Original article

IP-10 correlates with hepatitis C viral load, hepatic inflammation and fibrosis and predicts hepatitis C virus relapse or non-response in HIV–HCV coinfection

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Background: Interferon (IFN)-γ inducible protein 10 (IP-10) is increased in hepatitis C virus (HCV) mono-infection, correlates with hepatic inflammation and predicts non-response (NR) to antiviral therapy. We aimed to clarify the role of IP-10 in HIV–HCV coinfection.

Methods: Serum IP-10 levels of 30 HIV–HCV-coinfected patients treated with pegylated (PEG)-IFN-α2a (180 µg/week) and ribavirin (800–1,200 mg/day) were measured at baseline and 24 h after first IFN dose. The predictive value of IP-10 was compared with established markers of treatment outcome by applying a multivariate logistic regression model.

Results: Patients with NR (476 ±156 pg/ml) or virological relapse (508 ±298 pg/ml) had significantly higher baseline IP-10 levels compared with patients who had a sustained virological response (SVR; 293 ±97 pg/ml, P=0.001). The IFN-induced increase of IP-10 was significantly stronger in patients with an SVR (P=0.017). IP-10 levels were associated with HCV viral load, alanine aminotransferase (ALT) levels, hepatic inflammatory activity and fibrosis stage. Advanced fibrosis, high HCV viral load, hepatovenous pressure gradient and pretreatment IP-10 >400 pg/ml predicted NR to antiviral therapy. In the multivariate analysis, IP-10 was identified as the strongest baseline predictor of SVR with a specificity and sensitivity of 83.4% and 92.9%, respectively.

Conclusions: Pretreatment IP-10 levels correlated with HCV viral load, ALT levels, hepatic inflammation and fibrosis. An IP-10 cutoff level of 400 pg/ml might serve as a useful predictive marker for anti-HCV therapy in HIV–HCV-coinfected patients because it could discriminate patients with expected NR or HCV relapse after therapy from patients with an SVR before starting antiviral treatment.

Introduction

Hepatitis C virus (HCV) and HIV infections are among the leading causes of serious morbidity and death worldwide [1]. Approximately 180 million and 40 million people are infected with HCV or HIV, respectively. Because of shared routes of transmission, coinfection with HIV and HCV is common and the estimated number for HIV–HCV coinfection ranges from 4 to 5 million people [2]. Highly active antiretroviral therapy (HAART) has reduced HIV-related morbidity and mortality. However, HCV coinfection has become a predominant cause of mortality in the HIV-infected population [3,4].
non-response (NR) in order to spare unnecessary side effects of an expensive antiviral therapy.

In chronic HCV infection, viral load (HCV RNA<10^6 IU/ml), HCV genotype, absence of advanced fibrosis (Metavir scores 1 and 2) and a favourable initial virological response at treatment weeks 4 and 12 have been associated with SVR [8–11].

Less is known about the predictive value of host factors that influence treatment response. In HCV monoinfection, increased serum levels of cytokines, such as tumour necrosis factor-α, interleukins (IL; IL-1b, IL-10 and IL-8) [12–14] and IFN-γ inducible protein 10 (IP-10) [15,16], have been shown to correlate with poor response to antiviral therapy. IP-10 (also known as CXCL10) is a small chemotactic cytokine (chemokine) that attracts leukocytes to inflammatory sites by binding to its receptor, CXCR3. Specific chemo-attracted cells include T-cells, natural killer cells and monocytes. Thus, the IP-10 pathway probably plays an important role in the development of inflammation in HCV infection [17–19]. For HCV monoinfection, there is sufficient data that serum IP-10 levels of patients with NR are higher than those of responders to antiviral therapy and that IP-10 levels decrease significantly after HCV eradication [15,16,20]. Moreover, IP-10 seems to be an important predictor of liver disease progression in HCV infection, as its expression by hepatocytes correlates with severity of fibrosis and lobular inflammation [21]. To date, the role of IP-10 in HIV–HCV coinfected is not completely understood, but there exists some evidence that IP-10 is associated with other markers of HCV or HIV disease [22] and might be a predictive biomarker of SVR in these patients [23]. The aim of our study was to explore the value of IP-10 to accurately identify NR to antiviral treatment and to analyse the associations between IP-10 levels with known predictors of SVR, such as HCV genotype, HCV viral load, fibrosis stage and initial viral kinetic profile.

