Role of Serum Chemokines as Inflammatory Mediators in Chronic Hepatitis C Virus Infection with Different Stages of Cirrhosis

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Abstract

Hepatitis C virus (HCV) is a leading cause of chronic liver diseases that can progress to cirrhosis. Chemokines are chemotactic mediators that are implicated in viral hepatitis. The predominant chemokine receptor expressed in the liver is CXCR 3, suggesting that its specific ligands are important in the progression of chronic liver diseases. Also, the HCV-non-structural (NS) 5A protein of HCV (HCV NS5A protein) induces the CXC chemokine interleukin 8 (IL-8). Expression and affinity to IL-8 is different in the two receptors (CXCR 1>CXCR 2) that inhibit the antiviral actions of IFN. So, we analyzed the serum concentrations of the CXCR 3 ligand CXCL 10 (interferon-g-inducible protein 10) and CXCR 1 and CXCR 2 ligand interleukin 8 using ELISA technique in 30 patients with chronic viral hepatitis C with different stages of cirrhosis (19 males & 11 females, their mean ages were 64.50±6.60 years) compared to 20 healthy volunteers (10 males and 10 females with mean age 59.87±9.56 years) serving as controls. Serum chemokines, CXCL 10 and IL-8 were significantly increased in patients with HCV than controls (p<0.0001). Patients with established liver cirrhosis displayed significantly higher CXCL 10 and IL-8 levels than HCV infected patients without cirrhosis (p<0.0001). Highest CXCL 10 and IL-8 concentrations were found in patients with decompenated, Child C-staged liver cirrhosis. There were significant positive correlations between both of CXCL 10 and IL-8 and each of AST, ALT and γGT and significant negative correlation with serum albumin. Moreover, CXCL 10 showed significant positive correlation with γglobulin and IL-8. However, IL-8 revealed significant positive correlations with ALP and total bilirubin.

In Conclusion, the CXCL 10 and IL-8 chemokines are the most significantly expressed chemokines in chronic hepatitis C and most likely play a role in positioning T cells in the liver. Moreover, therapeutic agents that block chemokine receptors, thereby decreasing inflammation, may be evaluated in humans. Additional information about chemokines and their receptors might also be considered as potential therapeutic targets in HCV infection.

Key Words: Chemokines – Hepatitis C – IL-8 – CXCL 10.

Introduction

HEPATITIS C virus (HCV) is the leading cause of chronic hepatitis and liver disease-related morbidity worldwide, with a significant proportion of infected individuals developing cirrhosis, hepatic failure, and/or hepatocellular carcinoma [1]. Chronic hepatitis C (CHC) is characterized by the presence of an inflammatory infiltrate having various degrees of severity in both portal tracts and hepatic parenchyma and resulting in piecemeal necrosis. The underlying mechanism(s) driving disease progression is not well understood; however, there is increasing evidence that a direct immune response to HCV infected hepatocytes may play a role in the pathogenic process [2].

In nearly all liver diseases, progression from healthy tissue to cirrhosis is mediated by a chronic inflammatory reaction within the parenchyma that activates stellate cells and leads to the excess deposition of extracellular matrix proteins [3]. This inflammatory reaction is considered to be a main predictor of disease progression across different liver disease entities [4]. The recruitment of immune cells into the damaged liver is orchestrated by chemokines, class of soluble immune mediators with variable chemotactic and cytokine-like functions [5]. In hepatitis coinfections with primary biliary cirrhosis, a predominant chemokine receptor expressed by infiltrating lymphocytes is CXCR 3. In humans, CXCR 3 is present in two isoforms (CXCR 3 A and CXCR 3 B). While the isoform CXCR 3 A binds the chemokines CXCL 9 [monokine induced by interferon-γ (MIG)], CXCL 10 (interferon-inducible protein 10) and CXCL 11 (interferon-inducible T cell chemo-attractant), the isoform B binds the same ligands plus CXCL4 (platelet factor 4) [6]. However, evaluation of CXCL4 serum concentrations with respect to progression of liver disease is hampered by the fact
that decreased platelet counts lead to strongly reduced serum concentrations [7]. In contrast, CXCL 9, CXCL 10 and CXCL 11 serum concentrations have been associated with fibrosis progression towards cirrhosis in hepatitis C virus. The serum concentrations of these three chemokines seem to directly mirror their increased intrahepatic expression and have been considered as pro-inflammatory and profibrotic molecules [8].

