

Commentary

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Iron and hepatitis C

A relation between abnormal parameters of iron metabolism and chronic viral hepatitis has been known for over 20 years. Blumberg and colleagues described abnormal iron studies in patients with hepatitis B virus infection,^{1 2} and Prieto *et al* found a strong correlation between serum aspartate aminotransferase (AST) activities and ferritin values in patients with a variety of chronic liver diseases.³ More recently, Di Bisceglie *et al* reported serum iron studies and hepatic iron concentrations in two groups of patients with chronic viral hepatitis, demonstrating that approximately 35–40% of patients had abnormal serum iron studies, usually with normal hepatic iron stores. It was concluded from these reports that the abnormal iron values were a result of necroinflammatory changes induced by chronic hepatitis with hepatocytolysis and release of cellular iron or ferritin, or both, into the circulation.⁴

Extending these observations of abnormal iron metabolism in chronic viral hepatitis to another level, three recent papers have demonstrated that there was a higher hepatic iron concentration (HIC) in patients with chronic viral hepatitis who failed to respond to treatment with interferon compared with those who did respond.⁵⁻⁷ For example, Van Thiel *et al*⁵ found that the HIC was significantly higher in 29 non-responders to interferon compared with 50 complete or partial responders with all types of chronic viral hepatitis. Olynyk *et al*,⁶ in a series of 58 patients with chronic hepatitis C, confirmed these results demonstrating that the mean HIC was significantly higher in 34 non-responders compared with 24 responders. Furthermore, 85% of patients with an HIC of greater than 1100 µg/g and 87% of patients with a raised serum ferritin concentration did not respond to treatment with interferon.⁶ Finally, Piperno and colleagues also showed in a group of patients with chronic hepatitis C that those who responded to interferon had lower hepatic iron concentrations than those who did not.⁷ Other investigators have not found a difference in HIC between responders and non-responders, but rather have identified a significant difference in hepatic cellular iron distribution in non-responders to interferon compared with responders.⁸ Using detailed histomorphometric analysis in a small series of patients, Barton *et al* showed that non-responders to interferon had predominant distribution of iron in Kupffer cells compared with responders.⁸ As all of these studies were performed retrospectively, there is the possibility of some degree of selection bias, although this seems unlikely given the number of times this observation has now been made.

These findings have led to the consideration of whether patients might benefit by being depleted of excess iron stores by repeated therapeutic phlebotomy before treatment with interferon or to improve response rates in previous non-responders. One small study from Japan with a heterogeneous group of patients showed a significant reduction in serum concentrations of alanine aminotransferase (ALT) in all patients who were made iron deficient.⁹ Additionally, several other reports of phlebotomy therapy

in chronic hepatitis C have been published, consistently demonstrating a significant reduction in serum ALT concentrations; however, no consistent evidence of a change in hepatitis C virus (HCV) RNA levels has been shown.^{7 10 11}

The precise reasons for these associations between hepatic iron metabolism and chronic hepatitis C or responsiveness to treatment with interferon, or both, are poorly understood. A variety of immunological and virological effects of iron overload or iron deficiency, or both, are known, but it is not clear that any of these relate to the immunopathological manifestations seen in chronic hepatitis.^{6 8 12} Alternatively, patients with chronic hepatitis may have altered mechanisms of cellular iron uptake or hepatic iron deposition, or both.⁶

In this issue, Boucher and colleagues (page 115) have provided some additional interesting insights into the relation between hepatic iron metabolism and chronic hepatitis C. In their study, 55 patients were treated with interferon- α for six months and were evaluated for HIC and cellular distribution of hepatic iron before and six months after therapy was completed. They found no difference in HIC between non-responders and responders. However, they did identify a relation between HIC and histological evidence of inflammatory activity such that the iron load was higher in those patients with the greatest degree of histological inflammatory activity. Surprisingly, HIC decreased significantly following treatment. This was related to iron depletion in mesenchymal cells and was apparent regardless of whether patients responded to interferon (ALT normalisation, loss of HCV RNA) or not. These findings suggest that the presence of increased hepatic iron stores in patients with chronic hepatitis may be present predominantly as a result of the degree of inflammatory activity, presumably correlating cell injury or necrosis, or both, with subsequent hepatocyte phagocytosis by Kupffer cells resulting in progressive increases in Kupffer cell iron loading. Of greater interest, however, is the loss of hepatic iron deposits as a result of the loss of iron in mesenchymal cells with interferon treatment regardless of whether or not patients had a response. Potential mechanisms whereby this could occur are discussed by the authors and include up-regulation of transferrin receptor expression in macrophages induced by inflammation, with an anti-inflammatory effect of interferon presumably down-regulating this expression. Alternatively, the possibility of a shift of iron from the liver to extrahepatic sites such as the bone marrow was considered, although this mechanism was felt to be unlikely.

