Non-invasive Biomarkers FibroTest-ActiTest for Replacing Invasive Liver Biopsy: The need for Change and Action

Mona Munteanu

Service d'Hépato Gastro-entérolgie, Groupe Hopitalier Pitié-Salpetriere, Paris, France

Since September 2002, FibroTest-ActiTest have been used in several countries as an alternative to liver biopsy in order to estimate liver fibrosis and necroinflammatory activity in chronic viral hepatitis C. Several prospective studies have validated these panels of tests in chronic viral hepatitis C and demonstrated its predictive value and the better benefit:risk ratio than biopsy (1-5). Consequently, FibroTest had a global industrial development with an approval from the governmental organization evaluation in France (Haute Autorité de Santé: www.has-sante.fr). Achievement of similar objectives in countries with high prevalence of viral hepatitis requires evidence-based action. The article by Grigorescu *et al* (6) in the precedent issue of this Journal expands our current experience in noninvasive evaluation and management of chronic hepatitis C patients. By performing this first validation of FT in a Romanian PCR HCV positive genotype 1 naïve of treatment population, this study confirms the diagnostic value of FT-AT from the other available publications.

Grigorescu *et al* (6) first focus on the diagnostic value of FibroTest and that of each individual component for discriminating between "insignificant" (F0-F1 by METAVIR) and clinically "significant" fibrosis (F2 by METAVIR) estimated by liver biopsy as a gold standard. They found that all biochemical parameters of FibroTest discriminate F0-F1 from F2-F4 and correlate with the degree of liver fibrosis. FibroTest combines five biochemical parameters with gender and age and has better AUROC than each of its components alone. This study shows also there is no AUROC disparity or variation related to the geographic area or HCV genotype, population being mainly infected by genotype 1 HCV. Overall, this validation study confirms the findings of previous publications and creates a new perspective in Romanian chronic hepatitis C patients, for non-invasive assessment of liver fibrosis as initial evaluation.

Optimized clinical management of chronic hepatitis C requires estimation of the stage of liver fibrosis as the main determinant of prognosis and most therapeutic decisions. The authors stress that Romanian Guidelines established by the National House of Health Insurance require a minimum fibrosis stage of F2 METAVIR *according to the liver biopsy* for the eligibility of antiviral therapy. However, numerous studies strongly suggest that due to the limitations and risks of biopsy, as well as the emergence of biochemical markers with good diagnostic accuracy, liver biopsies should no longer be considered mandatory (7,8). The sampling error of liver biopsy has been previously demonstrated by using the entire liver as a gold standard[1] (9). Recently, in a study including over 1,300 chronic hepatitis C subjects from three different centers that had had contemporaneous FT and biopsy, Poynard *et al* demonstrated that liver biopsy is not a true gold standard at least because of insufficient length or specimen fragmentation (10). Therefore, diagnostic studies of fibrosis markers must take into account all the factors associated with the risk of biopsy failure; non-invasive biomarkers AUROC for discriminating between two adjacent fibrosis stages depends also on biopsy length and fragmentation (10). In this validation study, Grigorescu *et al* excluded from analysis biopsies with less than six portal tracts considered non-interpretable according to quality criteria suggested by some studies[2]. In spite of this precaution, they identified 12% of misclassified by FT that would have been missed for antiviral therapy with a non-invasive approach compared to a liver biopsy-based decision. But,

J Gastrointestin Liver Dis
June 2007 Vol.16 No 2, 173-174
Address for correspondence: Dr.Mona Munteanu
Service d'Hépato Gastro-entérolgie
Groupe Hospitalier Pitié-Salpetriere
47-83 Boulevard de l'Hôpital
75013 Paris, France
E-mail:

1 Bedossa et al. found the best diagnostic value for discriminating between F0-F1 and F2-F4 METAVIR that can be obtained for the liver biopsy versus the entire liver is 0.90 AUROC for a 20mm non-fragmented liver biopsy.

2 Regev et al. suggested that an adequate non fragmented liver biopsy sample contain more than five portal tracts and be at least 15mm in length.

*3 DANA= **D**ifferences between **A**dvanced and **N**on-**A**dvanced fibrosis stages.*

according to Poynard *et al*. data about biopsy fragmentations seems to be also essential in interpreting the misclassified results suggesting that much discordance with FT are related to biopsy failure among fragmented biopsies without cirrhosis (10). Another prospective study observed that 18% of discordances were attributable to biopsy failure (mostly due to small length) and 2% to the failure of the tests (11).

