Short communication

Pegylated interferon-α for the treatment of sexually transmitted acute hepatitis C in HIV-infected individuals

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Introduction

In recent years a rise of sexually transmitted acute hepatitis C infections among homosexual HIV-positive patients has been noticed in Europe [1–4], and recently in the USA [5]. First clinical data on the use of interferons (IFNs) in the setting of acute hepatitis C infection in HIV-infected patients were promising and showed high sustained virological response rates [6]. At present, optimal timing, type and length of IFN therapy are controversially discussed.

Methods

Forty seven HIV-positive individuals with the diagnosis acute hepatitis C infection were enrolled in this prospective, non-randomized, multicentre study between September 2002 and December 2004 [7]. Acute hepatitis C virus (HCV)-infection was defined if ≥2 criteria within 4 months prior to diagnosis were met: known or suspected exposure to HCV, documented anti-HCV antibody seroconversion, or serum ALT >350 IU/l with normal levels during the year before infection.

Background: Sexually transmitted acute hepatitis C among HIV-positive homosexual men has been noted as an emerging epidemic.

Methods: Forty-seven patients with mainly sexually acquired, acute hepatitis C were enrolled in this prospective, multicentre trial, and 36 of these patients were treated within the acute phase of hepatitis C infection with pegylated interferon (peg-IFN) therapy.

Results: Early treatment resulted in sustained virological response in 61% of patients. Peg-IFN alone showed similar treatment response rates and lower incidence of anaemia compared with peg-IFN+ribavirin combination therapy. Higher treatment response rates were observed in patients treated over 48 weeks compared with 24 weeks.

Conclusions: Treatment of hepatitis C in HIV-positive individuals in the acute phase of infection leads to high rates of sustained virological response. Optimal time and mode of therapy have yet to be defined.

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Symptomatic hepatitis (vomiting) at the time of diagnosis. Upper quadrant pain, fatigue, discoloration of stool and urine, nausea, liver transaminases/hepatitis C virus (HCV) antibody/HCV RNA testing.

Maximum alanine aminotransferase (ALT) increase measured in serum at time of diagnosis. HAART, highly active antiretroviral therapy.

Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>No treatment (n=11)</th>
<th>Treatment (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>39</td>
<td>37</td>
</tr>
<tr>
<td>CD4+ T cells, cells/µl</td>
<td>587</td>
<td>416</td>
</tr>
<tr>
<td>CD4+ nadir &lt;200 cells/µl</td>
<td>2 (18)</td>
<td>15 (42)</td>
</tr>
<tr>
<td>History of AIDS*, n (%)</td>
<td>2 (18)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>HIV RNA, copies/ml</td>
<td>62,491</td>
<td>55,474</td>
</tr>
<tr>
<td>On HAART, n (%)</td>
<td>5 (46)</td>
<td>22 (61)</td>
</tr>
<tr>
<td>HCV RNA, IU/ml</td>
<td>752,692</td>
<td>1,905,844</td>
</tr>
<tr>
<td>HCV genotype, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7 (64)</td>
<td>25 (69)</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>2 (6)</td>
</tr>
<tr>
<td>3</td>
<td>1 (9)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>4</td>
<td>3 (27)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>–</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Diagnostic window², n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 weeks</td>
<td>6 (55)</td>
<td>15 (42)</td>
</tr>
<tr>
<td>5–8 weeks</td>
<td>1 (9)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>9–12 weeks</td>
<td>1 (9)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>13–16 weeks</td>
<td>3 (27)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Maximum ALT, IU/l</td>
<td>834</td>
<td>510</td>
</tr>
<tr>
<td>Symptomatic hepatitis³</td>
<td>8 (73)</td>
<td>17 (47)</td>
</tr>
<tr>
<td>Jaundice³</td>
<td>3 (27)</td>
<td>3 (8)</td>
</tr>
</tbody>
</table>

Baseline characteristics of patients according to treatment versus no treatment. Values are given as mean, absolute number of patients, and percent of patients in parentheses. *According to the Centers of Disease Control and Prevention AIDS classification 1993. †Time between the last normal and first pathological liver transaminases/hepatitis C virus (HCV) antibody/HCV RNA testing. ‡Maximum alanine aminotransferase (ALT) increase measured in serum at time of diagnosis. §Presence of typical clinical signs and symptoms of hepatitis (right upper quadrant pain, fatigue, discoloration of stool and urine, nausea, vomiting) at the time of diagnosis. ‡Presence of scleral icterus or frank jaundice at time of diagnosis. HAART, highly active antiretroviral therapy.

