

Evolution of cellular immune responses to hepatitis C virus during antiretroviral therapy and its clinical implications

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Combination antiretroviral therapy (cART) has dramatically decreased the progression to acquired immune deficiency

syndrome (AIDS) and thus the human immunodeficiency virus (HIV)-related mortality in HIV-infected patients. Consequently, hepatitis C virus (HCV) has emerged as a leading cause of death in HIV/HCV co-infected patients. Pre-existing HIV infection increases the rate of chronicity in acute HCV infection¹ and is associated with higher HCV viraemia.² Most importantly, HIV/HCV co-infected patients show more rapid progression to cirrhosis and its complica-

tions.³ This particular observation is still incompletely understood and seems to contradict the assumptions that HCV by itself is not cytopathic, that the level of viraemia does not correlate with the risk of fibrosis and cirrhosis in HIV-negative patients and that liver inflammation is immune mediated.

The clinical outcome of acute hepatitis C in HIV-negative patients is associated with a strong and maintained HCV-specific CD4+ T-cell response against both structural and non-structural proteins,⁴ which is typically weak in patients with chronic hepatitis C. The role of HCV-specific CD4+ T-cell responses in treatment-induced viral clearance has been examined in several studies, yielding divergent results: while some studies found a moderate but significant increase in the HCV-specific CD4+ T-cell response during antiviral treatment with a peak late in the course of treatment, other studies have described a decrease in HCV-specific CD4+ T-cell responses during

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interferon/ribavirin treatment.^{5 6} From an immunologist's point of view this is remarkable because the removal of the viral antigen alone obviously is not sufficient for the recovery of T-cell function as would be expected from various animal models of T-cell exhaustion. An even further impairment of HCV-specific T-cell responses is a hallmark of HIV/HCV co-infected patients and this is in line with the higher rate of chronic viral persistence. The relationship to the less favourable course of chronic hepatitis C, however, is less clear. HIV as well as cART interfere with CD4+ T cells in multiple ways and may thus influence the clinical course of HCV infection. In the absence of a robust small animal model, studies in humans, like the one presented, are currently the only way to find new pieces for this puzzle, such as if and how cART can restore HCV-specific immune responses and reverse profibrotic processes.

In this issue of *Gut*, Rohrbach *et al* analysed the T-cell response in 80 HIV/HCV co-infected individuals before and during efficient cART by ex vivo γ -interferon enzyme linked immunospot technique responses to HCV core peptides, which predominantly stimulate CD4+ T cells (see page 1252).⁷ An increase of HCV-specific immune responses was found both in individuals with chronic and spontaneously cleared HCV infection. In addition, a slight long-term decrease in HCV RNA levels was shown.

What is the importance of recovering these T-cell responses associated with a decrease in viral load? Given the association of strong and broad T-cell responses with spontaneous recovery in HCV mono-infection, reconstitution of efficient immune responses was developed as a therapeutic strategy to treat chronic hepatitis C. Two recent phase I clinical trials, one from France using recombinant modified vaccinia ankara and the other from Sweden employing a desoxyribonucleic acid vaccine, provided a proof of concept with transient declines in viral load up to 2 log in some patients (http://www.transgene.fr/images/stories/en/pdf/communique_presse/communiqués_divers_2009/PR-US-23-04-2009-TG4040-HCV.pdf and <http://feed.ne.cision.com/wpyfs/00/00/00/00/10/1B/0C/wkr0011.pdf>, both accessed 23 June 2010). Importantly, the decrease in viral load was associated again with a transient induction of HCV-specific T-cell responses. From this point of view it is exciting that an obvious change in HCV-specific T-cell responsive-

ness could also be seen during cART of HIV/HCV co-infection. This is remarkable since it is believed that antigen removal is a requirement for reconstitution of functional antiviral T-cell responses.⁸ It is tempting to speculate that in the upcoming era of HCV-specific protease and polymerase inhibitors another step of recovering dysfunctional T cells might be achieved.

It is unclear to what extent HCV-specific T-cell responses insufficient to completely clear HCV contribute to liver damage in chronic persistent hepatitis. In view of the data from Rohrbach *et al* also a protective role of certain T-cell responses can be conceived. For example, Th2-type CD4+ T-cell responses have been found to be relevant for development of fibrosis in one model.⁹ This process can potentially be counteracted by γ -interferon, which in addition to its antiviral effect has anti-fibrotic properties. The relative lack of virus-specific γ -interferon production as found in HIV/HCV co-infection might thus be related to disease pathogenesis.^{10 11} Indeed, several studies examining the impact of cART on liver disease morbidity in HIV/HCV co-infection have generally found a protective effect on fibrosis progression.¹² The finding of increased production of γ -interferon might be an explanation for this observation.

A slight but significant decrease in HCV RNA levels was particularly evident in the subgroup of individuals with increasing HCV-specific immune responses. Similar findings and correlations between higher CD4+ T-cell counts and preserved immunity exhibiting lower levels of HCV viraemia have been described before.¹³ The presented data therefore provide further support for the concept that restoration of HCV-specific T cells may result in improved control of HCV viraemia in HIV/HCV co-infected patients. It remains open, however, whether the clinical benefit is mediated by the decreased level of viraemia or by other—for example, antifibrotic, effects of the improved HCV-specific CD4+ T-cell response.

In summary the lessons that can be learnt from interaction of cART in HIV/HCV co-infection and the resulting changes in the cellular immune response give interesting new insights into the mechanisms associated with viral load and liver disease progression. The study by Rohrbach *et al* provides some evidence that the benefits for HCV disease of an effective treatment for HIV could occur in part through restoration of HCV-specific immune responses. Given their overall

significance also in HCV mono-infection, a detailed phenotypical and functional analysis of the T-cell response during cART appears to be the next important step in defining surrogate markers of a favourable course of HIV/HCV co-infection. Growing evidence of the beneficial effects of cART in preventing adverse liver-related outcomes in HCV co-infected patients and increasing knowledge about the underlying mechanisms should be taken into account when treatment strategies of co-infected patients are discussed.

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