TM) (3) and in patients with CHB (4). Vaccine therapy with HBsAg was safe, but randomized-controlled trials failed to show its off-treatment efficacy (5). The safety and partial efficacy of this immune therapy has been assessed as pilot study in Bangladesh in adult (6) and pediatric patients with CHB (7). Cell-based vaccines have been applied in CHB patients (8), but, the inherent limitations of HBsAg-based vaccine therapy could not be overcome. In the mean time, it became evident that vaccine therapy containing only HBsAg may not be an appropriate approach to contain HBV replication and minimize liver damages in CHB patients because both HBsAg and HBcAg-specific immune responses are essential for these purposes. This has unfolded a new regimen of immune therapy for CHB patients. Safety and efficacy of a vaccine that contains both HBsAg and HBcAg has been assessed in HBV TM for moving forward to bring the information of the benches to bedsides of CHB patients. A phase-1 study has also been accomplished with HBsAg/HBcAg vaccine in CHB patients in Bangladesh. the first use of combined HBsAg/HBcAg vaccine in CHB patients worldwide (9). Also, application of vaccine has been made through mucosal route (nasal) in this trial. The scope and limitation of immune therapy as an evidence-based and innovative immune therapeutic approach in CHB patients would be discussed.

References

1. Shamiliyan TA, MacDonald R, Shaukat A, et al. Antiviral therapy for adults with chronic hepatitis B: A systemic review for a national institute of health consensus development conference. Ann Intern Med 2009;150:111-124.
2. Sprengers D, Janssen HL. Immunomodulatory therapy for chronic hepatitis B virus infection. Fund Clin Pharmacol 2005; 19: 17-26.
3. Akbar SMF, Kajino K, Tanimoto K, Michitaka K, Horiike N, Onji M. Placebo-controlled trials of vaccination with hepatitis B virus surface antigen in hepatitis B virus transgenic mice. J Hepatol 1997;26;131-137.
4. Pol S. Immunotherapy of chronic hepatitis B by anti HBV vaccine. Biomed Pharmacother 1995; 49: 105-109.
5. Pol S, Michel ML. Therapeutic vaccination in chronic hepatitis B virus carriers. Expert Rev Vaccines 2006; 5: 707-716.
6. Al-Mahtab M, Rahman S, Akbar SM, Khan SI, Uddin H, Karim F, Ahmed F. Combination therapy with antiviral drugs and hepatitis B vaccine in incidentally-detected and asymptomatic chronic hepatitis B virus carriers at Bangladesh. Viral Immunol. 2010; 23:335-8.
7. Al-Mahtab M, Rahman S, Akbar SM, Khan SI, Karim MF, Ahmed F. Combination therapy of lamivudine and interferon alpha in pediatric patients with chronic hepatitis B at Bangladesh: A safe and effective therapeutic approach for pediatric CHB patients of developing countries. Int J Immunopathol Pharmacol. 2010;23:659-64
8. Shi M, Fu J, Shi F, Zhang B, Tang Z, Zhang Z, Zhang H, Jin L, Chen L, Wang H, Akbar SM, Wang FS. Viral suppression correlates with dendritic cell restoration in chronic hepatitis B patients with autologous cytokine-induced killer cell transfusion. Liver Int 2008 Liver Int. 2009;29:466-74
9. Al-Mahtab MA, Akbar SMF, Rahman S, Rubido JCA, Mishiro S. Safety, efficacy and immunogenecity of a therapeutic vaccine containing HBsAg and HBcAg by nasal route in patients with chronic hepatitis B. Journal of Hepatology 2010; 52(1): p392.

Brief Communication

Fibroscan: Non-invasive liver diagnostic device for detection of liver fibrosis

*Grace Lai-Hung Wong

Centre for Liver Health, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong.

***Correspondence to**

Consultant Gastroenterologist and Hepatologist, Centre for Liver Health, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong. E-mail: wonglaihung@gmail.com

Transient elastography (Fibroscan®; Echosens, Paris, France) is a rapid, non-invasive and reproducible method of measuring liver stiffness[1]. A higher liver stiffness reflects more severe liver fibrosis. Recent meta-analyses have suggested liver stiffness measurement to be a reliable tool to detect advanced liver fibrosis and early liver cirrhosis[2, 3]. Most of the studies in the meta-analyses included patients with chronic hepatitis C from Western countries. More data from Asian populations were recently published. In a histologic series of 133 Chinese patients, among whom 50% have chronic hepatitis B, liver stiffness measurement correlated well with portal-portal bridging fibrosis on both

histologic staging and computerized morphometric analysis[4]. The most important confounding factor of liver stiffness measurement is the alanine aminotransferase (ALT) level. Hepatic inflammation, as reflected by higher ALT level, tends to increase the liver stiffness. Owing to the different study designs and characteristics of patients recruited by different investigators, different liver stiffness measurement cut-offs have been determined for advanced liver fibrosis (Table 1)[5-7]. Among patients with very high ALT levels, the liver stiffness measurement may be exceedingly high and gives a false positive signal for advanced liver fibrosis[8-11]. Therefore, transient elastography is not recommended among patients with severe acute exacerbation of chronic hepatitis B and should only be performed only after ALT has returned to lower levels[10, 11]. To accommodate the potential confounding effect of ALT level, different sets of liver stiffness measurement cut-off values have been derived for patients with normal and elevated ALT levels[7]. Based on this algorithm, a liver stiffness measurement of <5.0 kPa has over 90% accuracy to exclude the presence of liver fibrosis regardless of the ALT level. Bridging fibrosis can be confidently confirmed when liver stiffness is >9.0 kPa when ALT is normal and >12.0 kPa when ALT is elevated up to 5 times upper limit of laboratory normal. Liver cirrhosis can be confidently confirmed when liver stiffness is >12.0 kPa for normal ALT and >13.4 kPa for elevated ALT.

