits in patients with metabolic-associated steatotic liver disease (MASLD).
Aim: To explore the effects of statins on the long-term risk of all-cause mortality, liver-related clinical events (LREs) and liver stiffness progression in patients with MASLD.
Methods: This cohort study collected data on patients with MASLD undergoing at least 2 vibration-controlled transient elastography examinations at 16 tertiary referral centres. Cox regression analysis was performed to examine the association between statin usage and long-

term risk of all-cause mortality and LREs stratified by compensated advanced chronic liver disease (cACLD): baseline liver stiffness measurement (LSM) of ≥ 10 kPa. Liver stiffness progression was defined as an LSM increase of ≥ 20% for cACLD and from < 10 kPa to ≥ 10 or LSM for non-cACLD. Liver stiffness regression was defined as LSM reduction from ≥ 10 kPa to < 10 or LSM decrease of ≥ 20% for cACLD.

Results: The authors followed up 7988 patients with baseline LSM 5.9 kPa (interquartile range, 4.6–8.2) for a median of 4.6 years. At baseline, 40.5% of patients used statins, and cACLD was present in 17%. Statin usage was significantly associated with a lower risk of all-cause mortality (adjusted hazard ratio [aHR] = 0.233; 95% confidence interval [CI]: 0.127–0.426) and LREs (aHR = 0.380; 95% CI: 0.268–0.539). Statin usage was also associated with lower liver stiffness progression rates in cACLD (aHR = 0.542; 95% CI: 0.389–0.755) and non-cACLD (aHR = 0.450; 95% CI: 0.342–0.592), but not with liver stiffness regression (aHR = 0.914; 95% CI: 0.778–1.074).

Conclusions: Statin usage was associated with a relatively lower long-term risk of all-cause mortality, liver-related clinical events and liver stiffness progression in patients with metabolic-associated steatotic liver disease.

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Combination of carvedilol with variceal band ligation in prevention of first variceal bleed in Child-Turcotte-Pugh B and C cirrhosis with high-risk oesophageal varices: The 'CAVARLY TRIAL'

Objectives: Beta-blockers and endoscopic variceal band ligation (VBL) have been preferred therapies for primary prophylaxis of variceal bleeding. However, the choice of therapy in patients with advanced liver disease with high-risk varices is not clear. A comparison of these therapies alone or in combination to prevent the first variceal bleed in advanced cirrhosis patients was carried out.

Design: 330 Child-Turcotte-Pugh (CTP) B and C cirrhosis patients, with 'high-risk' varices were prospectively enrolled (n = 110 per group) to receive carvedilol (group A), VBL (group B) or combination (group C). Primary endpoint was reduction in the incidence of first variceal bleed at 12 months. The secondary endpoints included overall mortality, bleed-related mortality, new-onset

decompensation, change in hepatic vein pressure gradient (HVPG) and treatment-related adverse events.

Results: The patients were predominantly males (85.2%), aged 51.4 ± 10.5 years with CTP score of 8.87 ± 1.24, MELD score 15.17 ± 3.35 and HVPG-16.96 ± 3.57 mmHg. The overall incidence of variceal bleed was 23.8% (n = 78) at 1 year. Intention-to-treat analysis showed that the combination arm (group C) significantly reduced the incidence of first variceal bleed by 62.9% as compared with group B (hazard ratio [HR] = 0.37, 95% confidence interval [CI]: 0.192–0.716, p < 0.003) and by 69.3% as compared with group A (HR = 0.31, 95% CI: 0.163–0.578, p < 0.001). The overall mortality was 13.6% (45/330). The 1-year mortality in group C was lowest among the three groups (A, B, C = 20%, 14.5%, 6.3%, p = 0.012). Reduction in HVPG (20.8% vs. 25.1%, p = 0.54) and the rate of non-response to carvedilol (53.4% vs. 41.25%, p = 0.154) were not different between group A and C patients. The incidence of new-onset ascites, spontaneous bacterial peritonitis, shock, and acute kidney injury and postbleed organ failure was also comparable between the groups.

