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doi:10.3748/wjg.15.2305

World J Gastroenterol 2009 May 21; 15(19): 2305-2308
World Journal of Gastroenterology ISSN 1007-9327

EDITORIAL

Hepatitis C virus lymphotropism and peculiar immunological phenotype: Effects on natural history and antiviral therapy

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Received: March 12, 2009 Revised: April 7, 2009
Accepted: April 14, 2009
Published online: May 21, 2009

Abstract

Hepatitis C virus (HCV) has been recognized to be both a hepato- and lymphotropic virus. HCV lymphotropism represents an essential lap in the pathogenesis of virus-related autoimmune and lymphoproliferative disorders, ranging from clonal expansion of B-cells with organ- and non-organ-specific autoantibody production up to overt non-Hodgkin's lymphoma along a continuous step-by-step model of B-cell lymphomagenesis, where the intermediated mixed cryoglobulinemia could be considered as a stage of suppressible antigen-driven lymphoproliferation. HCV infection of lymphoid cells could set up privileged reservoirs able to interfere with the host viral clearance efficiency and may be implicated in viral recurrence after apparently successful antiviral therapy. The HCV long-lasting extrahepatic replicative state generates an abnormal systemic immunological response, easily detectable by searching simple laboratory and clinical parameters, mainly represented by vasculitis-like skin features and hypocomplementemia. The presence or absence of this hypersensitivity pattern seems to correlate with the antiviral response and could be identified as a novel immunological cofactor. Further research is required to fully verify the real impact on therapeutic choice/regimen.

Key words: Hepatitis C virus; Lymphotropism; Natural history; Antiviral therapy; Immunological co-factor

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Conca P, Tarantino G. Hepatitis C virus lymphotropism and peculiar immunological phenotype: Effects on natural history and antiviral therapy. *World J Gastroenterol* 2009; 15(19): 2305-2308 Available from: URL: http://www.wjgnet.com/1007-9327/15/2305.asp DOI: http://dx.doi.org/10.3748/wjg.15.2305

INTRODUCTION

Hepatitis C virus (HCV) infection has been currently identified as the leading cause of chronic liver disease, including cirrhosis and hepatocellular carcinoma, in Western countries. However, despite its large diffusion (with over 170 million of people infected world-wide), the lack of symptoms during the acute phase, together with the indolent course of the disease over time, hampers the difficulties to assess the natural history of the disease. This complexity can also be argued from the wide heterogeneity of disease complications' rate observed when different methodological approaches were used. Moreover, the progression of the disease could also be dramatically affected by many variables related to the host, the virus and the environment. The global socioeconomic burden of HCV is magnified by hundreds of thousands of infections identified every year. Finally, in the last few years, the long-term outcome of the infected subjects has been deeply modified by the use of efficient antiviral therapy.

HCV has been recognized to be both hepato- and lymphotropic virus; HCV lymphotropism represents an essential lap in the pathogenesis of virus-related immunological disorders[1], being responsible for poly-oligoclonal expansion and consequent wide organ- and non-organ-specific autoantibody production, including rheumatoid factor (RF) and cryo- and non-cryoprecipitable immune complexes.

IMMUNOLOGICAL MECHANISMS

HCV, belonging to the Flaviviridae family, is a positive single-stranded RNA virus, without a DNA intermediate of replication, unable to integrate into the host genome[2].

