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REGRESSION OF HCV CIRRHOSIS: TIME WILL TELL

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In patients with chronic hepatitis C (HCV) one of the ideal goals of viral elimination is to prevent progression across the different stages of disease thereby preventing the development of clinically-relevant outcomes. Viral elimination in chronic hepatitis C has been shown to prevent progression to more advanced stages of fibrosis/cirrhosis. Further, in patients with compensated cirrhosis, viral elimination has been shown to prevent/delay the development of varices, decompensation and hepatocellular carcinoma (HCC). In fact, these patients have been shown to have a life expectancy similar to the general population.

But regression of the disease is also an important outcome, perhaps an even more important one and this will depend on the stage of chronic liver disease at the time of initiation of antiviral therapy (Figure).

In chronic liver disease with only mild/moderate fibrosis one assumes that, because fibrogenesis and vascular/parenchymal alterations that lead to cirrhosis are ongoing and are not complete, viral elimination (in the absence of concomitant injurious agents/conditions) will eventually lead to regression to a normal liver.

In the sickest patients, those with decompensated cirrhosis, regression would be to a compensated stage as demonstrated in patients with decompensated HCV cirrhosis in whom HCV elimination has led to re-compensation (that is, return to a compensated stage) and delisting from the transplant list (1). However, in patients with decompensated cirrhosis, stromal and vascular alterations in the liver are likely irreversible and it would be essentially impossible for the liver to regress to a non-cirrhotic stage (2).

It is patients with compensated cirrhosis in whom regression to a non-cirrhotic stage is a possibility. Regression of fibrosis in HCV compensated cirrhosis has been described after viral elimination with interferon-based therapy (3). What is still undefined is the subgroup of patients with compensated cirrhosis in whom regression to a non-cirrhotic stage is possible and the substage at which regression will be unlikely (the point of no return) and how to determine whether such regression has occurred not only histologically but also clinically (absence of cirrhosis-related clinical events). In a position paper published in *HEPATOLOGY* that correlated clinical, hemodynamic, histological and biological aspects of chronic liver disease/cirrhosis, we postulated that the stage at which compensated cirrhosis

may not be reversible is the stage of clinically significant portal hypertension (CSPH), defined as a hepatic venous pressure gradient of at least 10 mmHg (2) (Figure). This was based on evidence showing that, in patients with compensated cirrhosis and mild portal hypertension, fibrous septa were more frequently thin while in those with CSPH, fibrous septa were mostly thick (4), in a pattern that has now been classified as “predominantly progressive” (5) and that is unlikely to regress. These concepts are being increasingly explored now that therapies for HCV lead to viral elimination in most patients.

In this issue of HEPATOLOGY, Mauro et al (6) investigate fibrosis regression in a relatively large group of patients (n=112) with post-transplant recurrent HCV with at least stage F1 fibrosis (METAVIR system) prior to therapy and with repeat liver biopsy 12 months after viral elimination. Fibrosis regression (defined by decrease by one METAVIR stage or more) occurred in 67% of patients overall, but occurred in a larger percentage (72–85%) of patients without cirrhosis (F1–F3) than in those with cirrhosis (F4) at baseline in whom fibrosis regression was observed in 43%. Importantly, regression to a non-fibrotic stage (F0) was observed in 72% with F1, 39% with F2, 15% with F3 and in none with F4 at baseline.

Of 37 patients with cirrhosis, 92% remained at F4 or decreased to F3, that is, most remained with advanced fibrosis. However, almost half of the patients with cirrhosis in the cohort had a history of decompensation and, when analyzed jointly with compensated patients, they find that a history of decompensation, together with the presence of CSPH and thick septa on liver biopsy were predictors of lack of fibrosis regression. This is not at all surprising since patients who decompensate have, by definition, CSPH and, as mentioned above, are more likely to have non-reversible thick fibrous septa (2).

The question that begged answering and that unfortunately is not answered by Mauro et al (6) is the identification of the subgroup of patients with *compensated* cirrhosis (i.e. without a history of decompensating events) in whom fibrosis regression occurred and the predictors of regression in this specific subgroup of patients. Evidence suggests that the presence of CSPH is the main predictor of lack of regression after viral elimination in these patients. In a recent study that included only patients with CSPH (but that also included patients with decompensated cirrhosis), CSPH persisted in 78% of the patients despite viral elimination (7). Studies looking at clinical outcomes demonstrate that decompensation post-viral elimination only occurs in compensated patients with pre-treatment CSPH (8) or in those with pre-treatment varices (who have CSPH by definition) (9). The study by Mauro et al further supports this contention by showing, in a subgroup of 25 patients with cirrhosis, a significantly lower pre-treatment HVPG (median 7 mmHg) in patients with regression than in those without regression (median 14 mmHg), and by showing that the lowest baseline HVPG in patients without fibrosis regression was 11.5 mmHg (i.e., CSPH).

