Improvement of chronic active hepatitis C in chronically infected chimpanzees after therapeutic vaccination with the HCV E1 protein

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Background

We previously reported that a vigorous immune response to the E1 protein could be induced in 2 chimpanzees with chronic active hepatitis C. As a consequence, HCV antigens in the liver fell below detection level. No significant changes in serum viremia levels could be observed whereas ALT and GGT levels steadily decreased. Most importantly, liver histology improved from chronic active hepatitis with interface hepatitis to chronic persistent hepatitis in both animals.

Methods

The HCV subtype 1b E1 protein was recombinantly expressed from mammalian cell lysates and purified as homodimers that were left to associate into monodisperse spherical particles of about 9 nm as assessed by electron microscopy. Two chimpanzees with a chronic active infection (Ton, subtype la, 11-year infection ; Phil, subtype lb different from the vaccine strain, 14-year infection) who previously received 6 shots of E1, were administered another 3 doses of the 50-μg therapeutic E1 vaccine (subtype lb) and were monitored for biochemical markers, HCV Ab, and HCV RNA levels at biweekly intervals. Viral antigen in monthly liver biopsies was stained using monoclonal antibodies to Core, El, and E2.

Results

In both animals, E1Ab titers had dropped to low or undetectable levels six months after the last of 6 shots of E1, at which time chronic active hepatitis and HCV antigens reappeared in the liver biopsy. Another 3 shots of the 50-mg E1 vaccine were administered which resulted in a prompt rebound of E1Ab. In just 1-2 months, initially high levels of HCV antigens again became undetectable and the histological activity index declined from 7-8 to 2-3 in Phil and from 4 to 1-2 in Ton. Furthermore, the vaccinees had mounted E1Ab that, with regard to epitope recognition and isotype, are very rarely encountered in the blood of chronically infected patients or chimpanzees with a natural E1Ab response. In addition, E1-specific T cell proliferation, IL-2, and IFN-γ production could be induced by the vaccine. Although HCV RNA levels remained unchanged throughout these experiments, preliminary density centrifugation experiments suggest that viral particles became complexed by antibodies at the time of high E1Ab, low histological activity, and undetectable antigen levels in the liver. Naked virus particles were detected before vaccination and in the period of low or undetectable E1Ab levels, higher HAI scores and high levels of HCV antigen in the liver.

Conclusion

In chimpanzees with a long-term chronic HCV subtype la or lb infection, a specific class of E1Ab can be efficiently raised by administration of a heterologous subtype 1b E1 vaccine, that may possess neutralizing capacity and may prevent reinfection of the liver. This resulted in considerable improvement of liver histology and an elimination of the bulk of viral antigen from the liver. An association between the presence of aufficiently high levels of immune response to the HCV E1 protein and the improvement of hepatitis C disease, could be established on 4 separate occasions (twice in the 2 vaccinees). These results open new perspectives for the treatment of chronic hepatitis C.

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