Plasma chemokine cxcl-10 level as apredictor of response to antiviral therapy in patients with hepatitis c

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Hepatitis C virus is the sole member of the hepacivirus genus in the flaviviridae family. Replication of the HCV genome is believed to occur through the synthesis of -an intermediate minus-strand HCV-RNA driven by the viral RNA-dependent RNA polymerase.The main site of infection for HCV is the liver, this hepatotropism leads to the development of liver injury that can be measured by measurement of the levels of serum aminotransferases. Despite a robust immune response in most individuals, hepatitis C is characterized by the chronicity of its infection.In chronically infected patients, liver fibrosis and cirrhosis develop, over decades, in 20% to 30% of infected patients and in some individuals, can eventually lead to HCC (Fried et al 2002).Current antiviral therapy of CHC viral infection with peginterferon and ribavirin can be successful in over 50% of patients (Radkowski et al 2005).Treatment decision of CHC viral infected patients should be individualized based on the severity of liver disease, the potential for serious drugs side effects, the likelihood of treatment response, the presence of comorbid conditions and the patient readiness for treatment. For patients in whom liver histology is available, treatment is indicated in those with bridging fibrosis or compensated cirrhosis provided, they do not have contraindication to therapy, so for CHC patients even with normal serum aminotransferases, the decision to initiate therapy should be based on the severity of histopathological changes by liver biopsy and the treatment regimens in this special situation or CHC with normal serum aminotransferases should be the same as that used for CHC patients with elevated serum aminotransferases (Marx et al 2009).)The first steps in leukocyte migration into the tissues are tethering and rolling of leukocytes along vascular endothelia, often mediated by interaction of selectins or □-4 integrins with their ligands (Pribila et al 2004), (Von et al2000).Chemokine recognition causes leukocytes to stop -rolling and to undergo tight integrin-mediated adhesion followed by integrin mediated directed migration across endothelial barriers, toward higher chemokine concentration (Pawlotsky 2004).Chemokine-chemokien receptor interactions are likely to be particularly important in CHC virus infections where T cells are recruited to the liver lobules to mediate clearance of virus infected hepatocytes (Siveke et al 1998).The Th-1 type CD4+ T ”helper” lymphocytes play a crucial role in the immune response against the hepatitis C virus (HCV) by activating cytotoxic CD8+ T cells, thereby stimulating cellular immunity (Beroletti et al 2003).A sustained

vigorous and virus-specific CD4+ T cell. response in peripheral blood is needed for spontaneous HCV clearance . Conversely a weak, delayed or transient response is associated with persistent infection (Napoliet al 1996).On the other hand, histological liver damage in CHC depends on increased intrahepatic expression of Th1-associared cytokines which favour cellular immunity (Mackay 2001).Therefore, both leukocyte trafficking and recruitment of T cells to specific liver compartments are strongly implicated in the physiopathology of HCV infection.Selective T cell recruitment depends on chemokine gradients and interactions between chemokines and chemokine receptors (Bonecchi et al 1998).Th1 cells preferentially express the CC-chemokine receptor 5 (CCR5) and the CXC-chemokine receptor 3 (CXCR3) (Farber et al 1997).CXCL-9, CXCL-10 and CXC-11 all bind with CXCR3. CXCR3 in turn is expressed by effector TH1 cells as well as subsets of other T and B cells (Pawlotsky 2004).CXCL-10 also known human IP-10, the interferon-gamma inducible protein-10, is a member of CXC chemokine family, produced mainly by monocytes but also T-cells, fibroblasts and endothelial cells, unlike other CXC chemokines HuIP-10 is a chemoattractant for activated lymphocytes, but not resting lymphocytes or neutrophils (Luster et al 1995).CXCL-10 (IP-10) is a potent inhibitor of angiogenesis, inhibits neovascularization and exerts antitumor effects, it inhibits proliferation of human endothelial cells (Sarris et al1993), and bone marrow derived hematopoietic progenitors (Luster et al 1987).The gene for human IP-10 (CXCL-10) has been mapped to chromosome 4q2 (Loetscher et al1996) and CXCR3 has been identified as the receptor for IP-10 (CXCL-10) (Taylor et al 2004).)Models for chemokine function typically involve the presentation of chemokines on endothelial surfaces near the site of chemokine production or release. The high level of these chemokines in the plasma may be a consequence of high local production in the liver, that is they may represent a type of overflow from surfaces already saturated with chemokines. Alternatively, they may be produced elsewhere, for instance in cells of hematopoietic origin (Hechtman et al 1991).Widespread production and secretion of chemokines may interfere with the gradient sensing needed for lymphocytes to enter specific tissues (Pribila et al 2004).Indeed, soluble plasma chemokines may act as antagonists for leukocyte migration (Luscinskas et al 1992), (Cyster 2002).Chemokines at high concentration might induce chemorepulsion (Poznansky et al 2002) and (Shields et al 1999).Thus, while T cells in the HCV-infected liver express CXCR3 (Boisvert et al 2003) and (Su et al 2002).It is not clear that the chemokines we measure in the plasma can promote specific T-cell migration into the liver. It is thought that IFN-□ secreted by activated T cells is crucial for the control of HCV replication (Salazar et al 2000).Natural killer (NK) cells and HCV-specific T cells must traffic to the liver to kill infected hepatocytes or to control the viral replication by nonlytic mechnisms such as directed IFN-□ secretion. In rodent models, the accumulation of NK and T cells in the infected liver is orchestrated by production of specific chemokines which recruit waves of antigen-specific and non-specific mononuclear cells (Kakimi et al 2001).Some of these cells mediate control of viral replication and some, non-specific inflammation. In a mouse model of hepatitis B virus (HBV) infection CXCL9 and CXCL-10 were not required for the recruitment and antiviral function of HBV-specific cytotoxic T lymphocytes but blocking these chemokines prevented hepatic

