short courses of steroids to prevent long-term disease complications.

- Does treatment prevent the development of organ dysfunction? It appears that progression to pancreatic atrophy occurs in 30–50% of AIP patients. We have seen progression to cirrhosis in patients with biliary disease. It is unclear whether steroid treatment prevents or decreases the likelihood of disease progression.
- Do different manifestations of IgG4-related systemic disease have different disease courses? IgG4-related systemic disease can involve multiple organs (pancreas, bile duct, retroperitoneum, kidneys, lungs, salivary glands). It is unclear if relapse rates and long-term prognosis differ with various manifestations of the disease. If so, then mode and duration of treatment may need to be tailored based on the involved organ.
- What is the significance of isolated serological relapse? Serological relapse is a common clinical scenario. Patients present with elevated IgG4 after treatment but no recurrent disease on imaging. The significance of this finding and whether these patients eventually progress to clinical relapse is unknown. If so, then this would

support the early treatment of serological relapses.

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Chronic hepatitis C

Ursodeoxycholic acid in chronic hepatitis C

Raoul Poupon, Lawrence Serfaty

Cytoprotective but anti-apoptotic

The history of ursodeoxycholic acid (UDCA) therapy has been provided by Makino and Tanaka.¹ Identified in 1902 from polar bear bile by Hammarsten, UDCA was isolated and crystallised by Shoda in 1927. In 1936, its chemical structure was determined by Iwasaki at Okoyama Medical University. Several years later (1954) a chemist at Tokyo Institute of Technology, Kanazawa, described a method of synthesising UDCA from cholic acid and chenodeoxycholic acid. Three years later, Tokyo Tanabe Pharmaceutical Company launched “Urso” as a choleretic that could improve symptoms related to liver dysfunction and maldigestion. In 1961, Ishida, reporting his experience of Urso administration in chronic hepatitis, noted an improvement

of liver function tests in patients receiving the bile acid. This observation was replicated several times during the following two decades in Japan. Actually, UDCA really drew the attention of the western scientific community when it was shown that it could promote dissolution of cholesterol gallstones as well as chenodeoxycholic acid. The proof of concept study of UDCA in primary biliary cirrhosis showing a marked improvement in cholestasis under UDCA therapy was a further impetus for many studies aimed to define the biological properties of this “very special” bile acid. The putative mechanisms of action of UDCA in cholestatic disorders included at least, in part, stimulation of hepato-biliary secretion through apical insertion of transporter proteins, as

well as their up-regulation and activation, immunomodulation and protection against cytokines and hydrophobic bile acid-induced apoptosis.

In this issue of *Gut* (page 1747), Omata *et al*² have confirmed in a large-scale randomised study that a 24-week course of UDCA in patients with chronic hepatitis C was able to decrease significantly serum liver enzymes despite no effect on viral load. As cholestasis is not a common feature of chronic hepatitis, the mechanism involved in the aminotransferase lowering effect of UDCA is likely related to its anti-apoptotic property rather than an antagonising effect towards toxic bile acids at a biophysical level. Several mechanisms have been shown to operate in the UDCA anti-apoptotic function. In addition to an effect at the mitochondrial level, UDCA inhibits c-jun N-terminal protein kinase-dependent Fas trafficking to the plasma membrane and activates survival signals such as the epidermal growth factor receptor and the mitogen-activated protein kinase (MAPK). In addition, UDCA inhibits endoplasmic reticulum stress-mediated apoptosis.³

Omata *et al*'s paper raises two main issues: what is the relevance of transaminase normalisation in terms of disease progression in chronic hepatitis C and

what could be the influence of UDCA on hepatocellular carcinoma (HCC) occurrence?

There is striking evidence that HCV eradication may prevent the progression of fibrosis and reduce the incidence of HCC in chronic hepatitis C.⁴ However, the benefit of interferon treatment on disease progression in non-virological responders remains debated.⁵ In a recently published randomised trial, we found no significant effect of prolonged interferon treatment on HCC occurrence in non-responding patients with HCV-related cirrhosis.⁶ However, in the subgroup of biochemical responders, several retrospective studies have suggested a beneficial effect of interferon treatment on fibrosis progression and HCC occurrence.⁷ These results are in keeping with the contention that transaminase level is a risk factor for fibrosis progression in chronic hepatitis C.⁸ Because serum transaminase activity mainly reflects the degree of liver inflammation that is involved in fibrogenesis or even carcinogenesis through NF- κ B modulation, it can be expected that transaminase normalisation with UDCA may prevent disease progression. Two controlled studies did not show a significant effect of UDCA on fibrosis progression between two liver biopsies.^{9,10} The short interval between paired liver biopsies could be an explanation. Another open-labelled study has suggested a beneficial effect of UDCA on HCC occurrence in cirrhotic patients, independently from alanine aminotransferase reduction, suggesting chemopreventive effectiveness of UDCA.¹¹ Accordingly, Omata *et al* suggest that UDCA could reduce the risk of liver carcinoma. Given the well confirmed anti-apoptotic function of UDCA, this hypothesis appears rather provocative. Long-term administration of UDCA has been shown to promote tumour development in the liver of HBV transgenic mice.¹² In this model, a UDCA-enriched diet was associated with liver tumour growth and hepatocyte proliferation in the absence of any toxic effect on the liver suggesting a direct anti-apoptotic effect of UDCA. On the other hand, a supplemental diet with UDCA was reported to be chemopreventive in the diethylnitrosamine-induced model of experimental liver carcinogenesis.¹³ Evidence for UDCA-induced apoptosis as well as inhibition of proliferation was provided in

this model. These apparently opposite effects of UDCA on hepatocarcinogenesis should be viewed through the balance between death and survival signals in a given cell model.^{14,15} In primary cultured hepatocytes exposed to bile acids, UDCA is able to stimulate the activation of the intracellular MAPK pathway through the activation of the epidermal growth factor receptor. In these experiments, when the MAPK pathway was blocked with inhibitors, UDCA was toxic by inducing apoptosis. Moreover, the pro-apoptotic or anti-apoptotic effect of UDCA is likely to depend on the nature and state of the cells exposed to the bile acid.^{16–18} The antiapoptotic action of UDCA was first demonstrated in HCC cells in a proapoptotic state induced by the hydrophobic bile acids, ethanol, TGF- β , Fas ligand and okadaic acid. In contrast, cells lacking bile acid importer, like the principal bile acid importer into hepatocyte NTCP, or having strong activation of the NF- κ B pathway are prone to proliferate or to resist to apoptosis when exposed to bile acids. The scenario is even more complicated when considering the recent report showing that incubated HCV replicon-harboring cells (genotype 1b, Con1) exposed to UDCA and other bile acids produced enhanced HCV RNA and proteins.¹⁹

All these *in vitro* and *in vivo* observations taken together indicate that there is currently no consistent rationale to advice UDCA treatment in chronic hepatitis C. Obviously more studies are needed to define the mechanisms of cell death and survival in pathological states before proposing new therapeutic targets.

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