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Invasive and non-invasive methods for the assessment of fibrosis and disease progression in chronic liver disease

Laurent Castera, M.D., Ph.D.

Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Université Denis Diderot Paris-7, 100 boulevard du General Leclerc, 92110 Clichy, France

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Chronic liver diseases represent a major public health problem, accounting for significant morbidity and mortality worldwide. Their prognosis and management greatly depend on the amount and progression of liver fibrosis with the risk of developing cirrhosis. Liver biopsy, traditionally considered as the reference standard for staging of fibrosis, has been challenged over the past decade by the development of novel non invasive methodologies. These methods rely on two distinct but complementary approaches: i) a 'biological' approach based on the dosage of serum biomarkers of fibrosis; ii) a 'physical' approach based on the measurement of liver stiffness using transient elastography (TE). Non invasive methods have been initially studied and validated in chronic hepatitis C but are now increasingly used in other chronic liver diseases, resulting in a significant decrease in the need for liver biopsy. However, they will likely not completely abolish the need for liver biopsy and they should rather be employed as an integrated system with liver biopsy.
This review is aimed at discussing the advantages and inconveniences of non invasive methods in comparison with liver biopsy for the management of patients with chronic liver diseases.
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Introduction

Prognosis and management of chronic liver diseases greatly depend on the amount and progression of liver fibrosis. For many years, liver biopsy has been considered the 'gold standard' for evaluation of hepatic fibrosis [1]. However, liver biopsy is an invasive procedure with rare but

E-mail address: laurent.castera@bjn.aphp.fr.

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potentially life-threatening complications and prone to sampling errors. These limitations as well as the availability of powerful viral tools and new antiviral drugs have rapidly decreased the use of liver biopsy in viral hepatitis and led to the development of non invasive methodologies for the assessment of fibrosis. Among the currently available non invasive methods, there are two distinct approaches: i) a 'biological' approach based on the dosage of serum biomarkers of fibrosis; ii) a 'physical' approach based on the measurement of liver stiffness using transient elastography (TE) [2]. Although complementary, these two approaches are based on different rationale and conception: TE measures liver stiffness related to elasticity, which corresponds to a genuine and intrinsic physical property of liver parenchyma, whereas serum biomarkers are combinations of several not strictly liver specific blood parameters optimized to mimic fibrosis stages as assessed by liver biopsy [3].

We review herein the different methods that are currently available for the non invasive evaluation of liver fibrosis and also discuss their advantages and inconveniences in comparison with liver biopsy for the management of patients with chronic liver disease.

Liver biopsy: advantages & inconveniences

Histological staging of fibrosis is a combinatorial assessment of amount of fibrosis and architectural disorganization. It is based on semi-quantitative scoring systems including the histological activity index [4], the Ishak's score [5] and the METAVIR scoring system [6] for viral hepatitis as well as Brunt [7] and Kleiner scores [8] for Non Alcoholic Fatty Liver Disease (NAFLD). There are two critical endpoints, i.e. the presence of significant fibrosis which is an indication for antiviral treatment in chronic hepatitis B and C and the presence of cirrhosis which is an indication for specific monitoring of complications related to portal hypertension and to the increased risk of developing hepatocellular carcinoma [9,10]. However, in NAFLD, the second most relevant clinical entity in Hepatology after viral hepatitis, the presence of significant fibrosis does not represent a critical endpoint in the absence of standardized treatment regimens. Thus only the presence of cirrhosis can be considered a universal endpoint.

Simultaneous evaluation of necro-inflammation (portal tract inflammation, interface hepatitis, lobular inflammation) enables assessing whether fibrosis is the result of a past event that has stabilized or even regressed, or is an ongoing process that may continue to worsen. Finally, apart from fibrosis, liver biopsy also detects associated lesions such as steatosis, steato-hepatitis, iron overload, and alcohol which provide useful information for patient management and prognosis [11].

Liver biopsy has however several limitations that should be acknowledged. It is an invasive procedure associated with transient pain, anxiety and discomfort in around 30% of cases [12–14] and rare but potentially life-threatening complications (haemorrhage in 0.3% of cases and mortality in 0.01%) [15]. Performing of biopsy by a trained physician, use of only a limited number of passes and ultrasound guidance can significantly decrease the risk of complications, thereby enhancing the safety of biopsy.

The accuracy of liver biopsy to assess fibrosis has also been questioned, in relation to sampling errors and intra- and inter-observer variability that may lead to over- or under-staging. The size of the biopsy specimen, which varies between ten and 30 mm in length and between 1.2 and two mm in diameter, represents 1/50,000 of the total mass of the liver and so carries substantial sampling error. For instance, it has been shown that only 65% of 15-mm biopsies and 75% of 25-mm biopsies were correctly staged [16]. Also a difference of at least one fibrosis stage between the right and left lobes has been reported in around 30% of cases [17]. Increasing the length of liver biopsy decreases the risk of sampling error [18]. However, cirrhosis may be missed on a single blind liver biopsy in 10–30% of cases [19]. Finally, apart from the characteristics (sample size) of the liver biopsy, the degree of experience of the pathologist (specialization, duration of practice, and academic practice) may also have an influence on inter-observer agreement [20].

Except for cirrhosis, for which micro-fragments may be sufficient, a 25 mm long biopsy is considered an optimal specimen for accurate evaluation, though 15 mm is considered sufficient in most studies [21]. In clinical practice, liver biopsy should always be performed only after carefully balancing risks of the procedure with potential benefits in terms of patient management.

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