Natural history of hepatitis C virus among injecting drug users
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Citation for published version (APA):
Beld, M. G. H. M. (1999). Natural history of hepatitis C virus among injecting drug users

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Summary

HCV infection is in the majority of infected individuals followed by a long and variable asymptomatic period. This prolonged and usually asymptomatic period of HCV infection is characterized by fluctuating RNA levels, ALT levels, and erratic antibody responses. The studies described in this thesis attempt to gain insight into the natural history of HCV, considering different markers for infection and possible predictors for a persistent infection.

The general characteristics of hepatitis and different features of HCV, from discovery to viral therapy, are reviewed in chapter 1.

In chapter 2, the length of the window-phase among 19 seroconverters is described. Sequential serum and independent plasma and PBMC samples were tested for HCV RNA to establish the antibody-negative carrier status among IDUs. HCV RNA was detected in serum before seroconversion in 12 (63.2%) of the 19 seroconverters independent of HIV status. In 7 of these 12, the window-phase was relatively short (2-10 months). The other 5, had low levels of HCV RNA before seroconversion for a period of more than 12 months, with a mean of 40.8 months (range 13-94). In all 5 individuals, independent repeats of the experiments confirmed the presence of HCV RNA in serum, and in 3 of these 5 individuals, HCV-positivity was confirmed in independently collected plasma and PBMC samples. These results support that HCV RNA detection is recommended for screening low and high risk groups in identifying silent carriers.

Different factors are proposed to determine the clinical outcome of HCV infection and in chapter 3, HCV RNA levels and genotypes were determined to assess the natural course of HCV infection in 19 untreated HCV seroconverters. Three distinct patterns were found, according to the HCV RNA load after seroconversion during a mean follow-up of 5 years (range 1-8). There was a significant increase in serum ALT levels (mean 55.5 U/l) in the early phase of HCV infection, compared with the basal serum ALT levels before HCV seroconversion and at the end of the follow-up. The 3 distinct HCV RNA load profiles had no relationship with genotype and serum ALT levels in the first 5 years of HCV infection.

In chapter 4, quantitative antibody levels to core, NS3, NS4, and NS5 were studied, in relation to genotype and HCV RNA levels in 13 untreated HIV-negative individuals. Subjects included 13 untreated HIV-negative individuals of whom 5 (38.5%) apparently cleared HCV, 3 (23.1%) showed transient viraemia, whereas the other 5 (38.5%) showed persistent viraemia. In individuals infected with HCV genotype 1, significant higher median antibody responses to core \( (P=0.02) \) and to NS4 \( (P=0.04) \) were found as compared to those infected with other genotypes, most probably due to the fact that the RIBA assay is based on genotype 1. In groups infected with HCV genotype 1, significantly higher median NS3 antibody titers \((2.61 \text{ RI vs } 0.38 \text{ RI}; P=0.003)\) were found in the individuals with persistent viraemia than in those with apparent resolution of HCV RNA in blood. In groups infected with genotypes other than genotype 1, significantly higher median NS3 antibody titers \((0.89 \text{ RI vs } 0.03 \text{ RI}; P=0.0004)\) and NS5 antibody titers \((1.86 \text{ RI vs } 0.01 \text{ RI}; P=0.006)\) were found in the individuals with persistent viraemia than in those with apparent resolution of HCV RNA in blood. Individuals with viral persistence had higher HCV RNA loads with higher antibody responses as compared to individuals with apparent viral clearance from blood. Apparent viral clearance from blood was observed in an unexpected high percentage (38.5%), associated with a significant decrease of antibodies to NS3, independent of HCV genotype, as compared to individuals with persistent viraemia \((P<0.005)\). Apparent viral clearance from blood with gradual loss of antibodies to various HCV proteins, independent of HCV genotype, was observed in 4 of the 5 individuals within approximately 1 year after HCV seroconversion, whereas 1 of these individuals apparently cleared the virus from blood with complete seroreversion.
In chapter 5, the RIBA HCV serotyping SIA was evaluated on 331 chronically infected IDUs, of which 167 were coinfected with HIV. Among the 331 specimens, serotype-specific antibodies were detected in 250 (sensitivity of 75.5%), in which serotype 1 was predominant (57.2%), followed by serotype 3 (26.8%). Excluding the HIV-coinfected individuals, serotype-specific antibodies were detected in 151 (sensitivity of 92.1%), in which serotype 1 was predominant (59.6%), followed by serotype 3 (33.8%). In a subset of 58 samples serotypes were compared with genotypes revealing a sensitivity of 65.5% with a specificity of 78.9%, and a positive predictive value of 51.7%. Of the 58 samples, 23 were coinfected with HIV and, when these were excluded, the total sensitivity increased up to 76.5% with a total specificity of 80.8%, and a total positive predictive value of 61.8%. The sensitivity of the RIBA HCV serotyping SIA assay is limited by the immunocompetence of the HCV-infected host. In general, samples from HIV negative individuals containing genotype 1a showed higher sensitivity, specificity, and concordance in the serotyping assay, where samples containing genotype 3a were found to be more cross-reactive and untypeable.

In chapter 6, the impact of HIV and the possible mechanism by which HTV influences HCV replication was described. HCV RNA levels were higher in HIV-positive subjects than in HIV-negative subjects. In subjects seroconverting for HIV, HCV RNA levels increased significantly immediately after HIV seroconversion (P<0.0001), while they remained stable over time in HIV-positive and HIV-negative subjects. HCV RNA correlated significantly with CD4+ cell counts in both the HIV-positive population (R=-0.22, P<0.05) and the HIV-negative population (R=-0.45, P<0.0001). In addition, when subjects were stratified according to CD4+ cell counts a significant difference was found in HCV RNA levels between HIV-positive and HIV-negative subjects with CD4+ cell counts >500 cells/ul (P=0.001), but not in the population with CD4+ cell counts <500 cells/ul. Both HIV infection and CD4+ cell counts are apparently associated with HCV RNA levels.

In chapter 7, a longitudinal study of markers of HCV infection due to HCV genotype 1 was conducted in 6 HIV-coinfected individuals in comparison with 5 HIV negative individuals. In the 6 HIV-positive individuals, a quantitative loss of antibodies to all tested antigens to HCV was seen overtime, despite persistent HCV RNA levels. Comparison of this group with the HIV-negative group revealed that individuals coinfected with HIV have significant lower antibody titers to NS3 (P=0.03) and NS5 (P=0.001) while having significant higher levels of HCV RNA (P=0.009). With marked decline of the HCV antibodies, there was a marked decline in CD4+ cell numbers in 50% of HIV coinfected individuals. However, titers of antibodies to core appeared most stable and persistent during HIV-coinfection. It is concluded that HIV infection influences the antibody response to certain HCV antigens, leading to decreased antibody titers to NS3 and NS5 accompanied by increased HCV RNA levels.

In chapter 8, the general discussion and findings of studies presented in this thesis are discussed in the light of other studies and their implications for future research are described.