Conclusion: In Child-Turcotte-Pugh B and C cirrhosis patients with high-risk varices, combination of carvedilol and variceal band ligation is more effective than either therapy alone, for primary prevention of variceal bleeding.

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Jachs M, Odriozola A, Turon F, Moga L, Téllez L, Fischer P, Saltini D, Kwanten WJ, Grasso M, Llop E, Mendoza YP, Armandi A, Thalhammer J, Pardo C, Colecchia A, Ravaioli F, Maasoumy B, Laleman W, Presa J, Schattenberg JM, Berzigotti A, Calleja JL, Calvaruso V, Francque S, Schepis F, Procopet B, Albillos A, Rautou PE, García-Pagán JC, Puente Á, Fortea JI, Reiberger T, Mandorfer M; SSM-100Hz/ ACLD Study Group; Baveno Cooperation

Spleen stiffness measurement by vibration-controlled transient elastography at 100 Hz for non-invasive predicted diagnosis of clinically significant portal hypertension in patients with compensated advanced chronic liver disease: A modelling study

Background: In patients with compensated advanced chronic liver disease (cACLD), risk of clinically significant portal hypertension (CSPH) can be estimated by applying non-invasive tests such as liver stiffness measurement (LSM), platelet count, and, in some cases, body mass index (BMI). The authors aimed to assess the diagnostic utility of spleen stiffness measurement (SSM) at 100 Hz as a standalone non-invasive test for CSPH and to evaluate its incremental value compared with the ANTICIPATE±NASH model in patients with cACLD.

Methods: For this modelling study, patients were recruited from 16 expert centres in Europe. Patients who underwent characterisation by hepatic venous pressure gra-

dient (HVPG) and non-invasive tests (i.e., LSM, platelet count, and SSM at 100 Hz) at one of the participating centres between January 1, 2020, and December 31, 2023, were considered for inclusion. Only patients aged 18 years or older with Child-Pugh class A cACLD, shown by LSM 10 kPa or more or F3 or F4 fibrosis on liver histology, were included. The overall cohort was split into the derivation cohort (patients recruited between January 1, 2020, and December 31, 2022) and the temporal validation cohort (patients recruited between January 1, 2023, and December 31, 2023). The ANTICIPATE±NASH model was applied to assess individual CSPH probability and SSM was investigated as a standalone non-invasive test for CSPH; in combination with platelet count and BMI; and in a full model of SSM, LSM, platelet count, and BMI (i.e., the Non-Invasive CSPH Estimated Risk [NICER] model). All models were binary logistic regression models. The primary outcome was CSPH. The authors evaluated the discriminative utility of the models by calculating the area under the receiver operating characteristics curve (AUC) and creating calibration plots and calibration of intercept, slope, and integrated calibration index.

Findings: 407 patients with cACLD were included, 202 (50%) in the derivation cohort and 205 (50%) in the validation cohort. Median age was 60.0 years (interquartile range [IQR], 55.0–66.8); 275 (68%) of 407 patients were male and 132 (32%) were female. 164 (40%) of 407 patients had metabolic dysfunction-associated steatotic liver disease (MASLD), 133 (33%) had MASLD with increased alcohol intake or alcohol-related liver disease, 75 (18%) had viral hepatitis (61 [81%] of whom had sustained virologic response of hepatitis C virus or suppression of hepatitis B virus DNA), and 35 (9%) had other chronic liver diseases. 241 (59%) patients had CSPH. Median SSM was 45.0 kPa (IQR, 32.1–65.4) and LSM was 21.4 kPa (IQR, 14.1–31.6). SSM and LSM had similar AUCs for prediction of CSPH in the derivation cohort (0.779 [95% confidence interval: 0.717–0.842] vs. 0.781 [0.718–0.844]; p = 0.97) and in the validation cohort (0.830 [0.772–0.887] vs. 0.804 [0.743–0.864]; p = 0.50). The SSM-based model comprising platelet count and BMI had a similar AUC as the ANTICIPATE±NASH model in both the derivation cohort (0.849 [0.794–0.903] vs. 0.849 [0.794–0.903]; p = 0.999) and in the validation cohort (0.873 [0.819–0.922] vs. 0.863 [0.810–0.916]; p = 0.75). The NICER model had a significantly higher AUC for prediction of CSPH than the ANTICIPATE±NASH model in the derivation cohort (0.889 [0.843–0.934] vs. 0.849 [0.794–0.903]; p = 0.022) and in the validation cohort (0.906 [0.864–0.946] vs. 0.863 [0.810–0.916]; p = 0.012).