**Methods**

**Patients**

Data of HIV–HCV-coinfected patients treated at the Division of Gastroenterology and Hepatology at the Medical University of Vienna (Vienna, Austria), from whom frozen serum samples were available and who had signed written informed consent to use their blood samples for scientific purposes, were analysed. All patients had proven HIV–HCV coinfection (positive HCV RNA results and HIV antibody tests), were HCV treatment-naive, had compensated liver disease and were seronegative for hepatitis B surface antigen. The required CD4+ T-cell count was >100 cells/μl and all patients with CD4+ T-cell counts <200 cells/μl had to be on HAART. A liver biopsy was performed in all but four patients. Routine laboratory testing including haematological (that is, haemoglobin, peripheral platelet count and leukocytes) and biochemical (that is, alanine aminotransferase [ALT] and aspartate aminotransferase) parameters was performed at baseline and monthly during therapy. Thirteen patients had indirect measurement of portal pressure by hepatovenous pressure gradient (HVPG) and 14 patients had IFN sensitivity testing by a single dose of 9 million IU IFN-α2a before starting antiviral therapy. IP-10 levels were determined in blood samples of 15 healthy volunteers and 15 HCV-monoinfected patients for comparison with the analysed HIV–HCV-coinfected group.

**Therapy and treatment outcome**

All patients were treated with 40 kDa PEG-IFN-α2a (Pegasys®, Roche, Vienna, Austria) 180 mg once weekly and ribavirin (Copegus®; Roche) daily for 48 weeks. The daily dose of ribavirin was 800 mg for HCV genotype 2 or 3 and 1,000–1,200 mg for HCV genotype 1 or 4. Rapid virological response (RVR) was defined by virus negativity at treatment week 4, early virological response (EVR) by either virus negativity or by a >2 log_10 drop from baseline at week 12. End-of-treatment (EOT) response and SVR were defined as virus negativity at EOT and 24 weeks after EOT, respectively. Patients with NR either did not become HCV RNA-negative during therapy (primary NR) or had negative HCV RNA results under therapy but became HCV RNA-positive again after cessation of therapy (relapsers).

**Virological tests**

Quantification of serum HCV RNA levels was performed by PCR assay (Cobas Amplicor HCV Monitor Test® version 2.0; Roche Diagnostics, Branchburg, NJ, USA). To evaluate virus negativity, a qualitative HCV RNA PCR assay with a detection limit of 50 IU/ml (Cobas Amplicor HCV Test; Roche Diagnostics) was used.

**Measurement of IP-10 levels**

IP-10 concentrations in serum samples obtained before and 24 h after the first IFN dose were measured by a commercially available ELISA (BD OptEIA Human IP-10 ELISA Set; BD Biosciences, San Diego, CA, USA). All blood samples were stored at -70°C until assayed. In a prior assessment, series of samples were tested both undiluted as well as diluted 1:10 and 1:50. The outcome showed that the relationship between diluted and undiluted IP-10 levels was not linear, but piecewise linear with increasing deviation from undiluted values with increasing concentration. The cutoff points for the pieces of linearity were 350 and 1,625 pg/ml, respectively. Therefore, samples with a concentration >350 pg/ml were diluted 1:10 and the undiluted concentration was estimated from the reverse function. Samples with concentrations >1,625 pg/ml were tested both with dilutions 1:10 as well as 1:50.
Interferon sensitivity test
Four patients received a test dose of 9 MU IFN-α2a (Roferon-A®; Roche). HCV RNA was determined prior to and 24 h after IFN test dose. This IFN sensitivity test, performed 7 days prior to commencement of antiviral therapy, was part of routine patient management at the Medical University of Vienna between 1999 and 2003 [24]. The magnitude of the initial drop in serum HCV RNA has been correlated with the decline in HCV RNA after 14 days of combination therapy with standard IFN plus ribavirin [24,25].