Results

All 47 patients were male, homosexual, and mean age was 37 years (Table 1). Transmission risk factor for hepatitis C was sexual in 38 patients and unknown in 9 patients. Eleven patients were not treated because they declined therapy (n=9) or treatment was further postponed after successful spontaneous reduction of HCV RNA during the first 12 weeks after diagnosis had occurred (amendment II, n=2). Eight of the 11 untreated patients progressed to chronic hepatitis C. Untreated patients who progressed to chronic hepatitis C did not differ significantly with regard to age, CD4+ T-cell count and nadir, HIV RNA, symptoms typical for hepatitis, maximum alanine aminotransferase (ALT) elevation, HCV-genotype, level of HCV RNA or observed decay of HCV RNA within the first 12 weeks after diagnosis compared with those who managed to spontaneously clear HCV infection. It is noteworthy that a negative HCV RNA (<600 IU/ml) at any one time point before 12 weeks after diagnosis of hepatitis C infection was observed in 7 of the untreated patients, 4 of whom progressed to chronic hepatitis despite temporary clearance of HCV. During the 24 weeks of follow-up of untreated patients severe adverse events occurred in one patient who suffered from atrial fibrillation in conjunction with a gastrointestinal infection. Atrial fibrillation spontaneously converted into sinus rhythm a day later following convalescence of gastrointestinalitis.

Thirty six patients started treatment according to our protocol [7] (Figure 1). Treatment was started a mean of 7 weeks after diagnosis of acute hepatitis C
(10 patients 0–2, 12 patients 3–6, 9 patients 7–14 and 5 patients >14 weeks after). After waiver request, protocol exemptions were granted in 6 cases who were allowed to continue therapy throughout week 48. In these patients a slow decay of HCV RNA was observed; that is, HCV-RNA was still >600 IU/ml at week 8, which had been shown to be a poor predictor for an end of treatment response in a first interim analysis. Protocol violations without request were observed in 5 patients: two patients with HCV genotype 2 and 3 had started peg-IFN RBV combination therapy and 3 patients had continued therapy throughout week 48. Throughout the study 1 patient was lost to follow up (week 12) and 4 patients stopped treatment early (non-response \( n =3 \), grade 4 liver transaminases under therapy \( n =1 \)).

By intent-to-treat analysis, an end-of-treatment response (negative HCV RNA at the end of treatment) was reached in 26/36 patients (72%), which was sustained (sustained virological response [SVR], negative HCV RNA 24 weeks after end of treatment) in 22/36 patients (61%). Patients who received ≥80 % of the planned treatment duration, ≥80 % cumulative doses of peg-IFN and where applicable ≥80 % cumulative doses of RBV reached sustained virological response in 70% of patients compared with 20% of patients who received <80%. Early virological response were predictors for SVR. A negative HCV RNA by week 8 was reached in 69% vs 20% (\( P=0.021 \)), a negative HCV RNA by week 12 in 96% of patients who reached an SVR vs 29% of patients who did not (\( P<0.0001 \)) Conversely, the negative predictive value for reaching SVR in this study population was 91% for patients without an early virological response.

We further investigated whether age, CD4+ T-cell count and nadir, HIV RNA, symptoms typical for hepatitis, maximum ALT elevation, HCV RNA, time between diagnosis of HCV-infection and treatment or type of peg-IFN had any influence on treatment outcome; however, none of them proved to be statistically significant (Table 2). By contrast, HCV genotype, combined peg-IFN+RBV treatment and prolonged treatment over 48 weeks reached statistical trends or significance. Performing binary multivariate regression analysis, only prolonged treatment was statistically of significant influence, with the odds of achieving SVR 11 times higher if the patient was treated 48 weeks compared with 24 weeks (\( P<0.042 \); Figure 2).

Treatment was considered generally safe and only one treatment discontinuation occurred due to a rise in liver transaminases (grade 4). After cessation of treatment in this patient, liver transaminases quickly returned within normal limits. Throughout the observation period 300 adverse events were recorded.