Grigorescu *et al* (6) add the issue of impact of prevalence of each fibrosis stage among "insignificant" (F0-F1) and "significant" (F2-F4) fibrosis groups, on observed diagnostic value, a crucial consideration for an understanding of possible causes of variability of AUROCs between two independent studies. This was first demonstrated by Poynard *et al* on the integrated database including all published prospective studies of patients with chronic hepatitis C and led to the observation that *the prevalence of fibrosis stages defining "significant" fibrosis* is a major factor of variability when assessing the diagnostic value of a fibrosis marker (12). Standardization was constructed to transform any different prevalence profile to a homogeneous distribution of fibrosis stages from F0 to F4. Without this standardization, the indirect comparisons between biomarkers are impossible. The originality of the study of Grigorescu *et al* is to adjust observed AUROC for significant fibrosis (F2-F4) according to the previously proposed standardization leading to an increase of the observed AUROC from 0.782 to 0.856 after adjustment. Difference between observed and adjusted AUROC could be explained in the study of Grigorescu *et al* by the particular distribution of individual stages of fibrosis with only 8% of each extreme fibrosis stage (F0 and F4, respectively), 84% of biopsies being of intermediate stages (F1, F2, F3). The DANA[3] of this study was low [DANA=1.80 for a normal range of 1 to 4]; for an equivalent DANA of the integrated database Poynard et al. found an AUROC (se) of 0.780 (0.01) comparable to that of the current study by Grigorescu *et al* (6).

Ngo *et al* demonstrated that FibroTest had a better 5-year prognostic value than liver biopsy, Child-Pugh or other scores for predicting complications and death related to chronic hepatitis C (13). Based on these results and on validation studies like that of Grigorescu *et a.,* the insight of non-invasive diagnosis of fibrosis change and could improve health care delivery to reduce not-justified invasive procedures like liver biopsy.

The study reported by Grigorescu *et al* also suggests that the use of non-invasive markers of liver fibrosis simplifies liver injury assessment and should accelerate the management of chronic hepatitis C. However, what is needed most right now is a comprehensive set of steps for action – some involving further implementation of non-invasive strategies in the fibrosis screening and in the dynamic testing of the efficacy of antifibrotic treatments, and some the involvement of health care system authorities to recommend their rational use in clinical practice.

References

1. Poynard T, Imbert-Bismut F, Munteanu M, et al. Overview of the diagnostic value of biochemical markers of liver fibrosis (FibroTest) and necrosis (ActiTest) in patients with chronic hepatitis C. Comp Hepatol 2004; 3: 8.
2. Callewaert N, Van Vlierberghe H, Van Hecke A, Laroy W, Delanghe J, Contreras R. Noninvasive diagnosis of liver cirrhosis using DNA sequencer-based total serum protein glycomics. Nat. Med. 2004; 10: 1-6.
3. Castéra L, Vergniol J, Foucher J, et al. Prospective comparison of transient elastography, FibroTest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005; 128: 343-350.
4. Halfon P, Bourliere M, Deydier R, et al. Independent prospective multicenter validation of biochemical markers (FibroTest-ActiTest) for the prediction of liver fibrosis and activity in patients with chronic hepatitis C. Am J Gastroenterol. 2006; 101: 547–555.
5. Sebastiani G, Vario A, Guido M, et al. Stepwise combination algorithms of non-invasive markers to diagnose significant fibrosis in chronic hepatitis C. J Hepatol. 2006; 44: 686-693.
6. Grigorescu M, Rusu M, Neculoiu D, et al. The FibroTest value in discriminating between insiginificant and significant fibrosis in chronic hepatitis C patients. The Romanian experience. J Gastrointestin Liver Dis 2007;16: 31-37.
7. Gebo KA, Herlong HF, Torbenson MS, et al. Role of liver biopsy in management of chronic hepatitis C: A systematic review. Hepatology 2002; 36: S161-S172.
8. Sebastiani G, Alberti A. Non invasive fibrosis biomarkers reduce but not substitute the need for liver biopsy. World J Gastroenterol 2006; 12: 3682-94.
9. Bedossa P, Dargère D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 2003; 38; 1449-1457.
10. Poynard T, Halfon P, Castera L,et al and FibroPaca Group. Variability of the area under the receiver operating characteristic curves in the diagnostic evaluation of liver fibrosis markers: impact of biopsy length and fragmentation.. Aliment Pharmacol Ther 2007;25:733-739
11. Poynard T, Munteanu M, Imbert-Bismut F, et al. Prospective analysis of discordant results between biochemical markers and biopsy in patients with chronic hepatitis C. Clin Chem 2004; 50: 1344-1355.
12. T. Poynard, P. Halfon, L. Castera, et al. Prevalence of each fibrosis stage is a major factor of variability when assessing the area under the roc curves in the evaluation of liver fibrosis markers. EASL 2007 9 (abstr.)
13. Messous D, Munteanu M, Morra R, et al. Time impact of serum storage temperature on stability of important liver enzymes and proteins, and on FibroTest-ActiTest results. Clin Chim Acta 2005; 335: 400.