Another explanation of theoretical interest relates to the recent discovery of an MHC class 1-like gene (HLA-H) thought to be responsible for haemochromatosis.¹³ Patients homozygous for the predominant mutation (Cys282Tyr) presumably have failure to express HLA-H on the surface of cells, resulting in increased gastrointestinal iron absorption and subsequent deposition of

iron in hepatocytes and other parenchymal cells in the body. It is known that interferon up-regulates the expression of MHC class 1 proteins and therefore, it could be that interferon results in a net decrease in absorption or uptake, or both, of iron into the liver providing an explanation for the observations made by Boucher *et al.*

Although the mechanisms whereby the interactions between iron metabolism and chronic viral hepatitis occur are still largely unknown, it is increasingly apparent that there is a definite relation between these two entities. Perhaps the recent discovery of the haemochromatosis gene can lead to a clearer understanding of iron absorption and disordered hepatic iron metabolism, helping us to understand what happens in chronic viral hepatitis.

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- 1 Sutnik AI, Blumberg BS, Lustbader ED. Elevated serum iron levels and persistent Australia antigen (HBsAg). *Ann Intern Med* 1974; **81**: 855-6.
- 2 Lustbader ED, Hann HWL, Blumberg BS. Serum ferritin as a predictor of host response to hepatitis B virus infection. *Science* 1983; **220**: 423-5.
- 3 Prieto J, Barry M, Sherlock S. Serum ferritin in patients with iron overload and with acute and chronic liver diseases. *Gastroenterology* 1975; **68**: 525-33.
- 4 Di Bisceglie AM, Axiotis CA, Hoofflagle JH, Bacon BR. Measurement of iron status in patients with chronic hepatitis. *Gastroenterology* 1992; **102**: 2108-13.
- 5 Van Thiel DH, Friedlander L, Faginoli S, Wright HI, Irish W, Gavalier JS. Response to interferon α therapy is influenced by the iron content of the liver. *J Hepatol* 1994; **20**: 410-5.
- 6 Olynyk JK, Reddy KR, Di Bisceglie AM, Jeffers LJ, Parker TI, Radick JL, *et al.* Hepatic iron concentration as a predictor of response to interferon alfa therapy in chronic hepatitis C. *Gastroenterology* 1995; **108**: 1104-9.
- 7 Piperno A, Sampietro M, D'Alba R, Roffi L, Fargion S, Parma S, *et al.* Iron stores, response to interferon therapy, and effect of iron depletion in chronic hepatitis C. *Liver* 1996; **16**: 248-54.
- 8 Barton AL, Banner BF, Cable EE, Bonkovsky HL. Distribution of iron in the liver predicts the response of chronic hepatitis C infection to interferon therapy. *Am J Clin Pathol* 1995; **103**: 419-24.
- 9 Hayashi H, Takikawa T, Nishimura N, Yano M, Isomura T, Sakamoto N. Improvement of serum aminotransferase levels after phlebotomy in patients with chronic active hepatitis C and excess hepatic iron. *Am J Gastroenterol* 1994; **89**: 986-8.
- 10 Bacon BR, Rebholz AK, Fried MW, Di Bisceglie AM. Beneficial effect of iron reduction therapy in patients with chronic hepatitis C who failed to respond to interferon- α [abstract]. *Hepatology* 1993; **18**: 150A.
- 11 Van Thiel DH, Friedlander L, Malloy P, Fagioli S, Wright HI, Gasbarrini A, *et al.* Retreatment of hepatitis C interferon nonresponse with larger doses of interferon with and without phlebotomy [abstract]. *Gastroenterology* 1994; **106**: A1002.
- 12 Caraceni P, Fagioli S, Van Thiel DH. Iron reduction therapy: simply camouflage, or a real weapon? *Am J Gastroenterol* 1994; **89**: 970-3.
- 13 Feder JN, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, Basava A, *et al.* A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* 1996; **13**: 399-409.