Interpretation: The addition of spleen stiffness measurement (SSM) to liver stiffness measurement (LSM), BMI, and platelet count outperformed the ANTICIPATE±NASH model for clinically significant portal hypertension (CSPH) risk stratification in this cohort of contemporary patients with compensated advanced chronic liver disease (cACLD). SSM improves the non-invasive diagnosis of CSPH, supporting its implementation into clinical practice.

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HCC

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Clinical outcomes of transarterial chemo-embolization in Child-Turcotte-Pugh class A patients with a single small (≤ 3 cm) hepatocellular carcinoma

Background and aim: Transarterial chemoembolization (TACE) is one of the standard modalities used to treat unresectable hepatocellular carcinoma (HCC), but the effectiveness of TACE for treating patients with a solitary small (≤ 3 cm) HCC and well-preserved liver function has not been definitively established. This study aimed to determine the therapeutic impact of TACE in patients with these characteristics.

Methods: This multicenter (4 university hospitals) retrospective cohort study analyzed the medical records of 250 patients with a solitary small (≤ 3 cm) HCC and Child-Turcotte-Pugh (CTP) class A liver function diagnosed over 10 years. Posttreatment outcomes, including overall survival (OS), recurrence-free survival (RFS), and adverse events, were assessed following TACE therapy.

Results: 138 of the 250 patients (55.2%) treated with TACE achieved complete remission (CR). Overall median OS was 77.7 months, and median OS was significantly longer in the CR group than in the non-CR group (89.1 vs. 58.8 months, p = 0.001). Median RFS was 19.1 months in the CR group. Subgroup analysis identified hypertension, an elevated serum albumin level, and achieving CR as significant positive predictors of OS, whereas diabetes, hepatitis C virus infection, and tumor size (> 2 cm) were poor prognostic factors of OS.

Conclusions: The study demonstrates the effectiveness of transarterial chemoembolization as a viable alternative for treating solitary small (≤ 3 cm) hepatocellular carcinoma in Child-Turcotte-Pugh class A patients.

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Circulating tumour DNA in patients with hepatocellular carcinoma across tumour stages and treatments

Objective: Circulating tumour DNA (ctDNA) is a promising non-invasive biomarker in cancer. The aim of this study was to assess the dynamic of ctDNA in patients with hepatocellular carcinoma (HCC).

Design: The authors analysed 772 plasmas from 173 patients with HCC collected at the time of diagnosis or treatment (n = 502), 24 hours after locoregional treatment (n = 154) and during follow-up (n = 116). For controls, 56 plasmas from patients with chronic liver disease without HCC were analysed. All samples were analysed for cell-free DNA (cfDNA) concentration, and for mutations in TERT promoter, CTNNB1, TP53, PIK3CA and NFE2L2 by sequencing and droplet-based digital PCR. Results were compared with 232 corresponding tumour samples.