The equilibrium or the disequilibrium between Tc-lymphocytes and Th lymphocytes (Th1 and Th2) plays a major role, expressed through disorders in the synthesis of cytokines. Th1 subpopulation secretes stimulating factors (interleukin-2 (IL-2), IL-12, gamma interferon (IFNγ), while subpopulation Th2 produces inhibitory factors (IL-4, IL-10, IL-13 so on) having as a role the deactivation of the Th1 subpopulation and of the macrophages that secrete the TNF-α and IL-8. The modification of the equilibrium between the immunostimulating and inhibitory cytokines has as a result the prolongation of the inflammation, which, in its turn, leads to necrosis, fibrosis and chronic disease of the liver [9].

IL-8, important mediator of the inflammation, is known as the most powerful chemotactic factor for neutrophils (in the smallest value for eosinophils, basophils) and T-lymphocytes. Its production is stimulated by IL-1, TNF-α, IL-6. It activates the neutrophils and induces degranulation with release of lactoferin. This type of inflammatory cells has been noticed in the hepatic tissue during chronic viral hepatitis. It seems that IL-8 is in direct relationship with the injuries evidentiated in the patients with such affections [10].

There are more receptors of the surface membrane capable to bind IL-8; the most frequently studied types are the G protein coupled serpentine receptors CXCR 1 and CXCR 2. Expression and affinity to IL-8 is different in the two receptors (CXCR 1>CXCR 2). The HCV-non-structural (NS) 5A protein of HCV (HCV NS5A) protein has been implicated in the resistance of HCV to antiviral therapy. It has been found that HCV (NS5A) induces the CXC chemokine interleukin 8 (IL-8) to inhibit the antiviral actions of IFN in vitro [11].

CXCL 10 also known as IP-10 (interferon-gamma inducible protein 10 kDa), was originally identified as an IFN-γ-inducible gene. It is induced in a variety of cells in response to IFN-γ and LPS. In contrast to other CXC chemokines, IP-10 has no chemotactic activity for neutrophils. It is a pleiotropic molecule that appears to target activated T cells and monocytes [12]. IP-10 inhibits bone marrow colony formation and angiogenesis. It can also stimulate NK and T cell migration, regulate T cell maturation and modulate adhesion molecule expression [13].

CXCL 10 was the only CXCR 3 chemokine elevated in the serum, suggesting that it may neutralize any CXCR 3 chemokine gradient established between the periphery and liver by CXCL 11 and CXCL 9. Thus, CXCR 3 chemokines may not be responsible for recruitment of T lymphocytes but may play a role in positioning these cells within the liver [14].

This study aimed to determine serum CXCL 10 (IP-10) and IL-8 levels in chronic liver hepatitis C and to estimate their relationship with liver functions, cirrhosis and clinical complications in order to explain if these chemokines have implications for understanding the pathogenesis, vaccine design and development of novel therapeutic strategies of chronic liver diseases.

Subjects and Methods

Thirty patients with chronic viral hepatitis C infection with different stages of cirrhosis (19 males & 11 females, their mean ages were 64.50 ± 6.60 years) treated at Department of Medicine, Ain Shams University Hospital. Twenty healthy volunteers (10 males and 10 females with mean age 59.87±9.56 years) served as controls after taking informed consents from them.

HCV infection was defined as the presence of serum HCV antibodies using ELISA kits and detectable viral RNA using PCR, diagnosed by polymerase chain reaction (PCR) by Promega, Madison USA.

Chronic hepatitis patients with different stages of cirrhosis which had been proven by liver biopsy and their grades were established by the Child-Pugh score system [15,16].

The inclusion criteria of the HCV-positive patients were: None of the patients had acute on top of chronic liver failure, absence of hepatocellular carcinoma or any suspicious space occupying lesion of the liver on ultrasonography or computerized tomography, no interferon treatment in the last 6 months before the study and no evidence of endocrine diseases.

As for the control group, 20 healthy volunteers were studied that were tested negative for hepatitis B virus (HBV), HCV, had normal blood counts, normal aminotransferase activities [aspartate aminotransferase (AST) alanine aminotransferase (ALT)] and who had no history of alcohol intake.
All patients and healthy controls were subjected to:

1- Full history taking including risk factors of occurrence of HCV (parenteral anti-bilharzial therapy, blood transfusion and previous operation) and thorough clinical examination with special stress on signs of liver cell failure, hepatomegaly, splenomegaly and/or ascites.

