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Acute infection with a single hepatitis C virus strain in dialysis patients: Analysis of adaptive immune response and viral variability☆

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***Background/Aims*: While the adaptive immune response is crucial for spontaneous resolution of acute hepatitis C virus (HCV) infection, it also constitutes the driving force for viral escape. For acutely HCV-infected dialysis patients, little is known about the host response and its impact on viral evolution.**

***Methods*: Four haemodialysis patients accidentally infected with the same HCV strain were prospectively investigated with respect to the clinical course, CD4+ and CD8+ T-cell responses, neutralizing antibodies, viral kinetics and sequence variability.**

***Results*: In one patient, a robust CD4+ T-cell response was associated with transient control of infection, while in the other patients, weak responses correlated with persistently high viremia. Despite the presence of CD8+ T-cell effectors in the first patient, no sequence differences were detected in targeted regions of the viral genome in any of the patients when viral persistence was established. Genetic stability in the envelope genes, including the hypervariable regions, correlated with low-level or absent neutralizing antibodies in all of the patients.**

***Conclusions*: The establishment of viral persistence in the special patient group of dialysis patients is due to a failure of the adaptive immune system, as shown by the absence of significant T-cell and antibody responses, as well as viral variability.**

***Keywords*: Hepatitis C virus; Acute hepatitis C; Dialysis; T-cells; Neutralizing antibodies; Virus host interaction; CD4; CD8; Immune response; Viral variability**

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Abbreviations: HCV, hepatitis C virus; TH1, T-helper cells type 1; RNA, ribonucleic acid; HVR1, hypervariable region 1; ELISA, enzyme linked immuno sorbent assay; PCR, polymerase chain reaction; NS3, non structural protein 3; NS4, non structural protein 4; IFN-gamma, interferon-gamma; TNF-alpha, tumor necrosis factor-alpha; SD, standard deviation; PBMC, peripheral blood mononuclear cells; HCVpp, HCV pseudotype particles; GFP, green fluorescent protein; PE, post exposure; LC, local controls; ALT, alanine aminotransferase; HLA, human leukocyte antigen; HVR2, hypervariable region 2.

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1. Introduction

The outcome of acute hepatitis C virus (HCV) infection is variable and determined by early virus-host interactions [1]. The T-cell response, with CD4+ T-helper cells as key regulators and CD8+ T-cells as main antiviral effectors, is a critical host factor [2,3]. An early, vigorous and sustained HCV-specific T-cell response with broad specificity and a predominantly T-helper cells type 1 (TH1) cytokine profile is associated with viral clearance. In contrast, absent or weak responses that are narrowly focused or functionally restricted have been linked to the establishment of chronic infection [2–8]. T-cells that initially control viral replication may eventually fail to contain HCV when their effector functions wane over time, leading to viral persistence [6,9–11].

The impact of the humoral immune response on the outcome of acute HCV infection is less well defined. Viral clearance can occur in the absence of neutralizing antibodies [12]. However, two studies have demonstrated that neutralizing antibodies are induced in the early phase of infection by patients who subsequently clear the virus or control viral infection [13,14].

While vigorous adaptive immune responses are apparently required for spontaneous resolution of HCV infection, they also exert selective pressure on the virus. A large body of evidence indicates that viral escape from CD8+ T-cells due to mutations in critical immunodominant epitopes is associated with progression to chronic infection [15–19]. The sequences of the genes encoding the viral E1 and E2 envelope proteins, the latter of which contains the hypervariable region 1 (HVR1) at its N-terminus, are under pressure by antibodies and exhibit considerable genetic diversity [20–22]. The degree of sequence variation in HVR1 has been shown to predict the outcome of acute HCV infection [20–22].

For acute HCV infection in dialysis patients there is only limited information on early virus-host interactions. Long-term dialysis patients bear an increased risk of acquiring HCV, face severe clinical consequences from hepatitis C and display a deficient T-cell system, as indicated by diminished proliferative capacities and decreased T-cell-receptor density on CD4+ and CD8+ T-cells [23–26]. Dialysis patients also suffer from functional restrictions of the humoral immune system, sometimes causing an impaired development of protective antibodies [24,27,28].

In this study, the course of acute HCV infection in four dialysis patients who were accidentally infected with a single HCV strain was prospectively investigated with respect to clinical parameters, CD4+ and CD8+ T-cell responses, neutralizing antibodies, viral kinetics and sequence variation to investigate the influence of host factors on the course of acute HCV infection in dialysis patients and find out whether their impaired immune system applies sufficient pressure to drive sequence evolution.

2. Patients and methods

2.1. Subjects

Clinical characteristics of the four HCV-infected haemodialysis patients are shown in Table 1. Acute infection with HCV genotype 1b was verified in patients #1, #2 and #4 by ELISA and PCR after they had previously tested negative. Patient #3 never developed antibodies to HCV, but HCV RNA was detected in this patient after a

Table 1
Clinical characteristics and HLA types of 4 dialysis patients infected with the same HCV strain.

Patients	Sex/age (yrs)	Duration of dialysis treatment (months)	HLA class I	HLA class II		Primary disease	Concomitant diseases	HCV infection		
				DRB1	DQB1			HCV load at diagnosis (IU/ml)	ALT at diagnosis (U/ml)	Symptoms
#1	f/32	28	HLA-A2,24; B51,44; CX	DR4,11; DR52,53	DQ3	Sclerotic kidney (Nephritic)	Renal hypertension Renal anemia Secondary hyper-parathyrodism	1.2×10^4	31	None
#2	f/62	41		Not available		Hypertonic nephropathy	Coronary heart disease Cardiomyopathy Hypertension Osteoporosis Renal anemia	3.7×10^7	103	None
#3	m/59	17 pre- & 2 post-trans-plantation	HLA -A3,74; B45,50; Cw2	DRB1*13, DRB3	DQB1*05,06	Sclerotic kidney (unknown origin) Renal transplantation	Hypertension Diabetes Cardiomyopathy St. p. Hepatitis B	3.9×10^6	20	Relapsing epigastric pain
#4	f/46	42	HLA-A3,26; B35,38; Cw4	DRB1*01,04; DRB4*01	DQB1*03,05	Sclerotic kidney (unknown origin)	Osteoporosis Secondary hyper-parathyrodism Renal anemia Renal hypertension	1.0×10^6	1539	Pruritus