Clinical Infectious Diseases

EDITORIAL COMMENTARY

Noninvasive Markers for Monitoring Fibrosis Regression After Hepatitis C Virus Cure: What Do They Promise?

Jürgen Kurt Rockstroh[1,2]

[1]Department of Medicine I, University Hospital Bonn, Bonn, Germany, and [2]German Centre for Infection Research, partner site Bonn-Cologne, Bonn, Germany

(See the Major Article by Kronfli et al on pages 468–77.)

Keywords. HCV; DAA therapy; sustained virological response; fibrosis regression; transient elastography.

Noninvasive markers of liver fibrosis such as aspartate aminotransferase-to-platelet ratio, Fibrosis-4 Index for Liver Fibrosis, and transient elastography (TE) have become the new gold standard for assessing fibrosis stage in individuals with chronic hepatitis C virus (HCV) infection with or without human immunodeficiency virus (HIV) infection prior to starting HCV therapy [1, 2]. According to European Association for the Study of the Liver guidelines, liver biopsy is now reserved only for cases where there is uncertainty or potentially additional etiologies. Identifying patients with cirrhosis (Metavir score F4) or advanced (bridging) fibrosis (Metavir score F3) is of particular importance, as the choice of direct-acting antiviral (DAA) treatment regimen and the posttreatment prognosis depend on the stage of fibrosis. The role of noninvasive markers in monitoring patients with chronic HCV infection after achieving sustained virological response (SVR) after HCV therapy, however, has been less clear. Several studies have assessed the impact of SVR on these noninvasive markers in HCV monoinfection, HIV/HCV coinfection, and in studies comparing both study populations, mostly in small patient cohorts with limited time points, and showing varying degrees of fibrosis regression following successful HCV therapy. In particular, biochemical markers or scores entail a risk of overestimating the fibrosis stage due to the impact of necroinflammatory activity on aminotransferases [3] and, as such, decreases in fibrosis stage after SVR may simply reflect normalization of liver aminotransferases. The article by Kronfli and colleagues in this issue of *Clinical Infectious Diseases* delivers new insights into this ongoing discussion by modeling the evolution of noninvasive markers over time [4]. The strength of the study is the introduction of generalized additive mixed models and the extended follow-up beyond SVR with multiple time points for fibrosis determination. Within this study, TE was identified as the best tool for fibrosis assessment after SVR. This was particularly meaningful in the DAA era for patients with fibrosis, where TE measurements increased before treatment, declined after treatment initiation, and continued to decline after treatment completion [4]. The question still unanswered by this study, however, is whether fibrosis regression by TE leads to a reduced risk of hepatocellular carcinoma (HCC) and other hepatic and extrahepatic outcomes. Future studies will be needed to assess the risk of HCC and other liver-related long-term outcomes according to trajectories of fibrosis regression measured using TE to determine if and when it will become safe to discontinue HCC screening. Although the regression of cirrhosis is possible, the proportion of patients who will experience such improvement is not known. In fact, it is tempting to speculate that most will not experience fibrosis regression at all, particularly those who are affected by comorbidities. Nevertheless, as has already been shown, large-scale longitudinal studies of noninvasive evaluations are currently increasing in number and suggest that even in cases of regression of these parameters, the risk of HCC remains high enough to justify surveillance [5]. In this case, patients with advanced fibrosis or cirrhosis will have to remain in lifelong HCC surveillance programs.

Another important finding is the observation that TE declined over the HCV treatment period as the measured TE values can also be influenced by necroinflammatory hepatic activity. Thus, estimation of fibrosis regression should only begin after obtaining SVR as changes after HCV cure are more likely to be a truer estimate of the level of fibrosis than the pretreatment TE measurements. As the cohort examined different HCV risk groups, including men who have

Received 6 May 2020; editorial decision 8 May 2020; accepted 3 June 2020; published online June 5, 2020.

Correspondence: J. K. Rockstroh, Department of Medicine I, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany (juergen.rockstroh@ukbonn.de).

Clinical Infectious Diseases® 2021;73(3):478–9

DOI: 10.1093/cid/ciaa698

sex with men as well as intravenous drug users, subanalyses by risk group would be interesting to see whether TE measurements remain valid independent of HCV transmission mode and affected risk population as there may be differences in amount of comorbidities and median duration of HCV infection between groups, all factors known to impact fibrosis development. This, however, would require an increase in patient numbers studied, as for some subgroups the number of patients followed is quite low.

Eventually, with emerging data suggesting an increased risk for weight gain and metabolic syndrome under modern HIV integrase inhibitor–based therapy, there also is the question about changing risks for hepatic steatosis and potentially hepatic fibrosis development in people living with HIV in general, but even more importantly in patients with preexisting HCV-associated liver disease [6]. Indeed, fatty liver is very common in HCV-monoinfected patients post-SVR [7]. In the fibrosis marker study by Kronfli et al, protease inhibitor therapy, but not integrase inhibitor therapy, was added as a covariate in sensitivity analysis [4]. Further studies in HIV/HCV coinfection are therefore needed to study the development of fatty liver disease and the potential impact of integrase inhibitor–based antiretroviral therapy over time. Under consideration of potential direct HIV effects as well as HIV treatment–related impact on fibrosis regression after SVR, more studies evaluating the role of TE as a noninvasive monitoring tool post-SVR in HCV monoinfection are also urgently needed.

Note

Potential conflicts of interest. J. K. R. has received honoraria for speaking at educational events or consulting from AbbVie, Gilead, Janssen, Merck, Theratechnologies, and ViiV. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. J Hepatol **2018**; 69:461–511.
2. European AIDS Clinical Society. EACS treatment guidelines. Available at: https://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html. Accessed 5 May 2020.
3. European Association for Study of Liver. EASL-ALEH clinical practice guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol **2015**; 63:237–64.
4. Kronfli N, Young J, Wang S, et al; Canadian Co-infection Cohort Study Investigators. Liver fibrosis in HIV-hepatitis C virus (HCV) co-infection before and after sustained virologic response: what is the best non-invasive marker for monitoring regression? Clin Infect Dis **2020**; 73:468–77.
5. Kanwal F, Kramer JR, Asch SM, Cao Y, Li L, El-Serag HB. Long-term risk of hepatocellular carcinoma in HCV patients treated with direct acting antiviral agents. Hepatology **2020**; 71:44–55.
6. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. N Engl J Med **2019**; 381:803–15.
7. Noureddin M, Wong MM, Todo T, Lu SC, Sanyal AJ, Mena EA. Fatty liver in hepatitis C patients post-sustained virological response with direct-acting antivirals. World J Gastroenterol **2018**; 24:1269–77.