The accuracy of transient elastography for the diagnosis of fibrosis and cirrhosis in patients with nonalcoholic fatty liver disease (NAFLD) has been confirmed in a group of 246 patients from Chinese and French populations[12]. The area under the receiver-operating characteristics curve (AUROC) of transient elastography for F3 or higher and F4 disease was 0.93 and 0.95, respectively, and was significantly higher than that of the aspartate aminotransferase-to-alanine aminotransferase ratio, aspartate aminotransferase-to-platelet ratio index, FIB-4, BARD, and NAFLD fibrosis scores (AUROC ranged from 0.62 to 0.81, $P < 0.05$ for all comparisons). At a cutoff value of 7.9 kPa, the sensitivity and specificity for F3 or greater fibrosis disease were 91% and 75% respectively. Liver stiffness was not affected by hepatic steatosis, necroinflammation, or body mass index. In conclusions, transient elastography is accurate to diagnose advanced fibrosis in different chronic liver diseases, and this non-invasive tool should be adopted in the assessment and monitoring of these patients (Table 1).

References

1. Fraquelli M, Rigamonti C, Casazza G, Conte D, Donato MF, Ronchi G, Colombo M. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. Gut 2007;56:968-73.
2. Talwalkar JA, Kurtz DM, Schoenleber SJ, et al. Ultrasound-based treatment transient elastography for the detection of hepatic fibrosis: systemic review and meta-analysis. Clin Gastroenterol Hepatol 2007;5:1214-1220.
3. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008;134:960–74.
4. Wong GLH, Wong VWS, Choi PCL, et al. Assessment of fibrosis by transient elastography compared with liver biopsy and morphometry in chronic liver diseases. Clin Gastroenterol Hepatol 2008;6:1027-1035.
5. Marcellin P, Ziol M, Bedossa P, Douvin C, Poupon R, de Ledinghen V, Beaugrand M. Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. Liver Int 2008 Epub ahead of print.
6. Chang PE, Lui HF, Chau YP, Lim KH, Yap WM, Tan CK, Chow WC. Prospective evaluation of transient elastography for the diagnosis of hepatic fibrosis in Asians: comparison with liver biopsy and aspartate transminase platelet ratio index. Aliment Pharmacol Ther 2008;28:51-61.
7. Chan HLY, Wong GLH, Choi PCL, Chan AWH, Chim AML, Yiu KKL, et al. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. J Viral Hepat 2009;16:36-44.
8. Sagir A, Erhardt A, Schmitt M, et al. Transient Elastography Is Unreliable for Detection of Cirrhosis in Patients with Acute Liver Damage. Hepatology 2008; 47: 592-595.
9. Arena U, Vizzutti F, Corti G, et al. Acute Viral Hepatitis increases Liver Stiffness Values Measured by Transient Elastography. Hepatology 2008; 47: 380-384.
10. Coco B, Oliveri F, Maina AM, et al. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. J Viral Hepat 2007;14:360-369.
11. Wong GL, Wong VW, Choi PC, Chan AW, Chim AM, Yiu KK, Chan FK, Sung JJ, Chan HL. Increased liver stiffness measurement by transient elastography in severe acute exacerbation of chronic hepatitis B. J Gastroenterol Hepatol 2009;24:1002-1007.
12. Wong VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, Choi PC, Kowo M, Chan AW, Merrouche W, Sung JJ, de Ledinghen V. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology. 2010;51:454-462.

Table 1. Validation of liver stiffness measurement against liver histology in studies with predominantly chronic hepatitis B patients.

	Marcellin et al	Chang et al	Chan et al
Number of patients	115	120	161
Race	French	87% Chinese, 8% Malay, 4% Indian	Chinese
Chronic hepatitis B	100%	55%	100%
Age	40.1±12.8	49.5 (20-79)	45±11
Body mass index	25.5±4.0	24.0 (13.8-36.3)	24±4
HBeAg positive	Not reported	Not reported	43%
ALT (IU/l)	54 (30-85)	79.5 (12-1336)	93±78
METAVIR score			
F0	9.2%	23.3%	6%
F1	40.5%	32.5%	17%
F2	25.4%	17.5%	29%
F3	16.8%	16.7%	40%
F4	8.1%	10%	25%
Median LSM (kPa)			
F0	5.1 (2.5-8.5)	6.9 (3.8-29.5)	5.9 (3.1 – 8.9)
F1	6.0 (2.7-35.3)		5.9 (2.5 – 10.2)
F2	7.0 (2.8-17.6)	12.2 (4.7-42.1)	7.0 (3.9 – 19.6)
F3	12.8 (5.9-45.1)		8.8 (4.8 – 34.3)
F4	23.7 (6.4-59.3)	24.8 (11.9-58.1)	14.2 (8.0 – 36.9)