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Biomarkers for liver fibrosis post-liver transplantation: not as easy as it looks.

S. Francque

Liver biopsy is a crucial tool in the precise diagnosis of disease aetiology and the accurate assessment of disease severity in many liver diseases, including in the context of alteration of liver tests after liver transplantation. The procedure comes, however, with several limitations. Pain and discomfort have a substantial impact on patient acceptability. The procedure is invasive, with an accompanying risk of complications. The biopsy represents only a small part of the liver; hence sampling variability has to be taken into account in the interpretation of the results and some lesions cannot be accurately assessed on small tissue samples. Finally, expertise is required to perform and *a fortiori* to correctly “read” the biopsy, the latter being particularly relevant in more rare liver diseases. Despite these limitations, the liver biopsy still has an important place in the technical armamentarium of the hepatologists, as the information it provides can hardly be delivered by another technical procedure (1).

Biomarkers for liver disease represent an intensive area of research. Fibrosis is one of the most extensively studied features of liver disease in this context. Fibrosis develops as a result of an underlying process of liver damage and inflammation, which, if unresolved and insufficiently counterbalanced by repair mechanisms, can result in progressive accumulation of fibrotic tissue, liver architectural (including vascular) remodelling and ultimately cirrhosis, with an increased risk of decompensation and hepatocellular carcinoma. Fibrosis is hence an important predictor of prognosis and understandably a target for diagnostic approach. Fibrosis stage then reflects disease severity in terms of evolution towards advanced disease and cirrhosis and its assessment, single point or repeatedly, can theoretically help guiding patient management in many ways.

In this issue of Liver Transplantation, Kimura *et al.* studied the utility of Mac-2-binding protein glycosylation isomer (M2BPGi) for the assessment of liver fibrosis in the post-transplant setting, a context in which not so many data on biomarkers are currently available (2).

M2BP is a secreted glycoprotein present in the extracellular matrix and has been shown to correlate with liver fibrosis (3). As specific glycan structures of M2BP change as liver fibrosis progresses, measuring M2BP with an altered glycan structure, *i.e.* M2BPGi, was postulated as a marker for fibrosis. Several studies have reported on its utility in the context of viral hepatitis (and to a lesser extent other aetiology of chronic liver disease) and cirrhosis and hepatocellular carcinoma prediction (4). In 233 patients with a post-transplant liver biopsy, Kimura *et al.* demonstrate that M2BPGi also in this setting correlates with the degree of fibrosis. Its diagnostic accuracy (using biopsy fibrosis staging according to METAVIR as the reference standard) is, however, moderate, and not superior to other biomarkers, including liver stiffness measurement and FIB-4.

Beyond the fact that the reference standard has the important limitation of sampling variability and that fibrosis patterns differ between diseases requiring disease-specific staging systems (METAVIR was designed for viral hepatitis but only 29 of these post-transplant patients had active viral hepatitis, *i.e.* hepatitis C recurrence), the study most interestingly

points towards the confounding effect of necroinflammatory changes as a factor that influences the results.

This highlights one of the most important issues the biomarker field is struggling with: the close intertanglement between fibrosis and the driving force of its development, namely the processes of cell damage, inflammation and cell death. The fibrosis pattern, stage or amount identified on a liver biopsy, which is a snap-shot observation, is, although a static image, the read-out of underlying active processes. The markers measured in serum samples mostly result from these processes, not from the fibrotic tissue seen on the biopsy. Signs of liver damage and inflammation on the liver biopsy, in the study by Kimura *et al* reflected by the necroinflammation activity index, therefore tend to correlate with fibrosis stage in several liver diseases and changes in disease activity over time also correlates with changes in fibrosis stage (5). It is hence not surprising that a biomarker like M2BPGi seems to tell as more about ongoing necroinflammatory changes than on the degree of liver fibrosis *as such*. The fact that it also correlated with the latter, is probably attributable to the aforementioned link between disease activity and fibrosis stage.

Therefore, this study helps us understand the true meaning of this particular biomarker and is therefore also helpful in improving our understanding on how to use biomarkers in general in clinical practice. Using a biomarker to assess fibrosis stage is probably mostly a too simplistic approach (6). We need to understand what the processes are that are reflected by the biomarker in order to know what the biomarker can tell us, and -at least as important- what it doesn't tell us. It is highly unlikely that biomarkers will give us the same complex information as does the liver biopsy. In many cases, we do, however, not need all the details a liver biopsy provides. Targeted questions can be addressed with different biomarkers, as long as it is clear what the biomarker represents and in which context. Liver stiffness, first validated in viral hepatitis as a marker for fibrosis, is rather accurate to rule-in advanced fibrosis and cirrhosis but is not accurate for the exact staging of the disease and needs disease specific cut-offs. As it rapidly declines after viral suppression (illustrating that the value is also influenced by inflammation), its significance in follow-up still warrants further study (7). FIB-4, another fibrosis index also tested in this study, also had only moderate utility in follow-up in a large population-based study (8).

In that context, elevation of M2BPGi post-transplant can tell us something about the presence of significant necroinflammation in the graft, but will not tell us whether this is rejection, disease recurrence or drug toxicity. The authors show in separate sections the relation of the marker with the rejection activity index or with the recurrence of hepatitis C, but again this illustrates that the level M2BPGi correlates with activity of the damage and inflammation, and hence the severity of the process, regardless of the aetiology. It is hence mainly a marker of disease activity and therefore, although this remains to be proven, might hold promise in follow-up to monitor the efficacy of treatment measures that are taken.

In summary, the study by Kimura *et al*. provides further insights in the value of M2BPGi as a biomarker of disease activity rather than fibrosis *per se* and provides insights, which are relevant to the biomarker field that needs to correctly interpret the performance of biomarkers and the information they can provide in a given context of use.

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