Measurement of hepatovenous pressure gradient
The HVPG was measured in 13 patients before they started antiviral therapy. The measurement of HVPG is an accepted, indirect and safe method to determine portal pressure. As previously described [26], under local anaesthesia, a venous catheter introducer sheath (Axcess; Maxxim Medical, Athens, TX, USA) was placed in the right jugular vein under ultrasonographic guidance by using the Seldinger technique. Under fluoroscopic control, a 7 French balloon-tipped catheter (Medi-Tech; Boston Scientific Cork Ltd., Cork, Ireland) was advanced into a main hepatic vein. This catheter allowed serial measurements of wedged and free hepatovenous pressures, and the HVPG was calculated from the difference of these two measured pressures.

Liver biopsy
Biopsy specimens were obtained in 26 of the 30 patients (two patients were haemophiliacs and two patients refused) within 3 months prior to first IFN dose. For each biopsy, a haematoxylin–eosin stain and a Sirius red stain were staged and graded by local experienced pathologists according to the Metavir score [27].

Statistical analyses
Differences between HIV–HCV-coinfected, HCV-monoinfected and healthy participants were identified by the Kruskal–Wallis test. Non-parametric Mann–Whitney U or Fisher’s exact tests were used to identify significant differences in baseline characteristics between patients with SVR or NR. Continuous variables are reported as mean (±SD), except where otherwise specified. After these tests, all variables that were conspicuous candidates for prediction of SVR were subjected first to univariate, and subsequently to a multivariate logistic regression analysis. In the multivariate analysis, included variables were stepwise removed based on the likelihood ratio criterion with P-value for removal set to P=0.1. Because HVPG was only available in 13 cases, a dummy variable was constructed for HVPG availability (yes/no) and the product of this dummy variable and the observed HVPG were included in the multivariate analysis; using this procedure, all cases could be analysed. For all statistical tests, a P-value of <0.05 was considered to be statistically significant.

For determination of the ability of IP-10 to discriminate patients with SVR from those with NR, we computed an area under the receiver operator characteristic (ROC) curve at baseline using GraphPad Prism version 4.0 (GraphPad Software Inc., San Diego, CA, USA). A ROC curve can quantify the probability that, in a randomly selected pair of SVR and NR patients, the marker permits correct identification. To quantify the clinical value of IP-10, we have also reported the positive and negative predictive values (and 95% confidence interval [CI]) for the chosen IP-10 cutoff value for SVR and NR, respectively. The selection of IP-10 cutoff values aimed to maximize the negative predictive value so that we would minimize potential misclassification to NR.

Results
Patient characteristics and treatment outcome
A total of 30 HIV–HCV-coinfected patients were included in the study (see Additional file). Mean ±SD values are age 37 ±8 years, body mass index 22.6 ±3.1 kg/m² and CD4+ T-cell count 568 ±276 cells/µl. Median HCV viral load was 1,090,000 IU/ml (range 30,900–7,000,000). The proportion of HCV genotype 1 or 4 infection was 73% (22/30). Mean ±SD serum levels of IP-10 were higher in HIV–HCV-coinfected patients compared with a control group of healthy participants (378 ±312 versus 99 ±91 pg/ml, P<0.0001), but were comparable with those of HCV-monoinfected patients (398 ±327 pg/ml, P=non-significant [NS]; Figure 1A). SVR was achieved in 56% (17/30) of all patients, in 50% (11/22) of genotype 1 or 4 patients and in 75% (6/8) of genotype 2 or 3 patients. A total of 76% (23/30) of patients had an EOT response with a relapse rate of 26% (6/23) within 24 weeks after therapy. Overall, 60% (18/30) of patients were currently on HAART. IP-10 levels were lower in patients treated with HAART than in patients without HAART (326 ±107 versus 690 ±65 pg/ml, P=0.038). Patients with effective HAART (undetectable HIV RNA) had significantly lower IP-10 levels than patients with detectable HIV RNA under HAART (327 ±119 versus 484 ±137 pg/ml, P=0.049).