A non-invasive way to detect this point of no return could be through liver stiffness measurements (LSM). Mauro et al also investigate paired LSM in a subgroup of patients, 34 of them with cirrhosis. In these, LSM decreased more in those with fibrosis regression, and the lowest LSM in patients without regression was 25.3 kPa (in line with cutoffs that define CSPH in non-transplanted patients). Parenthetically, post-treatment LSM below 10 kPa were observed in some patients who remained with advanced fibrosis. Because complications

such as HCC have been shown to occur in patients with regression to F3 fibrosis and normalization of LSM (3), it is dangerous to assume that LSM can confidently rule out the presence of advanced fibrosis and guide screening strategies, as proposed by the authors (6). With a sensitivity of only 82%, 18% of patients who remain with advanced fibrosis post-viral elimination and at risk for complications would not be screened.

Ultimately, cirrhosis-related clinical complications (or lack thereof) are the ones that should define cirrhosis regression. In the study by Mauro et al, clinical decompensation was present in 50% of patients with cirrhosis at the start of treatment and only 5% remained decompensated after therapy, confirming that regression from a decompensated to a compensated stage occurs after viral elimination, independent of histological fibrosis regression. A tendency for an improvement in survival was also observed in these patients, although again the lack of stratification by stage (Figure) does not allow identification of the subgroup that benefited the most.

In summary, the study by Mauro et al is a step forward in our understanding of the course of chronic liver disease after elimination of the etiological agent. We have learned that, in patients with post-transplant recurrent HCV, viral elimination (12 months) leads to fibrosis regression in a substantial number of patients but mostly those with non-cirrhotic stages and that patients with cirrhosis particularly those with clinically significant portal hypertension are unlikely to regress. This mirrors findings in immunocompetent patients with HCV cirrhosis although perhaps in patients with post-transplant HCV in whom fibrosis progression is much faster, regression will also be faster and may occur in an even larger number of patients with histological cirrhosis. Because cirrhosis regression is not only about fibrosis regression but also about reversal of vascular and parenchymal abnormalities which are not assessed by the METAVIR score and could be irreversible (10, 11), the best evidence and definition of regression of cirrhosis will be based on the assessment of long-term clinical outcomes. Further follow-up of Mauro et al's cohort with histological, hemodynamic, elastographic and clinical data, stratified by stage of liver disease, will provide invaluable data towards this definition. Time will tell.

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Stage of CLD	Non-fibrotic	Non-cirrhotic	Compensated cirrhosis			Decompensated cirrhosis
Fibrosis stage	F0	F1-F2	F3-F4			F4
Portal hypertension (PH)	No PH	No PH	Mild PH	CSPH Varices/collaterals absent	Varices/collaterals present*	Clinical evident complications of PH (ascites, VH, HE)
HVPG	3-5 mmHg (normal)		6-<10 mmHg	≥10 mmHg		≥12 mmHg
Fibrous septa	None	None	More often thin septa	More often thick septa		Thick septa
Regression with SVR**	NA	Most will regress to non-fibrotic	<ul style="list-style-type: none"> • May regress to non-cirrhotic • ? Regress to non-fibrotic 	<ul style="list-style-type: none"> • May regress to mild PH • No regression to non-cirrhotic 	<ul style="list-style-type: none"> • Less likely to regress to mild PH • No regression to non-cirrhotic stage 	<ul style="list-style-type: none"> • May regress to compensated stage • No regression to mild PH or non-cirrhotic stage
Clinical decompensation post SVR**	No risk	No risk	No risk	Still at risk	Higher risk than CSPH without varices	NA

Figure 1.

Conceptual framework of the stages of chronic hepatitis C defined by histology and portal pressure (hepatic venous pressure gradient) with the theoretical possibilities of regression and clinical decompensation after SVR.

CLD= chronic liver disease; CSPH= clinically significant portal hypertension; VH=variceal hemorrhage; HE=hepatic encephalopathy; HVPG = hepatic venous pressure gradient; SVR = sustained virological response (viral elimination); NA =not applicable

* Patients with varices and/or collaterals have, by definition, CSPH; **assumes no other injurious agents (alcohol, fat) are present