2- Imaging Techniques: Abdominal ultrasonography: It was done for all patients (to help the diagnosis and to exclude focal lesion and liver heterogeneity) and for controls (to exclude abnormalities involving the liver). Both patients and controls were asked to be fasting for 8-12 hours. Toshiba 38AS was used applying sector transducer.

3- Laboratory investigations: Venous blood samples of 10ml were collected from each patient and healthy individuals by venipuncture.

Laboratory Investigations: Routine biochemical parameters including complete blood picture (CBC) and liver function tests were done including: Serum transaminases; alanine aminotransferase (ALT) and aspartate aminotransferase (AST), bilirubin, alkaline phosphatase, γGTP, albumin and globulin.

Serum IL-8 was assessed using the ELISA Kit (Quantikine human IL-8, R and D Systems, Minneapolis, USA) according to manufacturer’s instructions.

Serum AFP concentrations were estimated using a sensitive radioimmunoassay technique capable of detecting concentrations of 2IU/ml (2.1ng/ml) [17].

Serum human CXCL 10/IP-10 was done using enzyme immunoassay (ELISA) Kit from clinilab designed to measure human IP-10 in serum [18].

Principle of the assay:

This assay employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for IP-10 has been pre-coated onto a microplate. Standards and samples are pipetted into the wells and any IP-10 present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for IP-10 is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of IP-10 bound in the initial step. The color development is stopped and the intensity of the color is measured.

Statistical analysis: The data was expressed as means±SD. The student’s t-test was used to differentiate between two groups and p<0.05 was considered as statistically significant. Pearson and Spearman’s correlation tests were used to correlate between each parameter and different variants in the same group to differentiate between positive and negative correlations and to find significant differences [19].

Results

The results are summarized in the following tables and figures:

The demographics and laboratory parameters of the infected patients with HCV comparing to age and sex matching healthy controls are shown in Table (1). Liver function tests showed, very highly significantly elevation of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γGTP), alkaline phosphatase (ALP), bilirubin (p<0.0001) and serum globulin (p<0.05) in HCV patients than controls, while serum albumin was highly significantly decreased (p<0.001). Also, serum α-feto protein was very highly significantly increased in patients compared to controls (p<0.0001). As for serum chemokines, CXCL 10 and IL-8, they were significantly increased in patients with HCV than controls (p<0.0001).

Table (1): Comparison of demographic and biochemical parameters in chronic Hepatitis C Virus (HCV) Infection and the control group.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls (n = 20)</th>
<th>HCV (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.87±9.56</td>
<td>64.50±6.60</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>10/10</td>
<td>19/11</td>
</tr>
<tr>
<td>AST (u/l)</td>
<td>21.70±3.20</td>
<td>100.25±41.56</td>
</tr>
<tr>
<td>ALT (u/l)</td>
<td>24.40±6.11</td>
<td>125.10±50.54</td>
</tr>
<tr>
<td>γGTP (u/l)</td>
<td>19.10±3.15</td>
<td>60.91±39.18</td>
</tr>
<tr>
<td>ALP (u/l)</td>
<td>84.59±30.11</td>
<td>210.19±90.14</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>0.74±0.19</td>
<td>1.90±0.35</td>
</tr>
<tr>
<td>Albumin (gm/dl)</td>
<td>4.35±0.39</td>
<td>3.21±0.51</td>
</tr>
<tr>
<td>γGlobulin (g/dl)</td>
<td>1.15±0.19</td>
<td>1.57±0.41</td>
</tr>
<tr>
<td>α-feto protein (ng/ml)</td>
<td>4.86±1.82</td>
<td>51.98±19.37</td>
</tr>
<tr>
<td>Serum CXCL 10 (Pg/ml)</td>
<td>47.91±10.11</td>
<td>499.82±259.43</td>
</tr>
<tr>
<td>Serum IL-8 (pg/ml)</td>
<td>39.19±13.16</td>
<td>264.55±91.85</td>
</tr>
</tbody>
</table>

NS: Non significant (p>0.05). <0.05: Is considered significant. <0.001: Is considered highly significant. <0.0001: Is considered very highly significant.
As seen in Table (2), patients with established liver cirrhosis displayed significantly higher CXCL10 and IL-8 levels than HCV infected patients without cirrhosis (p<0.0001). Highest CXCL10 and IL-8 concentrations were found in patients with decompensated, Child C-staged liver cirrhosis.