Results: In patients with active HCC, 40.2% of the ctDNA was mutated versus 14.6% in patients with inactive HCC and 1.8% in controls (p < 0.001). In active HCC, they identified 27.5% of mutations in TERT promoter, 21.3% in TP53, 13.1% in CTNNB1, 0.4% in PIK3CA and 0.2% in NFE2L2, most of the times similar to those identified in the corresponding tumour. CtDNA mutation rate increased with advanced tumour stages (p < 0.001). In 103 patients treated by percutaneous ablation, the presence and number of mutations in the ctDNA before treatment were associated with higher risk of death (p = 0.001) and recurrence (p < 0.001). Interestingly, cfDNA concentration and detectable mutations increased 24 hours after a locoregional treatment. Among 356 plasmas collected in 53 patients treated by systemic treatments, the authors detected mutations at baseline in 60.4% of the cases. In patients treated by atezolizumab-bevacizumab, persistence of mutation in ctDNA was associated with radiological progression (63.6% vs. 36.4% for disappearance, p = 0.019). In 2 patients progressing under systemic treatments, they detected the occurrence of mutations in CTNNB1 in the plasma that was subclonal in the tumour for 1 patient and not detectable in the tumour for the other one.

Conclusion: Circulating tumour DNA (ctDNA) offers dynamic information reflecting tumour biology. It represents a non-invasive tool useful to guide clinical management of hepatocellular carcinoma.

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Liver Transplantation

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Post liver transplant short-term and survival outcomes in patients living with obesity

The objectives of this study were to examine and compare patient and graft survival over a 5-year period across body mass index (BMI) groups, and examine immediate and short-term complications post LT. This was a retrospective study that examined all liver transplants that occurred at the authors' institution between January 2015 and October 2022. Patients were divided into 4 BMI groups (n = 888): normal–overweight (BMI 18.5–29.9 kg/m²), class I obesity (BMI 30–34.9 kg/m²), class II obesity (BMI 35–39.9 kg/m²), and class III obesity (BMI ≥ 40 kg/m²) patients. Kaplan-Meier curves with the log-rank test were created to assess survival outcomes and multivariate Cox regression analysis was performed. Patient and graft survival did not differ statistically between each BMI group. However, patient survival was significantly lower in patients with BMI ≥ 40 compared to patients with BMI < 40. In multivariate analysis, BMI ≥ 40, admission to the intensive care unit, and age were independent predictors of increased risk of mortality. Infection, arrhythmia, cardiac arrest, and myocardial infarction were more frequent immediate complications in the class III obesity group. Efforts to closely monitor patients with BMI ≥ 40 post LT to maximize survival are needed. Further studies are needed to improve post LT survival among patients with BMI ≥ 40.

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Prognostic scores for ursodeoxycholic acid-treated patients predict graft loss and mortality in recurrent primary biliary cholangitis after liver transplantation

Background and aims: Recurrent primary biliary cholangitis (rPBC) develops in approximately 30% of patients and negatively impacts graft and overall patient survival after liver transplantation (LT). There is a lack of data regarding the response rate to ursodeoxycholic acid (UDCA) in rPBC. The authors evaluated a large, international, multicenter cohort to assess the performance of PBC scores in predicting the risk of graft and overall survival after LT in patients with rPBC.

Methods: A total of 332 patients with rPBC after LT were evaluated from 28 centers across Europe, North and South America. The median age at the time of rPBC was 58.0 years (interquartile range [IQR], 53.2–62.6), and 298 patients (90%) were female. The biochemical response was measured with serum levels of alkaline phosphatase (ALP) and bilirubin, and Paris-2, GLOBE and UK-PBC scores at 1 year after UDCA initiation.

Results: During a median follow-up of 8.7 years (IQR, 4.3–12.9) after rPBC diagnosis, 52 patients (16%) had graft loss and 103 (31%) died. After 1 year of UDCA initia-

tion the histological stage at rPBC (hazard ratio [HR] = 3.97, 95% confidence interval [CI]: 1.36–11.55, p = 0.01), use of prednisone (HR = 3.18, 95% CI: 1.04–9.73, p = 0.04), ALP x ULN (HR = 1.59, 95% CI: 1.26–2.01, p < 0.001), Paris-2 criteria (HR = 4.14, 95% CI: 1.57–10.92, p = 0.004), GLOBE score (HR = 2.82, 95% CI: 1.71–4.66, p < 0.001), and the UK-PBC score (HR = 1.06, 95% CI: 1.03–1.09, p < 0.001) were associated with graft survival in the multivariate analysis. Similar results were observed for overall survival.

