Letters to the Editor


Reply to: Is there any association between HCV multiplication and iron induced liver injury in chronic hepatitis C?

This is a reply to the letter to the Editor by Sikorska et al.: We appreciate the interest of Sikorska et al. in our recent study [1] and would like to comment on the issues raised in their letter. We fully agree that, in light of clinical literature and earlier biochemical evidence, the iron-mediated inhibition of HCV replication is surprising. This matter has been extensively discussed in a previous related publication [2], which established that iron attenuates the expression of subgenomic HCV replicons in culture and blocks the enzymatic activity of recombinant HCV polymerase NS5B in vitro. Our recent study validated the antiviral activity of iron in a more physiologically relevant setting of infectious HCV in permissive Huh7.5.1 cells. Certainly, HCV replicon models do not recapitulate the entire range of molecular responses triggered in the host during acute infection with HCV and progression to CHC; nevertheless, they provide a valuable framework to elucidate important aspects of HCV biology in a reductionist approach. The employment of such models uncovered that iron inhibits HCV replication. We speculated that this surprising finding may account for some unexpected clinical observations, where HCV-infected patients with mutations in the HFE gene responded better to antiviral therapy [3–5].

Sikorska et al. challenge this idea by arguing that it is merely supported by selected reports. We believe that published clinical literature qualifies to accommodate hypotheses arising from biochemical data. Moreover, we wish to emphasise that an increased frequency of HFE gene mutations in HCV patients who are responders to antiviral therapy has been documented in major clinical studies (reviewed in [6]). Thus, in a cohort of 256 CHC patients, the presence of HFE C282Y mutation positively correlated with sustained response in multivariate analysis (p = 0.012) [3]. Likewise, CHC patients with HFE H63D mutation showed a significant improvement in both their primary response and sustained response to interferon, although statistical significance for the latter did not reach the level of 0.05 [5]. These data suggested that HFE may constitute part of a battery of host genes that affect responses to antiviral therapy. Similarly, in the largest study thus far, on the effects of HFE-related iron overload in anti-HCV therapy (HALT-C trial) that included 1051 patients, Bonkovsky et al. found that subjects harboring HFE mutations, particularly H63D, had significantly higher likelihood of both end-of-treatment virological response (p = 0.0078) and sustained virological response (p = 0.009) to re-treatment with pegylated interferon alpha-2a plus ribavirin [4]. Again, both the HFE mutation and/or associated genetic variants were considered as possible causes of the improved response to therapy.

The iron-dependent inhibition of HCV replication documented in our studies is consistent with the above clinical findings and it is tempting to speculate that even minimal HFE-related hepatic iron overload may contribute to viral clearance in HCV-infected patients subjected to antiviral treatment. There is no doubt that this hypothesis requires further validation in animal models of HCV infection. It should also be noted that the adverse effects of iron overload in the liver and in the immune system preclude any exploitation of the iron-dependent inhibition of HCV replication for therapeutic purposes.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References


Hepatocyte iron accumulation: A new string to ribavirin’s antiviral bow?

To the Editor:

Building on previous work, the recent article by Fillebeen and Pantopoulos elegantly demonstrates a role for iron as an inhibitor of hepatitis C virus (HCV) replication [1]. Using HCV-infected Huh7.5.1 hepatoma cells, the authors show a dose-dependent reduction in the expression of HCV viral proteins and RNA upon exogenous administration of iron. Moreover, the anti-viral effect of iron was attributed to the direct inhibition of the HCV RNA polymerase NS5B by iron [2].

However, the findings outlined in this article appear contrary to the prevailing perception of the role of iron in HCV infection. Disordered iron homeostasis is a frequent finding in HCV patients, and may be associated with adverse clinical outcomes [3]. An increased propensity to hepatic decompensation, an increased incidence of hepatocellular carcinoma, and a reduced response to treatment have all been reported in association with excess serum or hepatic iron [4–6]. The authors acknowledge these issues, and conclude by doubting whether iron-mediated inhibition of HCV replication would represent a realistic therapeutic target. These sentiments were echoed in the accompanying editorial [7].

The nucleoside analogue ribavirin forms a key component of the current standard of care for HCV treatment, in combination with pegylated interferon alpha. Despite its importance in augmenting treatment response and preventing relapse, its antiviral mechanism of action remains elusive [8]. Curiously, significant hepatic iron accumulation has been reported in HCV patients receiving ribavirin monotherapy for greater than 6 months [9,10]. These findings were attributed to the well-documented, dose-dependent haemolysis caused by ribavirin. However, excess iron accumulated predominantly in hepatocytes, rather than in phagocytic Kupffer cells, as might be expected following intravascular haemolysis [10]. Although hepatic iron accumulation during treatment was not associated with changes in liver transaminases, it is unclear whether treatment response was altered [10].

Iron accumulation in chronic HCV infection appears harmful. Given the findings by Fillebeen et al., it would be difficult to discount a potential role for iron in hepatocyte HCV eradication, which may be transiently facilitated by ribavirin therapy. At this very least, this potential mechanism of ribavirin action merits further investigation.

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References


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