Table (3) showed that, there were significant positive correlations between both of CXCL 10 and IL8 and each of AST, ALT and γGTP, and significant negative correlation with serum albumin. Moreover, CXCL10 showed significant positive correlation with γglobulin and IL8. However, IL–8 revealed significant positive correlations with ALP and total bilirubin.

Fig. (1) and 2 revealed different levels of serum CXCL 10 and IL–8 with different stages of cirrhosis in patients with HCV infection.

Table (2): Comparison of serum CXCL 10 and IL-8 levels in different stages of cirrhosis in chronic Hepatitis C Virus (HCV) Infection.

<table>
<thead>
<tr>
<th></th>
<th>No cirrhosis (n = 9)</th>
<th>Child A (n = 8)</th>
<th>Child B (n = 6)</th>
<th>Child C (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum CXCL 10 (Pg/ml)</td>
<td>80.14±45.86</td>
<td>245.9±113.00</td>
<td>386.0±170.84</td>
<td>453.1±231.45</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001**</td>
<td>&lt;0.0001**</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>Serum IL-8 (pg/ml)</td>
<td>98.7±30.87</td>
<td>178.1±32.78</td>
<td>258.3±56.93</td>
<td>295.2±91.45</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001**</td>
<td>&lt;0.0001**</td>
<td>&lt;0.001***</td>
</tr>
</tbody>
</table>

*: Compared to no cirrhosis      **: Compared to child A   ***: Compared to child B

Table (3): Correlations of serum CXCL 10 and IL-8 with different measured biochemical parameters in HCV infection.

<table>
<thead>
<tr>
<th></th>
<th>AST</th>
<th>ALT</th>
<th>γGTP</th>
<th>ALP</th>
<th>Bilirubin</th>
<th>Albumin</th>
<th>γGlobulin</th>
<th>IL-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXCL10</td>
<td>0.5901</td>
<td>0.4975</td>
<td>0.4467</td>
<td>0.0121</td>
<td>0.1543</td>
<td>-0.4009</td>
<td>0.3901</td>
<td>0.6593</td>
</tr>
<tr>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-8</td>
<td>0.4879</td>
<td>0.5090</td>
<td>0.4981</td>
<td>0.4021</td>
<td>0.3962</td>
<td>-0.4512</td>
<td>0.1201</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

N.S: Non significant (p>0.05), <0.05 : Is considered significa. <0.001: Is considered highly significant.

Fig. (1): Comparison of serum CXCL 10 in different stages of cirrhosis in HCV infection.

Fig. (2): Comparison of serum IL-8 in different stages of cirrhosis in HCV infection.
Discussion

Chronic hepatitis C (CHC) is characterized by the presence of an inflammatory infiltrate having various degrees of severity in both portal tracts and hepatic parenchyma and resulting in piecemeal necrosis. The underlying mechanism(s) driving disease progression is not well understood; however, there is increasing evidence that a direct immune response to HCV infected hepatocytes plays a role in the pathogenic process [20].

Chemokines are chemotactic mediators that are implicated in liver diseases. In viral hepatitis and primary biliary cirrhosis, a predominant chemokine receptor expressed in the liver is CXCR 3, suggesting that its specific ligands are important in the progression of chronic liver diseases across different aetiologies. In view of the known association between T-lymphocyte infiltration and negative prognosis in CHC, it is important to investigate the mechanisms governing recruitment of these cells to livers chronically infected with HCV. However, to date there is a paucity of information regarding the factors responsible for recruitment of T lymphocytes and other immune cells to the liver in CHC. Nevertheless, it is hypothesized that the CXCR 3 ligands CXCL 10, CXCL 9, and CXCL1 1 play a central role in the recruitment of activated T lymphocytes to this organ [21].

The results herein demonstrate that CXCL 10 and IL-8 were significantly increased in patients with HCV than controls ($p<0.0001$). Meanwhile, serum concentrations of CXCL 10 and IL-8 showed a further increase in patients with established cirrhosis compared with patients with chronic liver disease without established cirrhosis. CXCL 10 and IL-8 were found to be significantly elevated throughout all Child-Pugh stages compared with non-cirrhotic patients ($p<0.0001$). Highest CXCL 10 and IL-8 concentrations were found in patients with decompensated, Child C-staged liver cirrhosis.