Conclusion: Patients with recurrent primary biliary cholangitis (rPBC) and disease activity, as indicated by standard PBC risk scores, have impaired outcomes, supporting efforts to treat recurrent disease in similar ways to pre-transplant PBC.

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Liver transplantation plus chemotherapy versus chemotherapy alone in patients with permanently unresectable colorectal liver metastases (TransMet): Results from a multicentre, open-label, prospective, randomised controlled trial

Background: Despite the increasing efficacy of chemotherapy, permanently unresectable colorectal liver metastases are associated with poor long-term survival. The authors aimed to assess whether liver transplantation plus chemotherapy could improve overall survival.
Methods: TransMet was a multicentre, open-label, prospective, randomised controlled trial done in 20 tertiary centres in Europe. Patients aged 18–65 years, with Eastern Cooperative Oncology Group performance score 0–1, permanently unresectable colorectal liver metastases from resected BRAF-non-mutated colorectal cancer responsive to systemic chemotherapy (≥ 3 months, ≤ 3 lines), and no extrahepatic disease, were eligible for enrolment. Patients were randomised (1:1) to liver transplantation plus chemotherapy or chemotherapy alone, using block randomisation. The liver transplantation plus chemotherapy group underwent liver transplantation for 2 months or less after the last chemotherapy cycle. At randomisation, the liver transplantation plus chemotherapy group received a median of 21.0 chemotherapy cycles (interquartile range [IQR], 18.0–29.0) versus 17.0 cycles (IQR, 12.0–24.0) in the chemotherapy alone group, in up to 3 lines of chemotherapy. During first-line chemotherapy, 64 (68%) of 94 patients had received doublet chemotherapy and 30 (32%) of 94 patients had received triplet regimens; 76 (80%) of 94 patients had targeted therapy. Trans-

planted patients received tailored immunosuppression (methylprednisolone 10 mg/kg intravenously on day 0; tacrolimus 0.1 mg/kg via gastric tube on day 0, 6–10 ng/mL days 1–14; mycophenolate mofetil 10 mg/kg intravenously day 0 to < 2 months and switch to everolimus 5–8 ng/mL), and postoperative chemotherapy, and the chemotherapy group had continued chemotherapy. The primary endpoint was 5-year overall survival analysed in the intention to treat and per-protocol population. Safety events were assessed in the as-treated population.
Findings: Between February 18, 2016, and July 5, 2021, 94 patients were randomly assigned and included in the intention-to-treat population, with 47 in the liver transplantation plus chemotherapy group and 47 in the chemotherapy alone group. 11 patients in the liver transplantation plus chemotherapy group and 9 patients in the chemotherapy alone group did not receive the assigned treatment; 36 patients and 38 patients in each group, respectively, were included in the per-protocol analysis. Patients had a median age of 54.0 years (IQR, 47.0–59.0), and 55 (59%) of 94 patients were male and 39 (41%) were female. Median follow-up was 59.3 months (IQR, 42.4–60.2). In the intention-to-treat population, 5-year overall survival was 56.6% (95% confidence interval [CI]: 43.2–74.1) for liver transplantation plus chemotherapy and 12.6% (95% CI: 5.2–30.1) for chemotherapy alone (hazard ratio = 0.37 [95% CI: 0.21–0.65]; p = 0.0003) and 73.3% (95% CI: 59.6–90.0) and 9.3% (95% CI: 3.2–26.8), respectively, for the per-protocol population. Serious adverse events occurred in 32 (80%) of 40 patients who underwent liver transplantation (from either group), and 69 serious adverse events were observed in 45 (83%) of 54 patients treated with chemotherapy alone. Three patients in the liver transplantation plus chemotherapy group were retransplanted, 1 of whom died postoperatively of multi-organ failure.

Interpretation: In selected patients with permanently unresectable colorectal liver metastases, liver transplantation plus chemotherapy with organ allocation priority significantly improved survival versus chemotherapy alone. These results support the validation of liver transplantation as a new standard option for patients with permanently unresectable liver-only metastases.