IP-10 levels
The 13 patients without SVR had significantly higher baseline IP-10 levels than the 17 patients with SVR (497 ±285 versus 293 ±97 pg/ml, P=0.001; Figure 1B).

In a subgroup analysis of primary NR (n=7) and relapsers (n=6), we found that relapsers also had significantly higher baseline IP-10 levels compared with patients with SVR (n=17; 508 ±298 versus 293 ±97 pg/ml, P=0.011), whereas no difference in IP-10 levels between primary
NR and relapers was noted (476 ±156 versus 508 ±298 pg/ml, P=NS; Figure 1B).

IP-10 levels 24 h after an IFN-α₂a test dose of 9 million IU were similar in patients with SVR or NR (2,350 ±490 versus 2,876 ±618 pg/ml, P=NS), but there was a significant difference in increase of IP-10 levels between SVR and NR (6.4-fold increase versus 4.0-fold increase, P=0.017; Figure 1C). Increased levels of IP-10 were also measured in patients with advanced fibrosis (Metavir scores 3 and 4; n=12) compared with lower fibrosis stages (Metavir scores 1 and 2; n=14; 429 ±187 versus 298 ±90 pg/ml, P=0.011; Figure 1D). IP-10 levels were found to be significantly lower in patients with low histological necroinflammatory activity (320 ±31 pg/ml) and lower ALT levels (383 ±68 pg/ml) compared with patients with high necroinflammatory activity (716 ±296 pg/ml, P=0.049) and higher ALT levels (614 ±177 pg/ml, P=0.038; Figure 1D). Patients with high HCV viral load (>10⁶ IU/ml; n=15) had significantly higher serum IP-10 levels than patients with low HCV viral load (<10⁴ IU/ml; n=15; 439 ±63 versus 315 ±136 pg/ml, P=0.02; Figure 1D). For accurate prediction of SVR a threshold for IP-10 levels was identified at 400 pg/ml by computing an ROC curve (Figure 2A). This IP-10 cutoff value was able to identify NR to antiviral therapy at baseline with a sensitivity of 90.9% (95% CI 58.7–98.5) and a specificity of 86.7% (95% CI 59.5–98.0). The positive and negative predictive value of the selected cutoff IP-10 level was 84.6% and 92.9%, respectively.
A significant difference in HCV viral load was noted between SVR and NR \((P=0.014; \text{Table 1})\). The best cutoff value of HCV viral load for discriminating between SVR and NR in the ROC curve was \(10^6 \text{ IU/ml}\) with a positive predictive value (PPV) of 81.2\% and a negative predictive value (NPV) of 71.4\% (Figure 2B). In patients with high HCV viral load (>\(10^6 \text{ IU/ml}\)) only 33\% (5/15) had SVR compared with 80\% (12/15) of patients with low HCV viral load (<\(10^6 \text{ IU/ml}\)) who had SVR.

Liver fibrosis stage

A liver specimen was obtained in 26 of 30 patients with HIV–HCV coinfection and scored using the Metavir system. Early fibrosis (Metavir scores 1 and 2) was diagnosed in 50\% (13/26) of patients, whereas the other 50\% of patients had advanced fibrosis (Metavir scores 3 and 4). Mean ±SD values for fibrosis scores were 2.00 ±0.78 in patients with SVR and 3.33 ±0.71 in those with NR \((P=0.012)\). Advanced fibrosis represents a baseline risk factor for NR to antiviral therapy and, according to this, only 25\% (3/12) of those with advanced stages were able to achieve SVR. There was an association between IP-10 levels and histological fibrosis stage; IP-10 levels in patients with advanced liver fibrosis were significantly higher than in patients with early fibrosis \((625 ±188 \text{ versus } 298 ±77 \text{ pg/ml}, \text{respectively}, \; P=0.013; \text{Figure 1C})\).
Univariate analyses were HCV viral load ($P=0.014$), Metavir liver fibrosis stage ($P=0.008$), IP-10 level ($P=0.001$) and HVPG ($P=0.048$). No differences in other baseline parameters (BMI, CD4+ and CD8+ T-cell count, haemoglobin, leukocyte count, thrombocyte count, ALT and AST) or in response to IFN-sensitivity test were noted between patients with SVR and NR.