Our results are in harmony with the finding of Zeremski et al. [22] who had found elevation of serum CXCL 10 in HCV infection patients. They explained this elevation by that chemokines, chemotactic cytokines that attract leucocytes to inflammatory sites, may be important in the development of intrahepatic inflammation. They also stated that in CHC patients, IP-10 expression is increased both in the liver and in the peripheral blood and that intrahepatic IP-10 has been shown to be produced by hepatocytes, sinusoidal endothelial cells, or both cell types. They also explained that in CHC patients, intrahepatic IP-10 mRNA levels were found to be strongly correlated with lobular inflammation but not with portal inflammation or fibrosis, suggesting that intralobular inflammatory T cells may be attracted to the liver by IP-10 and peripheral IP-10 levels have also been found to be correlated with necroinflammation in CHC. They also suggested that besides its role in inflammation, IP-10 may also be a marker of a successful response to antiviral treatment.

Friedman et al. [3] agreed with our results and stated that in nearly all liver diseases, progression from healthy tissue to cirrhosis is mediated by a chronic inflammatory reaction within the parenchyma that activates stellate cell and leads to the excess deposition of extracellular matrix proteins. This inflammatory reaction is considered to be a major predictor of disease progression across different liver disease entities. Moreover, Chuang et al. [23] had reported that in hepatitis C infected liver cirrhosis, a predominant chemokine receptor expressed by infiltrating lymphocytes is CXCR 3. While, CXCL 10 serum concentrations have been associated with fibrosis progression towards cirrhosis.

Also, in accordance with our study, Helbig et al. [20] had demonstrated that the CXCR 3 family members CXCL 11, CXCL 9, and CXCL 10 are significantly increased in the livers of CHC patients and chimpanzees experimentally infected with HCV and are likely to play a role in T-lymphocyte traffic within the liver lobule. These chemokines play a role in driving T-lymphocyte accumulation in the HCV-infected liver and will further aid in the development of therapeutic intervention strategies for inhibiting or reducing the excessive inflammation observed in CHC.

Interestingly, Tacke et al. [24] observed a distinct pattern of serum concentrations of the three chemokines CXCL 9, CXCL 10 and CXCL 11 in patients with cirrhosis. While CXCL 9 was only increased in early cirrhosis of Child-Pugh class A, CXCL 11 was mainly elevated in the advanced stages of cirrhosis progression (Child classes B and C). In contrast, CXCL 10 was increased throughout all Child-Pugh stages compared with subjects with chronic liver disease but no cirrhosis. Moreover, the expression patterns of the chemokines argue against a non-specific higher grade of inflammation in the cirrhotic patients, which could drive chemokine expression. Their results reinforce the concept that chemokines, although formally binding to the same receptor might mediate different effects depending on the context in which they are expressed. As for the cohort with liver fibrosis, they did not
detect significant differences of any of the chemokines with respect to the aetiologies of cirrhosis. Furthermore, the different expression patterns of the chemokines argue against a non-specific higher grade of inflammation in the cirrhotic patients, which could drive chemokine expression.

The CXC chemokine IL-8 (CXCL 8) has long been identified as a major factor of acute inflammation, acting as a potent chemoattractant and activator of neutrophils by two receptors, CXCR1 and CXCR2 [25]. By comprehensively analyzing a group of patients with chronic liver diseases, we found high IL-8 levels in the serum of patients with HCV infection. IL-8 serum levels were closely associated with the progression of cirrhosis, as reflected by clinical scores (e.g. Child-Pugh, MELD) and laboratory tests indicating deteriorated liver function or progressed cirrhosis.

Interestingly, as described by Emadi et al. [26], IL-8 expression from CLD patients exceeded by far conditions of acute liver failure (ALF), in which IL-8-mediated neutrophil attraction has been described as an important mechanism of injury.