inflammation (Sitia et al 2004) and (Loetscher et al 2001).It is possible that CXCR3-binding chemokines in the plasma do not contribute to recruitment of antigen-specific T cells for control of viral replication, but instead to a neutral or detrimental inflammatory reaction. Members of the CXCR3 binding chemokine family are known to antagonize responses to CC chemokine ligand 5 (CCL5) (regulated on activation, normal T expressed and secreted, RANTS), eotaxins and several monocyte-macrophage chemoattractant proteins (Pelkovic et al 2004)and (Wasmuth et al 2004).Data from patient and chimpanzee studies support an important role for CCL5 in either spontaneous (Bonecchi et al 1998), or therapeutic clearance of HCV infection (Kameyoshi et al 1992), It is difficult to accurately measure plasma CCL5 levels or activity because of release of this chemokine by activated platelet (Clark et al 2003).CXCR3 binding chemokines may be proteolytically processed after release and such processing may reduce the ability of these chemokines to act as agonists for CXCR3 (Salazar et al 2000).Processing of CXCL-11 at its amino terminus changes it to a CXCR3 antagonist. Work is ongoing to determine whether plasma CXCL-10 in patients with HCV is truncated at the amino terminus, and whether there is any relationship between the relative frequencies of truncated or full-length chemokines and the outcome to antiviral therapy.Success of antiviral therapy (peg IFN-□2a-ribavirin combination) in CHC viral infected patients is defined as SVR, that is, elimination of HCV-RNA from the blood for at least 6 months after therapy. Serum HCV-RNA negativity is defined as undetectability using assays with sensitivity of at least 100 viral copies/ml. The question remains as to whether this response represents sterilization of the serum or very low persistent viral replication? It also begs the question as to whether, it also represent HCV sterilization of the liver.(268)Certainly, the liver histology -improved with successful treatment and may even normalize. In some studies HCV RNA was undetectable in the liver 1-5 years after achieving SVR with antiviral therapy.(269)In this study we have observed that patients with HCV infection have increased levels of CXCL-10 chemokine, that can stimulate CXCR3. CXCL-10 levels before the start of antiviral therapy were lower among those who had an EVR and then went on to have an SVR than among those who failed to respond to antiviral therapy.Elevated CXCL-10 measured in the plasma may represent over production in the liver, or it may be produced by cells distant from the liver as part of a broader antiviral response. It remains to be determined whether the measured CXCL-10 plays a neutral, positive, or negative role in the migration of effector T cells to the infected liver.Antagonism, if it occurs, may result from interference with the signaling of other chemokines such as CCL5, competition for recognition between -the soluble chemokine and chemokines presented at the site of infection, or amino terminal processing of the chemokines leading to altered functional effects on target cells.