Hepatitis C virus: epidemiology and immunology

van den Berg, C.H.S.B.

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Summary
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In this thesis the epidemiology of hepatitis C virus (HCV) in drug users (DU) and the immunology of HCV in DU, men who have sex with men (MSM) and hospital-recruited patients are described. This thesis starts with an overview of the epidemiological, viral, immunological and clinical characteristics of HCV (chapter 1).

Epidemiology

Injecting DU are at high risk for HCV and human immunodeficiency virus (HIV) infections through the sharing of needles and syringes. Within the Amsterdam Cohort Studies (ACS) among DU, originally initiated to investigate the epidemiology of HIV/AIDS, all participants are prospectively screened for HIV infection. To study the epidemiology of HCV, all participants with at least two visits were retrospectively screened for the presence of HCV antibodies.

In chapter 2.1, HCV prevalence, incidence and risk factors were studied in ever-injecting DU. HCV prevalence was very high, ranging from 63 to 93%. The yearly HCV incidence dropped substantially from 27.5/100 person years (PY) in the 1980s to 2/100 PY in recent years. Current injecting drug use and borrowing of needles was the main risk factor for HCV infection. The decline of HCV incidence was comparable to the decline in HIV incidence.

This declining HCV incidence led us to the investigation of the impact of harm-reduction programs on HIV and HCV incidence among ever-injecting DU from the ACS. Harm reduction participation was categorized by combining its two most important components (methadone dose and needle exchange program (NEP) use) and looking at 5 categories of participation, ranging from no participation to full participation. Methadone substitution treatment or NEP use alone were not significantly associated with HCV or HIV seroconversion. However, when these variables were combined, we found in chapter 2.2 that full participation in a harm reduction program was associated with a lower risk of HIV and HCV infection in ever-injecting DU, compared to no participation.

In self-reported never-injecting DU from the ACS, we found a higher prevalence of HCV (6.3%) compared to the general Dutch population (chapter 2.3). We studied incidence, prevalence, determinants, and molecular epidemiology of HCV infection to gain insight in transmission routes of HCV among never-injecting DU. HCV incidence was very low (0.49/1,000 PY). Risk factors for prevalent HCV infection were HIV-positive status, female sex, and starting injection drug use during follow up (a putative marker of past injection drug use). Using phylogenetic analysis, we found that HCV strains in never-injecting DU did not differ from HCV strains circulating in injecting DU, which implies a strong link with the injecting DU population. The increased risk could be related to underreporting of injecting drug use or to household or sexual transmission from injectors to non-injectors.

Natural history

Many aspects of the natural history of HCV are not yet well known, since acute HCV infection is usually asymptomatic and rarely recognized. In chapter 3.1 we show that spontaneous clearance occurred in 33.0% of HCV seroconverters in the ACS and that female sex was the most important predictor of clearance. No HCV viral or other
sociodemographic characteristics were significantly associated with spontaneous HCV clearance, but HIV and HBV co-infection might play a role. Progression to liver-related death is accelerated in HIV/HCV co-infected individuals. Since the life expectancy of HIV-infected DU improved after the widespread use of highly active antiretroviral therapy (HAART), HCV-related death is likely to become more important. In chapter 3.2 we describe the overall and cause-specific mortality between DU with HIV/HCV co-infection, HCV mono-infection, HIV mono-infection and DU without HIV or HCV. We show that HIV/HCV co-infected DU remain at increased risk of dying from liver-related death in the HAART era compared with HCV mono-infected DU.

Immunology in acute HCV

To understand parameters associated with resolved HCV infection, we analyzed HCV-specific T-cell responses in injecting DU with HCV seroconversion in chapter 4.1. We observed that the specificity of the CD4+ memory T-cell responses measured after 12-day expansion was most predictive of clearance: CD4+ T-cell responses predominantly targeting nonstructural proteins were associated with resolved HCV infection. Interestingly, we observed memory T-cell responses present before documented HCV seroconversion, suggesting that exposure had occurred before actual HCV infection.

In chapter 4.2, we describe the development of HCV-specific T-cell responses in 4 HIV-infected men having sex with men (MSM) with acute HCV infection. We show that an acute HCV infection in an HIV-1 infected individual can be suppressed in the presence of an HCV-specific CD4+ T-cell response targeting nonstructural proteins. To elucidate the role of HIV infection on HCV-specific CD4+ T-cell responses in acute HCV infection, we analyzed HCV-specific CD4+ T cells in 14 injecting DU shortly after HCV seroconversion in the presence or absence of acute HIV infection (chapter 4.3). In addition, we analyzed the influence of HIV infection on pre-existing HCV-specific CD4+ T-cell responses in already HCV-infected DU who subsequently acquired HIV. We show that both acute HCV/HIV co-infected DU who were previously exposed to HCV and mono-infected DU who developed chronic HCV infection tended to have higher responses to Core protein compared to DU that clear HCV. Furthermore, the HCV-specific T-cell responses were also skewed to unfavourable Core in 3/5 DU after HIV seroconversion. These results suggest that the effect of HIV infection on HCV-specific T-cell responses is not clear-cut, but is influenced by the sequence and outcome of previous HCV infection.

In chapter 4.4, we describe the unexpected finding that HCV-specific CD4+ T-cell responses were present in 3/3 HIV-infected MSM more than one year before HCV antibody seroconversion, indicating that these individuals had been exposed to HCV, but did not get (chronically) HCV infected until later.

Immunology in chronic HCV

A disadvantageous effect of HCV-specific T-cell responses directed against HCV Core protein in relation to spontaneous HCV clearance was observed in DU and MSM in chapters 4.1, 4.2 and 4.3, but we did not observe Core-specific T-cell responses in all individuals with chronic HCV infection. In chapter 5.1 we examined the relation between persistent exposure to HCV (by continuing risk behaviour) and skewing of the HCV-specific T-cell response towards Core in injecting DU with a high frequency of injecting
drug use and sharing of needles and self-reported never-injecting DU. We observed higher HCV-specific CD4$^+$ T-cell responses in injecting DU compared to never-injecting DU, suggesting that continuous exposure leads to boosting of the immune response. Interestingly, none of the HCV-RNA negative injecting DU had a detectable Core response, while such a response was present in 40-44% of HCV RNA-positive DU. This suggests that continuous presence of HCV RNA affects the T-cell response to HCV.

It has been suggested that HCV clearance during treatment with pegylated interferon (PEG-IFN) and ribavirin (RBV) is caused by killing of HCV-infected hepatocytes by HCV-specific T cells. HIV/HCV co-infection is associated with lower sustained viral response rates after HCV treatment. In chapter 5.2, we describe how HCV-specific CD4$^+$ and CD8$^+$ T-cell response evolve during treatment in HIV co-infected patients with HCV genotypes 1 and 3. During the first 12 weeks of HCV treatment, we did not observe an augmentation of these responses, on the contrary we observed a decline of the height and the breadth of HCV-specific CD4$^+$ and CD8$^+$ T-cell responses that paralleled the decline in viral load. This suggests that enhancement of HCV-specific T cells does not appear to play a major role in forced viral clearance. Furthermore, we observed a higher perforin content of CD8$^+$ T cells at baseline in genotype 3 patients, possibly indicating that there is a difference in general host immune activation between HIV-infected genotype 1 and 3 patients, for which the cause is unknown, but which may be associated to degree of liver inflammation.

Finally, in chapter 6, the main findings from our studies are discussed.