influence the ability of iron to participate in biological reactions.[94]

It is possible that iron deposition in sinusoidal cells, especially Kupffer cells, could alter the immune responsiveness of macrophages. This hypothesis is supported by observations that iron deposition within zone 1, portal tracts and sinusoidal lining cells is associated with a higher likelihood of non-response to interferon therapy.[27–34] There are reports of impaired phagocytic function by monocytes in hereditary hemochromatosis.[95,96] Intracellular killing of microorganisms may also be impaired by iron overload.[96,97] Interleukin 2 production by cytotoxic T-cells is reduced in the presence of iron overload.[83] We have studied the effect of chronic iron overload on Kupffer cell cytokine production.[98] Kupffer cells from iron loaded animal exhibit reduced proinflammatory cytokine production compared with Kupffer cells from control animals. Thus iron loading may impair immune clearance mechanisms *via* impaired macrophage function or interfere with the actions of interferon α on macrophage function.

Iron Status and Likelifood of Response to Interferon Therapy

Following the reports of the relationship between iron status and likelihood of response, investigators began evaluating the possibility that patients might benefit by being depleted of iron by repeated therapeutic phlebotomy before treatment with interferon or to improved response rates in previous non-responders. Hayashi *et al.*[34] reported that iron reduction alone led to the normalization of serum ALT levels in 5 of 10 patients with chronic hepatitis C. Four to 13 phlebotomies, with removal of 1–3 g of iron, over 2–9 months were required to achieve iron removal as judged by serum ferritin levels less than 10 ng/ml. Seven patients underwent repeat biopsy within 2 months of iron depletion, with no apparent change in the severity of portal fibrosis or inflammation. In another study of 8 patients with chronic hepatitis C who had previously failed to respond to treatment with interferon α, serum ALT levels fell in 7 of 8 following iron reduction.[38] Van Thiel *et al.*[99] randomized 30 non-responders to iron depletion followed by interferon α or interferon α alone. Twelve of 15 (80%) of patients treated with iron depletion and interferon had a virological response at 6 months compared with 6/15 (40%) in the interferon-alone group. Significantly higher sustained virological response rates were seen in the iron depleted group (60%) compared with interferon-alone group (13%). Iron chelation with desferoxamine has also been shown to improve response to interferon therapy.[100] However, there have been no clear effects of iron reduction on levels of HCV RNA in serum.[100–102]

Fong *et al.*[43] recently conducted a randomized study which evaluated the effect of iron depletion on aminotransferase activity, HCV RNA levels and response to interferon α therapy in patients with chronic hepatitis C. Serum ALT levels decreased in 15 of 17 patients after phlebotomy. Changes in iron indices and ALT levels were not accompanied by changes in HCV RNA levels. At the end of 24 weeks of interferon therapy, similar numbers of phlebotomized patients (7 of 17) had a response compared to control patients (6 of 21). However after 6 months of follow up, 5 of 17 phlebotomized patients remained HCV RNA negative compared with 1 of 21 controls ($p = 0.07$). Tsai *et al.*[103] have also shown that phlebotomy therapy may result in a sustained response in up to 15% of patients who have previously not responded to treatment with interferon but who are retreated following phlebotomy therapy.

Boucher *et al.*[27] provided additional information on the possible relationships between hepatic iron metabolism and chronic hepatitis C. In their study, 55 patients were treated with interferon for six months and the HIC and distribution of iron were evaluated before and after therapy. They found no difference in HIC between non-responders and responders. However, they did identify a relation between HIC and inflammatory activity such that the iron load was higher in those patients with the greatest degree of histological inflammatory activity. Interestingly, HIC decreased following treatment with interferon. This was related to iron depleted from sinusoidal cells and was apparent regardless of whether patients responded to interferon therapy or not. These findings suggest that increased iron stores may be present in patients with chronic hepatitis C predominantly as a result of the degree of inflammatory activity, presumably correlating with cell injury or necrosis, with subsequent phagocytosis by Kupffer cells resulting in progressive increases in Kupffer cell iron loading.

In summary, iron influences the response of chronic hepatitis C to treatment and perhaps the natural history of hepatitis C. The mechanisms responsible for the effects of iron are not clear but emerging data suggest that the cellular location of iron within the liver lobule and the subsequent effects on immune function are likely to be critical determinants for these effects. Continued evaluation of therapies for chronic hepatitis C which either remove iron or interfere with the action of iron at the cellular level may not only prove useful clinically but may also elucidate further the mechanisms of cellular injury in this disease.

References

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