Recent studies by Henning et al. [27] revealed that monocytes/macrophages may respond to IL–8, because mononuclear cells are responders to IL–8 receptors CXCR 1 and CXCR 2 can be induced by several mediators like the Th2 cytokines IL-4 and IL-13. Also they reported that, the numbers of macrophages significantly increased with progression of liver fibrosis, as evidenced by immunohistochemistry for CD 68. This finding suggested that monocytes/macrophages might be the primary responders to IL–8 in liver diseases. Moreover, their data implicated that the source of elevated circulating IL–8 in patients with chronic liver diseases is likely the injured liver, because intrahepatic IL–8 gene expression was strongly (about 12-fold) induced in patient in comparison to control tissue.

Bonecchi et al. [28] also reported that monocytes / macrophages might be the main IL-8 responding cells in chronic liver disease patients. It has been reported that the Th2-cytokines IL-4 and IL-13 promote the up-regulation of CXCR1 and CXCR2 on human monocytes, thereby converting IL-8 and related chemokines, prototypic neutrophil attractants, into monocyte chemotactic agonists. Interestingly, circulating monocytes from cirrhotic patients indeed had increased CXCR 1 expression, both on a gene and protein level. The enhanced mononuclear CXCR 1 expression could likely result from induction by Th2-cytokines, because IL-4 was found increase with progression of liver disease (not shown) and to correlate with serum IL-8 in their study.

Their findings are in line with the current concept that advanced fibrotic disorders are generally characterized by strong Th2-biased immune responses [29].

Avrămescu et al. [30] had concluded from their studies that, production of IL-8 which is stimulated by IL-1, TNF-a, IL-6 activates the neutrophils and induces degranulation with release of lactoferrine. This type of inflammatory cells has been noticed in the hepatic tissue during chronic viral hepatitis.

In other clinical studies, it has been demonstrated that chronic hepatitis C patients with high histologic activities have increased levels of IL-8 mRNA expression [31]. Also in agreement with the present study, one previous study also found that serum IL-8 protein levels were elevated in HCV infected patients [32].

In our study, positive correlations were found between CXCR10 and IL-8, serum levels of AST, ALT. This is supported by previous reports by Roe et al. [33] that showed that increased peripheral and intrahepatic IP-10 levels are associated with increased liver damage. They found that in HCV-monoinfected patients, increased serum IP-10 levels are associated with increased ALT and AST levels and with increased liver fibrosis and cirrhosis. These results strongly indicate that IP-10 may play an important role in the progression of liver fibrosis in patients with chronic HCV infection.

Also, in our study, positive correlations were found between IL–8 and serum levels of AST and ALT in all patients of HCV infections that indicate increased liver damage. Also, Chung-Pin et al. [34] showed positive correlation between plasma IL-8 and AST, ALT levels in post hepatitis cirrhosis. However, the study by Ulrike et al. [11] stated that Pretreatment ALT and AST levels were only significantly positive correlated with pretreatment IL-8 levels in genotype 1 infected patients if all patients were included in the analyses. After exclusion of cirrhotics no significant correlation between ALT and AST levels and IL-8 was observed. Comparable results were obtained for genotype 2,3 infected patients. Pretreatment AST levels correlated significantly with pretreatment IL-8 levels if all patients were included in the analysis but not after exclusion of cirrhotics. Pretreatment ALT levels did not correlate significantly with pretreatment IL–8 levels in genotype 2,3 infected patients at all, with or without cirrhotics.
In conclusion, although the current knowledge regarding chemokines in HCV infection is relatively limited, the role of chemokines as chemoattractants in several inflammatory diseases is rapidly evolving. Moreover, in some of these diseases, therapeutic agents that block chemokine receptors, thereby decreasing inflammation, are currently being evaluated in humans. The CXCL 10 and IL-8 chemokines are the most significantly expressed chemokines in chronic hepatitis C and most likely play a role in positioning T cells in the liver. Furthermore, HCV can selectively increase CXCL10 and IL-8 expression in response to IFN-γ and TNF-α stimulation that may play a role in the pathogenesis of HCV-related liver disease as well as the evolution of the existing inflammation at the level of the liver, hepatic alterations fibrosis, eventually necrosis. Thus, the association of CXCL10 and IL-8 during the progression of liver disease in HCV infection, shedding new light on their involvement in the pathophysiology of chronic liver disease.

A better understanding of the role of these chemokines in driving T-lymphocyte accumulation in the HCV-infected liver will further aid in the development of therapeutic intervention strategies for inhibiting or reducing the excessive inflammation observed in CHC.

Hence, chemokines and their receptors might be considered as potential therapeutic targets in HCV infection.

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