Otherwise, HCV affects cellular functions modulating the immune response, cell proliferation or apoptosis, so facilitating the clonal B-lymphocyte spread[3-5]. HCV may exert an antigen-driven chronic stimulus on the immune system through several viral proteins[6]. An important pathogenetic step is the interaction between the HCV envelope protein E2 and the CD81 molecule, a fairly ubiquitary tetraspanin present on both hepatocytes and B-cells surface[7], ending up to a strong and sustained polyclonal stimulation of B-cell compartment. CD81 is a part, on the B-cell, of a complex with CD21, CD19 and Leu 13; such complex lowers the threshold for B-cell activation by bridging antigen-specific recognition and CD21-mediated complement recognition[8]. Then, the interaction between HCV-E2 and CD81 could increase the frequency of VDJ rearrangement in antigen reactive B-cells[4,5,9], with possible bcl-2 proto-oncogene activation[4,5]. Again, the latter stage could be secondary to t(14; 18) translocation alone, repeatedly observed in B-cells of HCV-infected individuals, particularly in those with type Ⅱ mixed cryoglobulinemia (MC)[4,6]. Bcl-2 proto-oncogene is able to inhibit apoptosis, leading to abnormal B-cell survival[6]. Besides, the prolonged B-cell survival could prompt, in presence of additional factors (genetic, epigenetic, hormonal and immunological), other genetic aberrations up to overt non-Hodgkin's lymphoma (NHL), as late complication of the MC syndrome[1,9]. The critical question remains whether HCV replication occurs in normal B-cells and is directly lymphomagenic or is lymphomagenesis a stochastic process accompanying HCV-driven proliferation of B-cells[10]. At all, given its biological characteristics, HCV may be involved in several autoimmune and lymphoproliferative disorders, and the multifaceted HCV syndrome can fit in a continuous step-by-step model of B-cell lymphomagenesis, whereby MC could be viewed as marker of antigen-driven lymphoproliferation and frank NHL as loss of antigen-dependence[11].

CLINICAL IMPLICATIONS

At this point, the most scheming and open issue is the definite weight placed on the HCV natural history by its lymphotropism. Firstly, HCV infection of lymphoid cells could condition HCV persistence. In fact, lymphoid cells, and particularly long-living subsets and/or bone-marrow elements, may represent privileged reservoirs able to interfere with host viral clearance efficiency, by impairing the capability of immune response and/or by facilitating selection of distinctive viral variants[12]. Nowadays, it remains indefinite how infection of the immune cells by HCV may alter their functions, although impairment in the allostimulatory capability of HCV-infected dendritic cells derived from patients with chronic hepatitis C has been reported[13]. Interestingly, the entity of this extrahepatic reservoir seems to be correlated with the length of infection[12] and may be implicated in HCV recurrence after apparently successful antiviral therapy[1], the peripheral blood mononuclear cells (PBMC) being a potential viral tank resistant to interferon (IFN). In fact, in several researches PBMC infection appeared as a negative factor of patient on-IFN response[14-18] or predictive for relapse off-IFN monotherapy[15,18-20] or -combined (plus ribavirin) antiviral treatment[21]; on the other hand, such prognostic value was not observed in other studies and is still a controversial question[22-25]. Previous literature data report sustained response (SR) in a near 10% of patients with chronic HCV infection after IFN alone. Classical predictors of response include viral load and genotype, as well as histological (fibrosis score) and metabolic[26] features or alcohol as cofactor. Also the immunological background is associated with antiviral response, the cellular immune functions being essential to the elimination of HCV-infected hepatocytes. A basal low T-helper type 1 and type 2 ratio predicted a higher SR rate in a Japanese cohort[27]. Nevertheless, the immunological pattern remains poorly explored. Conflicting data have been reported on the prevalence of MC in chronic HCV patients, ranging from less than 5% up to 50 %[28,29]. In most cases type M immunoglobulins with RF activity have been found in cryoprecipitates[30], inducing the deposition of immune complexes in small vessels (vasculitis)[31]. The MC-related clinical manifestations, including purpura, arthralgias and weakness, and complications, as glomerulonephritis, neuropathic lesions, B-cell NHL, reflect a systemic involvement that may lessen the chance of viral eradication. In a recent effort[32], it was retrospectively confirmed that this immunological phenotype, also labelled as type Ⅲ or hypersensitivity disorder, is significantly associated with a higher risk of viral persistence after IFN monotherapy, with skin involvement and hypocomplementemia being independent predictors of lack of response; conversely, this study suggested that in the absence of common negative predictors, such as this last immunological cofactor, SR could be reached also by a therapeutic approach based on IFN monotherapy. What practical implications does HCV lymphotropism suggest? No factor is currently available to predict the productive HCV infection of PBMC, but such event is likely to be time-dependent during the natural history of HCV infection. In other words, we observe the serological response and the clinical effects of a long-lasting extrahepatic replicative state, i.e. an abnormal immunological status. This picture can be easily detected by looking for cryoglobulins, RF, antinuclear antibody, complement fractions, circulating immune complexes (C1q protein and C1q binding), mono-oligoclonal gamma-globulin expansion or vasculitis-related clinical manifestations including skin lesions (palpable purpura or hyperpigmented macule of the lower limbs), sensory-motor peripheral neuropathy (gait impairment associated with paresthesia and cramps), arthralgias, as well as urinary changes suggestive of glomerular derangement, i.e. microalbuminuria (in the absence of hypertension and diabetes), all variously combined (at least four out of the above mentioned laboratory and clinical parameters)[32]. This approach is reliable and less expensive or hard than direct detection of HCV in PBMC. The antiviral therapy (IFN plus ribavirin) significantly counteracts the

