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Assessment of liver fibrosis in co-infected patients

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The evaluation of liver injury in HIV patients co-infected with HBV and HCV should follow the same principles as the evaluation of any patient with chronic liver disease. The initial clinical evaluation should include documentation of risk factors for progressive disease. HIV history is important particularly with respect to a past history of significant or prolonged immunosuppression as this has been clinically correlated with more advanced liver disease. Liver transaminases are an important predictor of disease severity and progression in HIV patients. Liver biopsy has remained the 'gold standard' for the grading of inflammation and staging of disease. We would still recommend liver biopsy in HIV patients particularly those with HCV because recent community-based studies in the HAART era have suggested slower rates of progression for HIV/HCV than studies from tertiary care centres and older cohorts. Since, liver biopsy is invasive and expensive, non-invasive techniques including serological tests and novel imaging techniques have evolved to stage liver fibrosis. A novel technique for measuring hepatic elasticity has recently been validated alone and in combination with serum markers for HCV mono-infection. Future trends for staging liver disease must not only focus on cross sectional diagnosis but on utilizing novel techniques to stratify risk for disease progression over time.
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1. Introduction

The evaluation of liver injury involves the utilization of clinical and histological criteria to accurately determine the extent of liver injury so as to prognosticate clinical outcomes. The traditional approach is to evaluate patients with history, physical examination, laboratory tests, liver imaging and finally liver biopsy. Percutaneous liver biopsy has been the gold standard for the grading and staging of liver disease. The recognition of inter-observer variability and more significant sampling error associated with liver biopsy has highlighted the need for independent and complementary tests to evaluate liver fibrosis [1,2]. With our expanding knowledge of fibrosis, we are beginning to develop clinically applicable, novel and reproducible non-invasive tests for hepatic fibrosis that may be complimentary or replace liver biopsy. This article will focus on the current and future technologies that can be used in clinical practice to assess liver damage with a specific focus on the HIV patient co-infected with HBV or HCV.

2. Radiological assessment of liver fibrosis

The advent of cross sectional imaging with CT, MRI and ultrasound enables detailed images of the liver and surrounding structures to be made. However, resolution of hepatic parenchyma with any of the available modalities is insufficient to determine any of the earlier stages of fibrosis, prior to the establishment of cirrhosis and portal hypertension. Established cirrhosis with portal hypertension can be determined with a high specificity by identification of splenomegaly, an enlarged caudate lobe or the presence of large varices [3,4]. Both CT scan and MRI with spectroscopy can also be complementary in the evaluation of hepatic fibrosis [5,6].

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3. Liver biopsy

Over the past 50 years liver biopsy has been accepted as the gold standard in the assessment of hepatic fibrosis. However, despite its widespread use, undertaking a liver biopsy requires caution and concern for both physician and patient alike [7]. Significant complications, defined as hospitalisation or prolongation of hospital stay, occurs in 1–5% of patients with a reported mortality rate of between 1:1000 and 1:10,000 [8–11]. In addition to the complications associated with an invasive test, liver biopsy is also prone to two significant limitations;

- Sampling error
- Interobserver variability.

A standard liver biopsy represents only 1/50,000 of the whole organ. This small biopsy size is associated with sampling error. Autopsy and laparoscopic studies have clearly shown that cirrhosis is missed on a single percutaneous liver biopsy in 10–30% of cases [12–14]. A recent study of laparoscopic directed biopsy to both liver lobes noted that cirrhosis was reported on one side but not the other in 14.5% of cases and 33.1% had a difference of at least one stage between either side [2]. The sampling error associated with liver diseases that have less homogeneous fibrosis; such as PBC or PSC is likely to be significantly higher [15]. A recent study using computer generated modeling suggested that a 25 mm biopsy had a 25% error rate and that 40 mm biopsies were optimal [16]. Unfortunately, even in experienced hands, only 16% of biopsies are over 20 mm in size [17].

Interpretation of liver biopsies by a pathologist by the application of scoring systems such as Ishak, Metavir and Knodell improves consistency in interpretation of hepatic fibrosis with a somewhat weaker reproducibility for hepatic inflammation grade [1,18,19]. Computer assistance with morphometric analysis of fibrosis can determine the percentage area of fibrosis in a biopsy specimen but the correlation of fibrosis area with disease stage is very variable and performs best when there is advanced fibrosis [20,21]. An adequate, non-fragmented biopsy is still essential.

4. Hepatic elastography (Fibroscan™)

Transient elastography is an emerging technology that rapidly and non-invasively measures the mean hepatic tissue stiffness [22,23]. Using a probe (Fibroscan, Echosens, Paris, France), a vibration of low frequency (50 Mhz) and amplitude is transmitted into the liver. The vibration wave induces an elastic shear wave that propagates through the organ. The velocity of this wave as it passes through the liver correlates directly with tissue stiffness. The probe contains a pulse-echo ultrasound, which simultaneously measures the velocity of the wave. The harder or stiffer the tissue, the faster the shear wave propagates. Results are expressed in kilopascals (kPa). Fibroscan measures liver stiffness of a volume that is approximately a cylinder of 1 cm diameter and 2 cm long which is 100 times greater in size than a standard liver biopsy, and thus effectively reduces sampling error [24].

Hepatic elastography of 327 HCV mono-infected patients was a reliable tool to detect significant fibrosis or cirrhosis. The area under the receiver operating curve (ROC) were reported 0.79 for $F \geq 2$, 0.91 for $F \geq 3$ and 0.97 for $F = 4$. Using a cut-off value of 8.7 kPa correctly diagnosed those with clinically significant fibrosis ($F \geq 2$) with an area under the ROC curve of 0.79. Similarily a cut-off value of 14.5 kPa reliably correlated with cirrhosis (F4)[24].

Limitations of hepatic elastography include an inability to perform in the setting of ascites or in patients with narrow intercostal spaces. Furthermore a significant limiting factor relates to morbid obesity. Adipose tissue attenuates both elastic and ultrasound waves rendering elastography difficult or even impossible. Further technical developments in refining the probe may overcome some of these limitations.

5. Serum markers

Serum markers of hepatic fibrosis refer to the measurement of one or more molecules within a blood or serum sample as a surrogate marker of fibrosis in the liver [25]. We prefer to consider fibrosis markers as biomarkers rather than true surrogate markers. A true surrogate marker would reflect not only the stage of fibrosis but correlate with clinical outcomes of disease such as is predicted by the CD4 count in HIV. There are several proposed biomarkers or combinations of biomarkers. Ideal features of such serum markers have previously been described and are listed in Table 1 [25].

Experience of these emerging serum markers for estimation of hepatic fibrosis amongst the co-infected population is limited to two reports [26,27], however, it is anticipated that they will be as relevant for the co-infected

Table 1
Ideal features of serum markers of fibrosis

Liver specific
Independent of metabolic alterations
Reproducible performance characteristics
Reflect fibrosis irrespective of cause
Sensitive enough to discriminate between stages of fibrosis
Correlate with dynamic changes in fibrogenesis or fibrosis resolution
Similar predictive value as seen for liver biopsy

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