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EDITORIAL

Is complete regression of liver injury achievable?



Chronic liver injury (CLI), regardless of the cause, results in an inflammatory response that leads to fibrosis and ultimately the replacement of normal liver architecture by regenerative nodules. The most common causes of CLI include chronic infection with hepatitis C virus (HCV), heavy alcohol misuse, and non-alcoholic fatty liver disease (NAFLD). Other common causes include chronic infection with hepatitis B virus, primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis. Chronic hepatitis C infection, the liver disease of the 20th century is being replaced by NAFLD, which represents the liver disease of the 21st century, as the most common cause of CLD in Western countries.¹ In each of these etiologies, the liver is chronically injured in some way; this injury leads to inflammation, and the inflammation results in fibrosis.

Liver pathologists have proposed that the term cirrhosis must be replaced by advanced liver disease, in order to underlie the dynamic processes of this condition.² Furthermore, growing evidence has documented the regression of mild, moderate and even advanced fibrosis in many etiologies of CLD. For example, patients who were successfully treated for HCV infection, documented by negative HCV RNA, who underwent a repeated biopsy, showed no evidence of the fibrosis documented in the index biopsy.^{3,4} However, although fibrosis regresses in early stages, it is not fully reversible in most patients with advanced cirrhosis. This important issue is presented in this number of *Medicina Universitaria* in the article entitled "Mechanisms involved in liver damage resolution after HCV clearance". The authors clearly depicted the mechanism of liver fibrosis and the relevance of hepatic stellate cells, the different types of collagen and the key role of metalloproteinases. The question is, what is the point of no return that stymies reversal of fibrosis? The cause might be structural.

In fibrosis, the normal composition of the extracellular matrix (ECM) in the Space of Disse is replaced by a matrix rich in fibrillar collagens I and III. This fibrillar and the non-fibrillar collagens are digested by matrix metalloproteinases (MMPs). As fibrosis progresses, there is a rampant synthesis and deposition of EMC by activated stellate cells (aHSC), and these combined by a failure of matrix degradation mediated by the inhibition of MMP activity by tissue inhibitors of MMP

which are also produced by aHSC. Further liver damage leads to extensive crosslinks in the ECM, and some are irreversible, so that the MMP cannot then degrade it. The point of no return may be when this extensive crosslinking has occurred. Once the scar is fully stable the organism has no way to remove it.⁵

When this scenario ultimately results in the need for liver transplantation, it is not so much because of the fibrosis but because of the consequences of fibrosis. Fibrosis may cause portal hypertension, leading to variceal bleeding, ascites, and portal systemic encephalopathy. With liver failure comes coagulopathy and failure of the liver to clear toxins from the body. Fibrosis itself is not the threatening condition per se, because a person can have some fibrosis and be just fine, but as fibrosis progresses to the point of causing liver decompensation, or if, over time, enough inflammation and fibrosis occur, then hepatocellular carcinoma (HCC) results. It is very unusual that HCC develops in the normal liver; it is almost exclusively seen in the setting of fibrosis.⁶

Hepatitis C is a curable infection and now the issue here is if we will see it completely eradicated someday. Although it is a wonderful goal, there is still a lot of work to do before that. Identifying all patients who are infected, preventing the spread of the infection, and providing access to therapy is still challenging in low-income or developing countries.

Since the late 1990s with the highly active anti-retroviral therapy for HIV there has not been such an explosion of new drugs and regimens in virology. The slow beginnings of this new era of the direct-acting antiviral (DAA) therapy for hepatitis C, started a few years ago with the first protease inhibitors, boceprevir and telaprevir, each being compared with interferon and ribavirin, leading to a significant improvement in response rates, but only in the easiest-to-cure population such as the treatment-naïve patients with genotype 1 HCV. For other populations, the poor benefit/risk profile did not justify the widespread use of such toxic agents. When the new oral regimens became available, previous predictors of treatment failure were eliminated, including gender, ethnicity, weight, previous treatment failure, post-transplanted patients, HIV/HCV co-infection, and even cirrhosis.

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So, that made it easier, right? Well, this is absolutely true for the patient and at some point for the clinician who now faces fewer and less severe side effects with these new drugs. However, the field has become more complex for the clinician in terms of understanding mechanisms of how these medications work, the development of resistance, and drug–drug interactions.

Unfortunately, “one size does not fit all”. Different regimens are still required based on genotype and presence or absence of cirrhosis, both of which may alter duration,⁷ however new regimens are still being developed, and some novel targets are still investigated. Maybe, it will require few years and other drugs to reach the target of having an “easy button: one regimen for all patients”. This will make it simple for physicians, patients, and the health-care systems.

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