Results are shown in percent of patient group (y-axis). On the x-axis, all patients are compared with regard to treatment or no treatment. Treated patients are analysed with regard to the effect of HCV genotype (Genotype) combined pegylated interferon plus ribavirin therapy (Ribavirin) and length of therapy (Duration). ETR, end-of-treatment response; GT genotype; peg-IFN pegylated interferon-α; RBV, ribavirin; SVR, sustained virological response.
Adverse events were mostly mild to moderate (grade 1–2, n=286) and were mainly related to IFN therapy. HIV-related adverse events were observed in 4 patients (herpes zoster in 3 patients and oral candidiasis in 1 patient) and were of mild to moderate degree (grade 1–2). HIV-RNA of patients without HAART declined under the antiviral effect of IFN therapy by a mean of 0.52 log10. Absolute CD4+ T-cell count also fell due to the haematotoxic side effect of IFN therapy; however, baseline values were regained 24 weeks after the end of treatment (mean CD4+ T-cell count at baseline was 416 cells/ml, at end of treatment was 356 cells/ml and at 24 weeks after end of treatment was 404 cells/ml). Sixteen severe or life-threatening adverse events (grade 3–4) occurred in 11 patients. Liver transaminases >5 times upper limit of normal accounted for 8 events; with the exception of one patient all these elevations were observed in patients who had increased transaminases at baseline or in patients who suffered from viral breakthrough. Grade 3–4 hematotoxicity accounted for 5 events, leading to dose modifications of IFN/RBV therapy. Other severe adverse events (all grade 3) were depression (n=1), grand-mal seizure (n=1) and abdominal pain (n=1).

**Discussion**

Overall, 61% of our treated patients reached a sustained virological response, which was significantly higher compared with those patients who were not treated. These results compare well to recent data on the treatment of acute hepatitis C in HIV-infected and HCV-monoinfected patients, who showed similar treatment results [1,4,9]. Noteworthy, prolonging treatment to 48 weeks enhanced SVR-rates to almost
90%. The subgroup of patients treated for 48 weeks was small, however, and with one additional patient failing treatment a significant difference in treatment outcome would no longer be observed. Nevertheless, all patients who had been treated over 48 weeks carried genotype 1 or 4 infections and the majority showed a slow decay of HCV RNA under treatment. Both of these factors are considered unfavourable predictors on treatment outcome and strengthen our finding of a high SVR rate in this subset of patients. Postponement of treatment was not associated with a loss of treatment response and this finding has been also reported by Gilleece et al. [1]. However, caution may be warranted if treatment is started beyond week 16, as Kamal et al. [10] showed that treatment response in HCV-monoinfected patients with genotype 1 infection was almost halved in those who started at week 20 compared to those who started at week 8 after diagnosis of acute HCV infection.

Surprisingly, peg-IFN plus RBV combination therapy did not result in higher SVR rates compared with peg-IFN only. Moreover this finding was irrespective of underlying HCV genotype or duration of treatment (data not shown). On the other hand, peg-IFN plus RBV combination therapy resulted in significantly higher rates of anaemia (6/21 patients) compared with patients treated with peg-IFN only (0/15, P=0.030). Though anaemia was not associated with a worse treatment outcome (data not shown), our data indeed suggest that peg-IFN monotherapy in the setting of acute hepatitis C infection may be as effective as peg-IFN RBV combination therapy, and at the same time, less toxic. Future clinical trials are needed to further investigate into this matter.

Spontaneous clearance of HCV infection occurred in 27% of patients. Importantly, in our cohort 4 patients progressed to chronic hepatitis C despite a temporary negative HCV RNA <600 IU/ml. Therefore, continued controls of HCV RNA beyond apparent clearance of HCV appear prudent to rule out a chronic course. High sensitivity assay for the detection of HCV RNA may also better discriminate between those who spontaneously eliminate infection and those who do not.

Conclusion

Peg-IFN therapy significantly improves outcome after acute infection with hepatitis C in HIV-infected patients. The role of prolonged treatment over 48 weeks as well as the role of peg-IFN monotherapy in the treatment of acute hepatitis C infection in HIV-infected patients needs to further elicited in future trials.

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References


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