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TRANSLATIONAL SCIENCE CORNER

IBD

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A longitudinal single-cell atlas of anti-tumour necrosis factor treatment in inflammatory bowel disease

Precision medicine in immune-mediated inflammatory diseases (IMIDs) requires a cellular understanding of treatment response. The authors describe a therapeutic atlas for Crohn's disease (CD) and ulcerative colitis (UC) following adalimumab, an anti-tumour necrosis factor (anti-TNF) treatment. They generated ~1 million single-cell transcriptomes, organised into 109 cell states, from 216 gut biopsies (41 subjects), revealing disease-specific differences. A systems biology-spatial analysis identified granuloma signatures in CD and interferon (IFN)-response signatures localising to T cell aggregates and epithelial damage in CD and UC. Pretreatment differences in epithelial and myeloid compartments were associated with remission outcomes in both diseases. Longitudinal comparisons demonstrated disease progression in non-remission: myeloid and T cell perturbations in CD and increased multi-cellular IFN signalling in UC. IFN signalling was also observed in rheumatoid arthritis (RA) synovium with a lymphoid pathotype. This therapeutic atlas represents the largest cellular census of perturbation with the most common biologic treatment, anti-TNF, across multiple inflammatory diseases.

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EXPERT OPINION

Dr. Lena Sophie Mayer

Longitudinal Spatial Immune Profiling in Advanced Therapies: Enhancing Personalized Medicine for IBD

Chronic inflammatory bowel diseases are caused by an intestinal barrier disorder, increased translocation of bacteria into the intestinal wall, and a subsequent excessive inflammatory reaction. Despite significant advancements in treatment options in recent years, durable remission remains unattainable for a substantial proportion of patients. Currently, biomarkers capable of predicting therapeutic responses are lacking. According to current guidelines, available advanced therapies can be used with equal priority. To establish a logical sequence of therapies within the context of personalized medicine, it is important to understand how specific therapeutic agents modulate the disease at the cellular level. In this study, the authors investigated the immune landscape and the spatial organization of cells in the tissue at the single-cell level in patients with Crohn's disease and ulcerative colitis before and after treatment with anti-tumor necrosis factor (anti-TNF) antibodies. Anti-TNF antibodies are still the most frequently used substance class when advanced therapy is needed. The authors generated approximately 1 million single-cell transcriptomes from 216 biopsies obtained from 41 individuals and identified 109 different cell types and states. This revealed both similarities and relevant differences between Crohn's disease and ulcerative colitis. A comparison of patients who later achieved remission with those who did not respond to treatment with adalimumab revealed baseline differences in epithelial cells and myeloid cells. During therapy, certain cell profiles and cell interactions were associated with non-response to therapy, including increased interferon signaling in epithelial, immune, and stromal cells. In adalimumab-treated patients with rheumatoid arthritis, gene expression of the TNF signaling pathways and interferon signaling was found to be analogous to that in inflammatory bowel disease. This suggests shared pathological mechanisms across distinct immune-mediated diseases and indicates that Jak- or selective p19 inhibition may be useful after failure of anti-TNF therapy, as these modulate interferon signaling. Limiting factors for this study were the heterogeneous sampling time points during therapy (8 weeks to 1.5 years after the start of therapy), its sole focus on anti-TNF therapy effects, and the identification of inflammatory drivers at the RNA level, but not sufficiently at the protein level. Moreover, neutrophils, which play a central role in inflammatory bowel disease, were not captured in this dataset due to technical constraints. However, longitudinal profiling strategies such as these are crucial for understanding the dynamic development of immune-mediated diseases at the cellular level, thereby providing a foundation for selecting the most promising therapeutic agents and determining a logical sequence of treatments for individual patients. Moreover, such detailed analyses contribute to the identification of potential novel therapeutic targets. ■

