GI highlights from the literature

Philip J Smith

BASIC SCIENCE

Fungal trans-kingdom dynamics linked to responsiveness to faecal microbiota transplantation (FMT) therapy in ulcerative colitis

► Leonardi I, Paramosothy S, Doron I, *et al*. Fungal trans-kingdom dynamics linked to responsiveness to faecal microbiota transplantation (FMT) therapy in ulcerative colitis. *Cell Host Microbe* 2020; 27: 823–829 e823 doi: 10.1016/j.chom.2020.03.006.

Faecal microbiota transplantation (FMT) has become an emerging treatment for UC. Previous meta-analysis including four randomised controlled trials on FMT in UC showed that FMT was associated with higher rates of clinical remission (OR: 2.48; 95% CI 1.18 to 5.21) and endoscopic remission (OR: 2.69; 95% CI 1.07 to 6.74) compared with placebo. However, the reasons why some UC patients responded to FMT better were largely unknown. Previous work by Paramosothy *et al* had revealed that UC patients who had higher levels of *Roseburia*, *Ruminococcus* and *Eubacterium* at baseline were associated with beneficial response to FMT. In this study, Leonardi *et al* used the samples from the same study and looked at the intestinal mycobiota using the internal transcribed spacer-1 (ITS-1)-based barcoding approach to deep sequence the ITS-1 region of fungal ribosomal DNA in faecal samples. Interestingly, they found that UC patients with high abundance of gut *Candida* were associated with clinical response after FMT and decrease in *Candida* post-FMT was indicative of reduced disease severity, supporting the theory that *Candida* is linked to proinflammatory activity in IBD. UC patients with high *Candida* abundance at baseline had increased bacterial alpha-diversity that persisted 8 weeks after FMT and *Ruminococcus* had a significant positive correlation with *Candida* abundance, signifying a complex trans-kingdom relationship. This highlights the potential role of personalised medicine in IBD where identifying microbiome signatures at baseline could potentially guide future treatment options. With a better understanding of microbiome, virome and mycobiome signatures, a personalised IBD management strategy is an achievable target.

Kallikrein 5 and proteinase-activated receptor 2 molecules may represent potential novel therapeutic targets in eosinophilic oesophagitis

► Azouz N, Klingler A, Pathre P, *et al*. Functional role of kallikrein 5 and proteinase-activated receptor 2 in eosinophilic esophagitis. *Sci Transl Med* 2020; 12 (545): eaaz7773 doi: 10.1126/scitranslmed.aaz7773.

Eosinophilic oesophagitis (EoE) is a chronic disease with increasing incidence characterised by type 2 immunologic responses to food that lead to topical eosinophilic inflammation. In this study, Azouz *et al* using a variety of techniques in carefully selected murine models as well as human oesophageal tissue demonstrated that the previously observed deficiency of the serine peptidase inhibitor, Kazal type 7 (*SPINK7*) in EoE, leads to dysregulated expression of kallikrein 5 (*KLK5*) and its substrate, protease-activated receptor 2 (*PAR2*). *KLK5* upregulation in the oesophageal epithelium is associated with degradation of desmoglein-1 and barrier impairment. Moreover, *KLK5* plays a proinflammatory role by activating *PAR2* in turn, a crucial step in the process of generating Th2 cells that are involved in disease pathogenesis. Conversely, when the *KLK5*/*PAR2* pathway was inhibited, the allergen-induced oesophageal eosinophilia was attenuated significantly via downregulation of protease activity and cytokine production. This raises the possibility that targeted proteolytic inhibition may exert a protective role against the inflammatory responses resulting in EoE development. Taking this into account, the authors administered α1 anti-trypsin, a clinically approved protease inhibitor, and observed amelioration of experimental EoE. Thus, a convincing argument can be made regarding EoE being a protease-mediated disease. Subsequently, there seems to be considerable potential for specific molecules such as *KLK5* and *PAR2* that affect the protease/protease inhibitor balance to serve as novel therapeutic targets in EoE.

CAR T cell infusion as a novel treatment option for liver fibrosis

► Amor C, Feucht J, Leibold J *et al*. Senolytic CAR T cells reverse senescence-associated pathologies. *Nature* 2020 doi: 10.1038/s41586-020-2403-9

Chimeric antigen receptor (CAR) T cells are genetically engineered T cells, which target specific proteins and cause death of cells expressing the protein. CAR T cell therapy is used in treating haematological malignancies. In this article, Amor *et al* describe the use of CAR T cells in treating other disorders such as liver fibrosis. They focused on cellular senescence, an important pathogenic pathway in many disorders including chronic liver disease. To enable targeting of senescent cells while minimising off-target effects, they identified urokinase-type plasminogen activator receptor (*uPAR*) as a protein, which was upregulated on the surface of senescent cells with minimal expression in healthy human tissues. They confirmed *uPAR* expression in fibrotic human liver, while carbon tetrachloride (CCl_4) injury in mice resulted in increased hepatic and serum *uPAR* levels. They proceeded to generate CAR T cells targeting mouse *uPAR*, confirming effective clearance of *uPAR*-expressing cells in vitro and senescent mouse hepatocytes in vivo. Administration of *uPAR*-specific CAR T cells to mice following chronic CCl_4 resulted in a striking reduction in liver inflammation and fibrosis, potentially mediated via depletion of senescent hepatic stellate cells. Similar anti-fibrotic efficacy for *uPAR*-specific CAR T cells was also observed in two mouse models of non-alcoholic steatohepatitis, while anti-tumour properties were demonstrated in a model of lung adenocarcinoma. Overall, these data indicate the potential utility of CAR T cell therapy as a treatment for chronic liver diseases. Future work should explore underlying mechanisms and identify the most rational cellular targets in patients with liver fibrosis.

