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Editorial

Liver biopsy interpretation & the regression of hepatitis B virus related cirrhosis

Globally, chronic hepatitis B virus (HBV) infection affects over 350 million people, and up to 40 per cent of these may progress to cirrhosis, liver failure, or hepatocellular carcinoma (HCC)[1,2]. India represents the second largest pool of chronic HBV infection worldwide with an estimated 40 million infected people[3], and every year over 100,000 Indians die due to HBV–related disease and its complications[4]. Chronic HBV infection in India is acquired in childhood, presumably before 5 years of age, through horizontal transmission, although the prevalence of chronic HBV infection in pregnant females is 0.82 per cent and during pregnancy, HBV infection carries a risk of vertical (mother-to-child) transmission[5]. It is now generally accepted that the intrinsic characteristics of the HBV, the individual patient's characteristics and disease dynamics, and also the type of drugs used to treat the disease can all influence the treatment response and risk of relapse. The management of HBV has become more complex with the increasing use of long-term oral nucleotide analogue antiviral therapies, including lamivudine, adefovir dipivoxil, entecavir and telbivudine[6]. HBV is characterized by a high degree of genetic heterogeneity due to the use of a reverse transcriptase during viral replication. Thus, monitoring HBV genotypic resistance and shared resistant pathway pertaining to antiviral agents would help to optimize or rescue current antiviral therapies and avoid the outbreak of clinical deterioration[7]. There is also a lack of robust data for guiding optimal management including the selection of therapy, duration of treatment, potential antiviral side effects and the treatment of special populations. In addition, common risk factors for HCC include persistent hepatitis C viral infection, alcohol abuse, haemochromatosis or metabolic syndrome (non-alcoholic steatohepatitis or NASH)[8]. Steatohepatitic HCC has been recently recognized as a peculiar morphologic variant of HCC in non alcoholic fatty liver disease (NAFLD)-associated cirrhosis and significantly associated with metabolic risk factors[9]. Today, levels of serum alanine aminotransferase (ALT) represent a biomarker of hepatitis B severity and response to treatment. However, ALT levels may be of limited utility during the immune clearance phase of chronic hepatitis B (CHB), and can be influenced by the patient's age and weight, and by concomitant liver disease. In addition, a considerable proportion of patients with slight increase in ALT-levels have significant fibrosis.

Given the possibility of advanced liver disease, the ALT threshold for antiviral treatment needs to be identified. Recently, Marcellin *et al*[10] assessed histological improvement (≥2point reduction in Knodell necroinflammatory score with no worsening of fibrosis) and regression of fibrosis (≥1 unit decrease by Ishak scoring system) in a series of patients with CHB treated with tenofovir disoproxil fumarate, a nucleotide analogue, inhibitor of HBV polymerase/ reverse transcriptase and active against lamivudine-resistant HBV infection, during 4-5 years; 348 of the 489 patients underwent repeat liver biopsy. Liver histology showed improvement in inflammation and necrosis in almost all patients and a decrease in fibrosis in 51 per cent patients[9]. An impressive finding was a regression of cirrhosis, defined as a ≥1 unit decrease in Ishak score in 71 of the 96 patients (74%) of those with on initial biopsy a score of cirrhosis (Ishak 5 or 6). In 2011, Schiff *et al*[11] investigated a subset of patients from phase III and long-term roll-over studies who received entecavir for at least three years, had advanced fibrosis or cirrhosis, and evaluable biopsies at baseline and after long-term treatment. They found that after approximately 6 years of cumulative entecavir therapy, all 10 patients showed improvement in liver histology and Ishak fibrosis score[11]. A reduction

in Ishak fibrosis score to four or less was observed for all 4 patients who had cirrhosis at baseline. They concluded that CHB patients with advanced fibrosis or cirrhosis demonstrated histologic improvement and reversal of fibrosis and cirrhosis after long-term treatment with entecavir[11]. Using a computerized image analysis system, Traber *et al*[12] have evaluated the effect of complex carbohydrate drugs that bind to galectin-3 protein, as well as galectin-1 using a model of hepatic fibrosis and cirrhosis in rats. They found that the two agents, galactoarabino -rhamnogalaturonan and galactomannan have a marked therapeutic effect on the collagen surface density (*i.e.* liver fibrosis) induced by thioacetamide treatment. In addition to a reduction in collagen amount, these agents reduced the bridging fibrosis and histological cirrhosis despite continued exposure to thioacetamide. Moreover, there was a significant reduction in portal hypertension. Therefore, it appears that treatment with these agents not only led to degradation of collagen and regression of histological findings of advanced fibrosis and cirrhosis, but also attenuated the pathophysiologic consequences of cirrhosis. Liver histology remains the best standard for diagnosing cirrhosis, assessing prognosis, and making therapeutic decisions[13]. The current scoring systems apply the same principles for describing the status of liver disease but, remarkably, none of these specifically relates to the amount of fibrosis[14]. Furthermore, the assigned scores are not measurements, *i.e.* assessments of a quantity, but shorthand labels of morphological descriptions: *i.e.* these are categories rather than arithmetically related numbers; that is, stage 2 is not half of stage 4[15]. Moreover, a scoring system devised for one particular liver disease is not automatically applicable to a different aetiology[16]. A number of alternative and non-invasive tests containing serum markers, including serum aspartate aminotransferase, aspartate aminotransferase to platelet ratio index, Fibrosis 4, Forn's index, fibrometer, Hepascore, Shanghai Liver Fibrosis Group's index have been investigated[17]. These models are mainly based on indirect serum markers, which have no direct link with liver fibrosis, but reflect liver dysfunction or other phenomena caused by fibrosis. Goyal *et al*[18] investigated transient elastography (Fibroscan®) and liver biopsy in 382 consecutive patients with HBV, and found that transient elastography accurately assessed fibrosis and could avoid liver biopsy in more than two third patients with HBV. The usefulness of transient elastography in assessing fibrosis remains, however, widely debated. It is expensive, operator-dependent and may be limited in subjects with narrow intercostal spaces, morbid obesity or significant ascites. Additionally, further studies comparing elasticity values of normal and pathologic tissues are needed to detect the diagnostic role of the recently proposed shear wave ultrasonographic elastography[19]. Quantitative computer-aided image and texture analysis of parametric apparent diffusion coefficient maps have been proposed as effective tools in quantifying liver fibrosis in routine practice[20-22]. Liver biopsy may remain the reference method for identifying a state of cirrhosis, but a comprehensive study of chronic liver disease requires a combination of histological and clinical data that incorporate clinical endpoints such as the onset of complications of cirrhosis, portal pressure measurements and death as the "metric" of the fibrosis, which cannot be interchangeable with that of cirrhosis[15,21,23,24]. The challenging goal of cirrhosis reversal must take into account aspects other than fibrosis regression alone: *i.e.* architectural changes, vascular shunts, and liver cell regeneration. The development of effective anti-fibrotic therapies is now possible and the Government of India is also supporting planned State programmes for introducing new vaccines as part of routine immunization for hepatitis B[4]. However, there still remain several open questions, the first one being the importance of quantitative systemic thinking in medicine[25] with emphasis on the importance of understanding the quantifiable determinants of the baseline scale of life, defining the average, idealized, healthy individual[25], and as important second the present lack of a definitely reliable method of assessing reversal of cirrhosis in its different stages.

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