exaggerated immune response, also independently from the viral outcome[33], through different mechanisms: IFN could affect the intrahepatic T-cell response and inhibit interleukin (IL) 10 production[34], meanwhile ribavirin suppresses IL 10, IL 12 and tumor necrosis factor-alpha[35]; since the hypersensitivity disorders are the expression of a polyclonal activation of B-cells, due to stimulation by T-cells, it could be hypothesized that the changes induced by the combined therapy in the cytokine pattern determine a down-regulation of the mechanism of stimulation T-cells/B-cells. Sometimes, polyclonal B-cell hyperactivity partially escapes from the immune modulation effects of the antiviral treatment, so that the immunological spectrum persists after HCV clearance and suppression of the antigenic stimulus[33]. On the other hand, the undetectability of serum HCV RNA does not mean complete viral clearance, since genomic material has been found in PBMC of SR patients[12], and, therefore, an ongoing immune-stimulation cannot be excluded; interestingly, in those same patients with occult PBMC infection, a persistence of the MC syndrome, even if to a lesser degree with respect to the pre-treatment period, was observed, suggesting a potential advantage of using a prolonged course of antiviral treatment to obtain a sufficient consolidation. The discovery of occult HCV infection has challenged the paradigm that apparent complete resolution of hepatitis C, either spontaneously or therapeutically-induced, would be indicative of eradication of HCV[36]; persistent HCV replication in hepatocytes and PBMC would likely drive the continuous antigenic stimulation of the immune system in immunocompetent patients, which, in turn, allows the host to keep this silent infection under relative control[37]; again, such prolonged HCV replication associated with the chronic presentation of HCV antigens by infected B-cells and monocytes could contribute to the immune tolerance of HCV, thus supporting even further HCV persistence[37]. Finally, negativization of anti-HCV antibody, unrelated to an immunosuppression context, occurs in a percentage of long-term (on average 4 years) SR patients showing a weaker CD4+-specific HCV reactivity; such lessened immunological spur could mirror a full disappearance of the minimal, residual viral amounts, although the potential localization of a further load within PBMC, without release of viral particles into the serum, cannot be ruled out[38]. Only a prolonged follow-up will be able to verify the definitive clearance.

In conclusion, the treatment of hepatitis C is expensive, often demanding, from the patients' perspective, and difficult as far as the decision about whom, when and for how long to treat. Another predictor of response to antivirals is recognized, as immunological cofactor, i.e. the HCV lymphotropism. Further studies are warranted to evaluate alternative antiviral schedules depending on the presence or the absence of this additional cofactor.

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