The four baseline parameters significantly associated with SVR in univariate analyses were included in the multivariate analysis (Table 1). HVPG, fibrosis stage and HCV viral load were then stepwise removed and the $P$-value for IP-10 decreased to 0.03, 0.004 and 0.001. Only pretreatment serum IP-10 levels remained an independent predictor for antiviral treatment response in the multivariate logistic regression analysis ($P=0.04$). Fibrosis stage was strongly correlated with high IP-10 ($r=0.702$), but IP-10 was a stronger predictor than fibrosis stage in multivariate analysis.

Table 2 shows the predictive power of early viral kinetics and baseline parameters. We compared the predictive power of each baseline parameter reaching significant difference between patients with SVR and NR by calculation of its specificity, sensitivity and positive and negative predictive value in HIV–HCV-coinfected patients. RVR and EVR were the best on-treatment predictors of SVR, having a high specificity of 92.3% and sensitivity of 100%, respectively. Among all baseline parameters IP-10 levels had the highest sensitivity (92.9%) and specificity (84.6%) for predicting treatment outcome. Moreover, serum IP-10 levels were able to distinguish between patients with SVR and virological relapsers at baseline.

### Discussion

We identified an association between the levels of serum IP-10 and other markers of HCV disease and determined the predictive value of IP-10 compared with other baseline parameters in 30 HIV–HCV-coinfected patients undergoing antiviral therapy. In the present study a cutoff value for baseline IP-10 levels was established that discriminates patients with SVR from those with NR or relapse with a positive and negative predictive value for SVR of 84.6% and 92.9%, respectively. The high prognostic value of pretreatment serum IP-10 levels in HIV–HCV coinfection was confirmed by multivariate analysis.

Our data are in accordance with those of a previously published study [23], but provide additional information on early viral kinetics under antiviral treatment. In addition, our data strongly suggest that IP-10 levels could also be used to discriminate between SVR and virological relapse. Early identification of patients who will have a virological relapse is of particular importance, as this might influence the decision for treatment prolongation.

### Table 1. Factors associated with treatment outcome in HIV–HCV-coinfected patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>SVR</th>
<th>NR or REL</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>17 (56)</td>
<td>13 (44)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.901</td>
<td>–</td>
</tr>
<tr>
<td>Male, n</td>
<td>11</td>
<td>8</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Female, n</td>
<td>6</td>
<td>5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>37 (22–50)</td>
<td>42 (19–47)</td>
<td>0.145</td>
<td>–</td>
</tr>
<tr>
<td>Median BMI, kg/m² (range)</td>
<td>21.6 (19.1–29.1)</td>
<td>22.5 (17.8–29.4)</td>
<td>0.967</td>
<td>–</td>
</tr>
<tr>
<td>Mean IP-10, pg/ml (± s.d.)</td>
<td>293 (97)</td>
<td>497 (285)</td>
<td>0.008*</td>
<td>0.284 [step 2]*</td>
</tr>
<tr>
<td>Mean CD4+ T-cell count, cells/µl (± s.d.)</td>
<td>596 (301)</td>
<td>531 (245)</td>
<td>0.001*</td>
<td>0.040*</td>
</tr>
<tr>
<td>Nadir CD4+ T-cell count, cells/µl (± s.d.)</td>
<td>353 (254)</td>
<td>253 (266)</td>
<td>0.174</td>
<td>–</td>
</tr>
<tr>
<td>Mean HVPG, mmHg (± s.d.)</td>
<td>2.71 (0.29)</td>
<td>6.67 (3.39)</td>
<td>0.048*</td>
<td>0.998 [step 1]*</td>
</tr>
<tr>
<td>Mean IFN test, log₁₀ drop (± s.d.)</td>
<td>1.84 (1.25)</td>
<td>1.44 (0.74)</td>
<td>0.699</td>
<td>–</td>
</tr>
</tbody>
</table>