Hepatology

Shu DH, Ho WJ, Kagohara LT, Girgis A, Shin SM, Danilova L, Lee JW, Sidiropoulos DN, Mitchell S, Munjal K, Howe K, Bendinelli KJ, Kartalia E, Qi H, Mo G, Montagne J, Leatherman JM, Lopez-Vidal TY, Zhu Q, Huff AL, Yuan X, Hernandez A, Coyne EM, Zaidi N, Zabransky DJ, Engle LL, Ogurtsova A, Baretti M, Laheru D, Durham JN, Wang H, Sunshine JC, Johnston RJ, Deutsch JS, Taube JM, Anders RA, Jaffee EM, Fertig EJ, Yarchoan M

Immunotherapy response induces divergent tertiary lymphoid structure morphologies in hepatocellular carcinoma

Tertiary lymphoid structures (TLS) are associated with improved response in solid tumors treated with immune checkpoint blockade, but understanding of the prognostic and predictive value of TLS and the circumstances of their resolution is incomplete. Here the authors show that in hepatocellular carcinoma treated with neoadjuvant immunotherapy, high intratumoral TLS density at the time of surgery is associated with pathologic response and improved relapse-free survival. In areas of tumor regression, they identify a non-canonical involuted morphology of TLS marked by dispersion of the B cell follicle, persistence of a T cell zone enriched for T cell-mature dendritic cell interactions and increased expression of T cell memory markers. Collectively, these data suggest that TLS can serve as both a prognostic and predictive marker of response to immunotherapy in hepatocellular carcinoma and that late-stage TLS may support T cell memory formation after elimination of a viable tumor.

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and has been identified as a positive predictor for check-point therapy across multiple cancers. However, TLS may potentially also serve as a niche for malignant cells (Finkin et al., DOI: 10.1038/ni.3290). The biology of TLS is not fully understood. Different stages of TLS maturation are recognized among which a "mature" TLS stage is defined based on the presence of germinal center (GC) organization similar to secondary lymphoid tissue, involving GC B cells, T cells, follicular dendritic cells, fibroblastic reticular cells, and specialized high endothelial venules, all in a spatially clearly organized follicular structure. However, many distinct variants of TLS have been found and early stages of TLS maturation may involve only few immune cell aggregates.

In their current study, Shu et al. analyzed TLS in patients with HCC who underwent tumor resection following neoadjuvant checkpoint therapy. They found that the presence of CD20+CXCL13+ lymphatic aggregates in pretreatment fine-needle aspirates was associated with a pathologic response at resection. Moreover, they observed a correlation between TLS density and both pathologic response and relapse-free survival at resection. However, the authors identified novel types of TLS morphology extending beyond the traditional 3-phase TLS trajectory of lymphoid aggregates, immature TLS, and mature TLS. In areas of tumor regression, the authors identified a distinct TLS morphology that they termed "involuted." These involuted TLS are characterized by a decrease in B cells and disrupted follicular organization but enhanced T cell-dendritic cell interactions within the T-cell zone. Transcriptional and clonal analyses after microdissection indicated that involuted TLS serve as sites of B-cell hypermutation and exhibit more diverse T-cell repertoires. The authors also observed a higher number of memory T cells in involuted lymph nodes. The study thus highlights the post-therapeutic involuted TLS as a correlate of successful immunotherapy. The data suggest that these structures are enriched for tumor-reactive lymphocytes and may play a role in tumor-specific memory. Nevertheless, our mechanistic understanding of TLS formation and maturation requires further study. Strategies to induce TLS during checkpoint therapy warrant further exploration. ■

Prof. Dr. Dr. Bertram Bengsch

Tertiary Lymphoid Structure Changes in HCC Immunotherapy – Novel Type with Predictive Potential?

The development of ectopic "tertiary" lymphoid structures (TLS) in non-lymphoid organs is observed in cancers such as hepatocellular carcinoma (HCC). The formation of TLS is considered to be transient and driven by an inflammatory microenvironment. Their presence is associated with reduced early recurrence after HCC resection (Calderaro et al., DOI: 10.1016/j.jhep.2018.09.003)

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