CLINICAL PRACTICE

Tranexamic acid in acute GI bleeding—time to halt its use?

► The HALT IT collaborators. Effects of a high-dose 24 hours infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double blind, placebo-controlled trial. *Lancet* 2020; 395: 1927–36.

Tranexamic acid has previously been shown to reduce death by bleeding in the setting of trauma or postpartum haemorrhage. Previous smaller studies have suggested a modest reduction in the risk of death in patients with acute GI haemorrhage treated with tranexamic acid. The HALT IT collaboration performed a large multicentre, randomised, double-blind, placebo-controlled trial in the setting of acute GI bleeding, recruiting 12 009 patients across 164 hospitals in 15 countries over 6 years. Patients received either 24 hours of tranexamic acid (4 g) or a placebo infusion. The majority of patients were thought to be bleeding from an upper GI source

rather than lower (89% vs 11%) and 41% of patients had liver disease. The placebo and treatment arms were well matched. The primary endpoint was risk of death due to bleeding at 5 days, with secondary endpoints including risk of death at 28 days or rebleeding at 24 hours, 5 days or 28 days. There was no difference in risk of death at 5 or 28 days (risk ratio (RR): 0.99; 95% CI: 0.82 to 1.18) or in rebleeding at any measured time point. The risks of venous thromboembolism and seizures were increased in those patients receiving tranexamic acid (RR: 1.85; 95% CI: 1.15 to 2.98 and RR: 1.73; 95% CI: 1.03 to 2.93, respectively). There were no significant differences in the proportion of patients having endoscopic, radiological and surgical interventions or need for transfusion between treatment arms. This well-constructed large negative trial demonstrates that there is no significant role for tranexamic acid in acute GI bleeding.

The arrival of immunotherapy in unresectable hepatocellular carcinoma?

► Finn R, Qin S, Ikeda M *et al*. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020; 382 (20): 1894-1905 doi: 10.1056/NEJMoa1915745

Most patients with hepatocellular carcinoma present with unresectable disease and have a poor prognosis. Sorafenib and lenvatinib are currently the only approved first-line systemic treatments. IMbrave150 was a global, open-label, phase 3 trial evaluating 3-weekly intravenous atezolizumab (checkpoint inhibitor targeting programmed death-ligand 1 (PD-L1)) plus bevacizumab (monoclonal antibody targeting vascular endothelial growth factor (VEGF)) in 336 patients versus oral sorafenib in 165 patients. Patients had not previously received systemic therapy, often had macrovascular tumour invasion, were Child–Pugh A and required variceal eradication due to the bleeding risk associated with bevacizumab. Atezolizumab plus bevacizumab resulted in better overall survival (HR for death: 0.58; 95% CI: 0.42 to 0.79; p<0.001). Overall survival at 12 months was 67.2% with atezolizumab–bevacizumab and 54.6% with sorafenib. Median progression-free survival was 6.8 months (95% CI: 5.7 to 8.3) and 4.3 months (95% CI: 4.0 to 5.6) in the respective groups (HR for disease progression or death: 0.59; 95% CI: 0.47 to 0.76; p<0.001). Fifteen per cent discontinued atezolizumab–bevacizumab due to adverse events and 10% in the sorafenib group. Diarrhoea and rash, well-known side effects of sorafenib, were less common with atezolizumab–bevacizumab. Hypertension and pruritus were more common with atezolizumab–bevacizumab with higher rates of GI bleeding. Despite the impact of requiring three weekly intravenous infusions versus oral therapy, there was delayed deterioration in patient-reported quality of life in the atezolizumab–bevacizumab group (median time 11.2 vs 3.6 months). There are clear indications for this regimen for patients who have limited options; however, cost and GI bleeding risk need to be considered prior to widespread clinical use.

First-line pembrolizumab and trastuzumab in HER2-positive gastro-oesophageal cancer

► Janjigian Y, Maron S, Chatila W *et al*. First-line pembrolizumab and trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: an open-label, single-arm, phase two trial. *Lancet Oncology* 2020; 21 (6): 821–831.

The addition of the immunotherapy agent, trastuzumab, to chemotherapy regimen for the treatment of metastatic gastric cancer has proven beneficial. Janjigian *et al* assessed the safety and activity of pembrolizumab in combination with trastuzumab and chemotherapy in first-line HER2-positive metastatic oesophagogastric (gastric, oesophageal or gastro-oesophageal junction) cancer. They utilised a study design of an investigator-initiated, open-label, non-randomised, single-arm, single-centre, phase 2 trial in patients aged 18 years or older with HER2-positive metastatic oesophagogastric cancer. The primary endpoint was 6-month progression-free survival, defined as the proportion of patients alive and free of progression at 6 months, assessed in patients who received at least one dose of trastuzumab and pembrolizumab, with a median follow-up among survivors of 13 months. Seventy per cent of patients achieved the primary end point of 6 months progression-free survival. Adverse events were common in the study group, including neuropathy (97%), electrolyte disturbance (16%) and lymphopaenia (19%). Serious adverse events occurred in two patients (both grade 3 nephritis leading to treatment discontinuation). Four patients discontinued pembrolizumab because of immune-related adverse events. There were no treatment-related deaths. The combination of pembrolizumab and trastuzumab appears safe and effective in the treatment of HER2-positive oesophageal, gastric or gastro-oesophageal junction cancer.

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JOURNALS REVIEWED

Cell Host Microbe, *Science Translational Medicine*, *Nature*, *Lancet*, *New England Journal of Medicine* and *Lancet Oncology*

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Smith PJ. *Gut* 2020;**69**:1706–1707. doi:10.1136/gutjnl-2020-322387

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