IN BRIEF

NONALCOHOLIC STEATOHEPATITIS

No anti-fibrotic effect of selonsertib in NASH

Two randomized, double-blind, placebo-controlled phase III trials have evaluated the safety and anti-fibrotic efficacy of the selective ASK1 inhibitor, selonsertib, in patients with nonalcoholic steatohepatitis (NASH) with bridging fibrosis (STELLAR-3 trial) or compensated cirrhosis (STELLAR-4 trial). Patients were randomly assigned to groups receiving 6 mg or 18 mg of selonsertib or placebo daily for 48 weeks, with liver biopsies performed at the start and end of the trials and noninvasive fibrosis tests also evaluated. Although selonsertib had dose-dependent effects indicating pharmacodynamic activity, and statistically non-significant improvements were seen in noninvasive tests, both trials failed to reach the primary efficacy endpoint of fibrosis improvement without worsening of NASH at week 48. Adverse events were similar between groups.

ORIGINAL ARTICLE Harrison, S. A. et al. Selonsertib for patients with bridging fibrosis or compensated cirrhosis due to NASH: results from randomized Ph III STELLAR trials. *J. Hepatol.* https://doi.org/10.1016/j.jhep.2020.02.027 (2020)

LIVER CANCER

Aspirin associated with lower risk of liver cancer

A Swedish nationwide registry-based study has examined the risk of hepatocellular carcinoma (HCC) and liver-related mortality associated with low-dose aspirin use in patients infected with hepatitis B or hepatitis C viruses. A total of 50,275 patients who received a diagnosis of chronic hepatitis B or hepatitis C between 2005 and 2015 were identified, 14,205 of whom were established as low-dose aspirin users according to prescription data. On the basis of a median 7.9 years follow-up, the estimated cumulative incidence of HCC was shown to be significantly lower among aspirin users than nonusers (4.0% versus 8.3%; $P < 0.001$), an association that was also found to be dependent on the duration of aspirin use. The 10-year liver-related mortality was also significantly lower among aspirin users than nonusers (11.0% versus 17.9%; $P < 0.001$), but importantly, there was no significant difference in the 10-year risk of gastrointestinal bleeding between the groups.

ORIGINAL ARTICLE Simon, T. G. et al. Association of aspirin with hepatocellular carcinoma and liver-related mortality. *N. Engl. J. Med.* **382**, 1018–1028 (2020)

GERD

Increasing global burden of gastro-oesophageal reflux disease

A systematic review has used data from the Global Burden of Diseases, Injuries and Risk Factors Study to report the burden of gastro-oesophageal reflux disease (GERD) in 195 countries between 1990 and 2017. From 144 location-years of prevalence data, a mean estimate of age-standardized prevalence for all locations in 2017 was determined, ranging between 4,408–14,035 cases per 100,000 population. The highest values were in the USA, Italy, Greece and New Zealand, and the lowest were in high-income Asia Pacific regions, east Asia and European countries including France, Iceland, Denmark and Switzerland. Although global age-standardized prevalence was stable between 1990 and 2017, the all-age prevalence increased by 18.1%, suggesting that the epidemiology of GERD has not changed but that the burden of disease is increasing as a result of ageing and population growth.

ORIGINAL ARTICLE GBD 2017 Gastro-oesophageal Reflux Disease Collaborators. The global, regional, and national burden of gastro-oesophageal reflux disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol. Hepatol.* https://doi.org/10.1016/S2468-1253(19)30408-X (2020)

Credit: Laura Marshall/ Springer Nature Limited

IBD

Mitochondrial dysfunction in Crohn's disease

Two new studies published in *Gut* provide more evidence for the role of mitochondrial impairment and Paneth cell dysfunction in inflammatory bowel disease (IBD).

"Many studies have revealed the involvement of mitochondrial stress in the pathophysiology of IBD but whether this is a cause or consequence of the disease is not known," explains the corresponding author of the first study, Arianne Theiss. The researchers observed that mice lacking prohibitin 1 (PHB1, a major component of the inner mitochondrial membrane) in intestinal epithelial cells (IECs) developed spontaneous ileal inflammation that was preceded by mitochondrial dysfunction in IECs and early abnormalities in Paneth cells. Crucially, treatment with a mitochondrial-targeted antioxidant to suppress mitochondrial reactive oxygen species alleviated mitochondrial dysfunction, Paneth cell abnormalities and ileitis in these mice. Paneth cells were found to be critical and highly susceptible to mitochondrial dysfunction; deletion of *Phb1* in Paneth cells specifically was sufficient to cause ileitis in the mice. Moreover, *Phb1* deficiency in intestinal organoids induced loss of viability of the intestinal stem cell (ISC) niche and Paneth cell defects.

In the second study, Dirk Haller and colleagues investigated the influence of intestinal inflammation on Paneth cell function and the ISC niche. In patients with Crohn's disease and mice with Crohn's disease-like ileitis, inflammation correlated with decreased gene expression of the ISC marker LGR5 and reduced Paneth cell granularity. This aberrant Paneth cell phenotype and *LGR5* expression correlated with active ileal Crohn's disease and predicted risk of recurrence in patients after surgical resection. Crucially, induction of mitochondrial dysfunction via specific deletion of *Hsp60* in ISCs in mice led to reduced *Lgr5* expression and differentiation of $Lgr5^{+}$ cells into aberrant Paneth cells. "We demonstrate that impaired mitochondrial respiration not only antagonizes intestinal stemness, but forces ISCs to acquire a Paneth cell-like phenotype and provide evidence that inflammation-associated mitochondrial dysfunction in the intestinal epithelium triggers a metabolic imbalance, causing reduced stemness and acquisition of a dysfunctional Paneth cell phenotype," notes Haller.

Further work is needed to examine the key mechanisms underlying mitochondrial dysfunction in IBD and their potential as therapeutic targets. "Ongoing studies will elucidate whether abnormal Paneth cells in patients with Crohn's disease also exhibit mitochondrial dysfunction or altered PHB1 expression," says Theiss, adding that the role of mitophagy will also be explored. "We provide proof-of-concept that metabolic injury is a putative drug target to prevent inflammation-associated damage of the ISC niche," remarks Haller, adding that restoration of mitochondrial metabolism could have potential as an adjuvant therapy to prevent recurrence.

Katrina Ray

ORIGINAL ARTICLES Jackson, D. N. et al. Mitochondrial dysfunction during loss of prohibitin 1 triggers Paneth cell defects and ileitis. *Gut* https://doi.org/10.1136/gutjnl-2019-319523 (2020) | Khaloian, S. et al. Mitochondrial impairment drives intestinal stem cell transition into dysfunctional Paneth cells predicting Crohn's disease recurrence. *Gut* https://doi.org/10.1136/gutjnl-2019-319514 (2020)

RELATED ARTICLES Rath, E. et al. Mitochondrial function — gatekeeper of intestinal epithelial cell homeostasis. *Nat. Rev. Gastroenterol. Hepatol.* **15**, 497–516 (2018)