*Indicates statistical significance ($P<0.05$). †Removed after step 1, 2 or 3 of multivariate analysis, as indicated; the $P$-value for interferon (IFN)-γ inducible protein 10 (IP-10) decreased to 0.03, 0.004 and 0.001 after each respective step. BMI, body mass index; HCV, hepatitis C virus; HVPG, hepatovenous pressure gradient; NR, non-response to therapy; REL, virological relapse after end of therapy; SVR, sustained virological response.
Serum IP-10 levels were markedly increased, both in HCV-monoinfected and HIV–HCV-coinfected patients compared with a healthy control group, with no differences between HIV–HCV coinfection and HCV monoinfection. This suggests that HIV does not have a measurable additive effect on IP-10 production. In contrast, the study by Roe et al. [22] revealed significantly higher IP-10 levels in HIV–HCV coinfection compared with HCV monoinfection. As IP-10 levels correlate with HCV RNA load, this discrepancy might be explained by the fact that in the present study, HIV–HCV-coinfected patients had significantly higher HCV viral loads compared with the HCV-monoinfected patients. This is also in line with our finding that patients with higher viral replication rates (viral load >10^6 IU/ml) had significantly higher IP-10 levels than patients with low viral replication.

IP-10 reflects the degree of local chemokine signaling in HCV-infected hepatocytes intended to recruit CXCR3-expressing cytotoxic T-cells and natural killer cells which kill target cells, including primary hepatocytes [18,19]. HCV-induced liver injury is mainly mediated by a host cytotoxic immune response, characterized by a dramatic lymphocyte infiltration. For HCV monoinfection, a clear correlation of intrahepatic IP-10 messenger RNA and lobular inflammation in the liver has been reported [21]. The data of the present study demonstrate an association between serum IP-10 and hepatic necroinflammatory activity and fibrosis stage in HIV–HCV coinfection, as it has been shown for HCV monoinfection [28]. Moreover, patients with higher ALT levels had significantly higher IP-10 levels. Together, these findings could suggest a pathogenetic role of IP-10 in HIV–HCV coinfection, probably reflecting the importance of IP-10 for chemo-attraction of lymphocytes, which aggravates hepatic injury.

Elevated levels of various other cytokines stimulated by IFN have been described in NR to antiviral treatment [14,29], which could be explained by increased activation of the endogenous IFN pathway in NR. Our data revealed a significant difference in HVPG between SVR and NR. Because the number of patients included in this analysis was rather small, HVPG might be a stronger predictor than could be demonstrated in the present study. The HVPG increases when hepatic fibrosis progresses and in our univariate analysis both factors are predictors of treatment outcome. Further studies are needed to evaluate whether HVPG is a stronger predictor of treatment outcome than fibrosis stage.

The decision to treat HIV–HCV-coinfected patients with an IFN-based regimen is often difficult to make, because side effects are common and SVR rates are still discouraging. Many useful parameters (HCV genotype, fibrosis stage, early viral kinetics and baseline HCV viral load) have already been established to predict treatment outcome to an acceptable degree, but it would be of great clinical benefit to find predictors with a better sensitivity and specificity. The results of the present study show that IP-10 is an accurate predictor of treatment outcome in HCV–HIV coinfection. An IP-10 cutoff point of 400 pg/ml can identify patients at baseline with NR to antiviral therapy or virological relapse. The predictive value of IP-10 levels is only secondary to virus negativity at week 4 of treatment (RVR), but from a practical point of view has the advantage that it can be determined without starting antiviral therapy. This should be especially helpful for treatment decisions in HIV–HCV-coinfected patients.

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Disclosure statement

The authors declare no competing interests.

Additional file

The additional file ‘Supplementary Table 1: Patient characteristics at baseline’ can be accessed via the Volume 13 Issue 8 contents page for Antiviral Therapy, which can be found at www.intmedpress.com (by clicking on ‘Antiviral Therapy’ then ‘Journal PDFs’).

References