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Commentary

A model to predict liver damage in patients with HBeAg-positive chronic HBV infection

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The European Association for the Study of the Liver (EASL) has proposed a new nomenclature to describe the status of patients chronically infected with hepatitis B virus (HBV), which is based upon the main characteristics of chronicity: infection vs. hepatitis, and five phases are defined [1]. Phase 1 is the status of hepatitis B e antigen (HBeAg) positive chronic HBV infection and is defined by alanine aminotransferase (ALT) persistently within the normal range according to traditional cut-off values (upper limit of normal 40 IU/L) and high HBV DNA levels. It is specified that in this phase there is minimal or no liver necroinflammation or fibrosis [1].

In this issue of the journal, Chang et al. report the results of a multicenter prospective study on 336 patients HBeAg-positive with ALT persistently within the normal range, of whom more than half fulfilled the criteria for phase 1, also defined as immunotolerant phase [2]. They found that one out of three patients in phase 1 status had evident histological liver injury (EHLI). This result confirms findings observed in previous studies with small series of patients [3–5]. Moreover, in a meta-analysis including nine studies it was found that 20.7% of HBV−infected patients with ALT levels ≤40 IU/L had significant fibrosis regardless of HBeAg status, high HBV DNA levels, ethnicity or age [6]. Of note, this rate didn't decrease when applying the lower upper limit of normal for ALT recommended by the American Association for the Study of Liver Disease (AASLD) guidelines [7].

Chang et al. propose a model for predicting evident histological liver injury (EHLI) [2]. The model, obtained in a derivation cohort of 233 treatment-naïve patients, was validated in an independent cohort of 103 treatment-naïve patients and showed AUROCs of 0.92 in the derivation cohort and 0.90 in in the validation cohort, with accuracies of 89.2% and 87.3%. respectively. It was tested also in the 127 patients with EHLI from the two cohorts who underwent a second liver biopsy after 72 weeks of treatment with entecavir, showing lower performance (AUROC: 0.81, accuracy: 78.2%).

The analysis of the data is robust, and several statistical tests were used to assess the discrimination power of the model.

The model, named "EHLI-nomogram", combines liver stiffness measurement with other four readily available parameters: age, ALT, alkaline phosphatase, and albumin.

As for age, it must be underscored that the EASL guidelines already recommend to treat all patients with HBeAg positive chronic HBV infection older than 30 years regardless of the severity of liver histological lesions [1]. However, this recommendation was graded as weak using the GRADE system (evidence level III, grade of recommendation 2) [1]. Of note, in the study of Chang et al. the age was dichotomized at 40 years; however, roughly 75% of patients in this cohort were infected with genotype C HBV and a longer duration of the immunotolerant phase in this setting has been reported [8].

In the past few years, liver stiffness measurement has become a surrogate of liver biopsy for the assessment of liver fibrosis, and transient elastography (TE) is the most validated technique. However, guidelines have underscored that TE performs better for detection of cirrhosis than for detection of significant fibrosis [9]. Of note, Chang et al. found that one patient out of four in the immunotolerant phase with ALT <35 had HELI even though the TE value was less than 6 kPa, i.e., in the range of no/mild fibrosis.

EASL guidelines highlight that when TE values and serum biomarkers are in accordance the diagnostic accuracy for detecting significant fibrosis increases; however, it is underscored that this strategy is referred to hepatitis C patients whereas in patients with hepatitis B validation is needed [9]. The study of Chang et al. shows that the combination of several parameters increases the accuracy for the detection of HELI. The results are interesting and shed light on the fact that the complex relationship between HBV replication and host immune response may decrease the accuracy of the non-invasive markers of liver damage in this setting.

Chang et al. report that HELI monogram, which includes five variables, has high accuracy in treatment-naïve patients with HBeAg

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positive chronic HBV infection. However, it must be highlighted that very few patients were provided by each participating center even though this study was performed in a highly endemic area. Larger prospective studies are needed to assess the validity of the proposed model also in a Western population.

Contributors

Giovanna Ferraioli designed the study, Giovanna Ferraioli and Laura Maiocchi searched the literature and analyzed the data, drafted the article, revised it critically for important intellectual content and approved the final version.

Declaration of Competing Interest

Laura Maiocchi: Speaker's bureau: Esaote SpA. Support for attending meetings and/or travel: Hitachi Ltd.

Giovanna Ferraioli: Speaker's bureau: Canon Medical Systems, Hitachi Ltd, Mindray Medical Systems, Philips Medical Systems. Support for attending meetings and/or travel: Canon Medical Systems, Hitachi Ltd, Mindray Medical Systems.

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