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# Treatment of acute hepatitis C infection in HIV-infected patients: a retrospective analysis of eleven cases

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SUMMARY. Studies on hepatitis C virus (HCV) monoinfected patients suggest high sustained treatment response rates of up to 98% when interferon monotherapy is administered during the acute phase of HCV-infection. To clarify whether early treatment of acute hepatitis C is similarly efficient in human immunodeficiency virus (HIV) positive patients, we conducted a retrospective survey of HIV-positive patients with acute HCV infection. Eleven HIV-positive patients who had been treated with interferon or interferon/ribavirin were identified at eight HIV-specialty outpatient clinics. The patients had been treated over a median 25 weeks with standard interferon (two patients), pegylated interferon (four patients) and pegylated interferon in combination with ribavirin (five patients). A post-treatment response (negative serum HCV-RNA at the end of treatment) was seen in 10 of 11 patients and HCV-RNA remained undetectable 24 weeks after the end of treatment in all the 10 responders. Alanine aminotransferase (ALT) normalized in eight patients while two virological responders and one nonresponder showed persistent mild ALT elevations. In conclusion, early treatment of acute hepatitis C seems to achieve high sustained virological treatment response rates also in patients with HIV-infection.

*Keywords*: hepatitis C, human immunodeficiency virus, interferons, ribavirin.

## INTRODUCTION

Acute hepatitis C virus (HCV) infection takes a chronic course in about 50–85% of human immunodeficiency virus (HIV)-negative patients and significantly higher rates of chronicity are observed in HIV-positive patients [1]. A major step in the evolution of chronic HCV infection may be the development of immune escape, that is, the development of a broad quasi-species range and loss of 'targets' on one hand [2] and the development of immune tolerance as a result of dysregulated host immune responses on the other [3]. These ideas led to the concept of early interferon therapy during the acute phase of HCV infection in order to counteract progression to chronicity.

In immunocompetent patients without HIV infection, several trials have reported high-sustained virological response rates of up to 98% of the treated patients, when interferon therapy was initiated within the acute phase of hepatitis C [4,5]. In this retrospective survey, we wanted to find out whether the concept of interferon treatment early after acute HCV infection can be successfully transferred to HIV-positive patients.

## METHODS

A telephone survey among 16 HIV outpatient clinics and practices from six major cities in Germany (Berlin, Hamburg/Kiel, Frankfurt/M, Munich, Duesseldorf, Cologne/Bonn) was conducted. A two-step approach was chosen to acquire the data. In a first screening call, physicians were asked to identify any HIV-positive patients with a history of acute hepatitis C. Acute HCV infection was defined by the simultaneous presence of two of the following three criteria within 4 months prior to diagnosis: (i) known or suspected

Abbreviations: AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; CDC, centre of disease control and prevention; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

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exposure to HCV, (ii) documented seroconversion to positivity for antibodies against HCV and (iii) a serum alanine aminotransferase (ALT) level of more than 350 IU/L with documented normal levels during the year before infection.

Next, a structured questionnaire was mailed to the responding physicians for detailed data acquisition. Apart from general characteristics of HIV infection, particular attention was given to clinical symptoms of the acute hepatitis, route of HCV transmission, dates of the last available normal and first pathological test results concerning HCV-RNA, anti-HCV and ALT serum levels, date and levels of maximum ALT elevation and HCV genotype. Physicians were also asked to report types and doses of interferon and ribavirin, start and stop dates of therapy, any adverse events, as well as reasons and dates of dose reduction or treatment discontinuation. Follow-up data (HCV-RNA, ALT, CD4+ cells, HIV-RNA) were obtained at the beginning (baseline), after 12 weeks, and 24 weeks after the end of interferon therapy. All patients had provided written informed consent and the study was conducted in full agreement with the declaration of Helsinki and its subsequent revisions. All laboratory testing was performed at the participating centres. Serum levels of HCV-RNA were reported as international units (IU) per millilitre to standardize results. HCV genotypes were determined via a second generation assay (INNO-LiPA HCV II Kit; Innogenetics, Heiden, Germany).

## RESULTS

### *Baseline*

Our survey identified 13 HIV-positive patients who had acquired acute HCV infection. Two patients had not been treated with interferon within the acute phase and showed progression to chronic infection (data not shown). Basic demographic data of the remaining 11 patients are given in Table 1. Median age at the time of diagnosis was 36 years (range 26–60). Risk factors of HCV transmission were sexual activity in 10 patients and intravenous drug abuse in one patient respectively. Nine of the 11 patients showed typical symptoms of hepatitis in terms of fatigue, upper-right quadrant pain, diarrhoea, loss of appetite, nausea and discolouring of stool and urine. Five patients presented with jaundice. At the time of diagnosis all patients showed elevated liver enzymes. Median maximum ALT serum levels at the time of diagnosis was 534 IU/L range 122–1689). ALT serum levels had decreased by the start of interferon therapy in all patients (Table 1), to a median ALT of 344 IU/L (range 68–1586 IU/mL Table 1). Eight patients were infected with HCV-genotype 1 isolates, two patients with genotype 4 and one patient with genotype 2. Median HCV-RNA before interferon therapy was 785 000 IU/mL (range 5346–4 359 410 IU/mL).

### *HIV infection*

At the time of acute hepatitis C, HIV infection was classified according to the centre of disease control and prevention (CDC) classification system [6] as (A) asymptomatic in eight patients, (B) symptomatic in two patients and (C) acquired immunodeficiency syndrome (AIDS) in one patient. The patient with AIDS had a history of kaposi sarcoma 8 years before with no active opportunistic infection present at the time of HCV diagnosis. Median CD4+ cell count at baseline was 507 cells/μL (range 150–1157) and median HIV-RNA viral load was 3000 copies/mL (range <50–84 000). Eight patients received highly active antiretroviral therapy (HAART) at the time of diagnosis of acute HCV infection. Four patients continued HAART throughout their course of HCV therapy. One patient stopped permanently, and three other patients temporarily stopped HAART at the time of HCV diagnosis; the latter patients reinitiated antiretroviral therapy after 1, 4 and 21 weeks of interferon treatment respectively.

### *Interferon therapy*

Interferon therapy was started at a median of 2.6 weeks after diagnosis of acute hepatitis C (range 1–12 weeks) and a median of 17 weeks after the last normal reported ALT serum level or the last negative anti-HCV (range 8–25 weeks), whichever was earlier (Table 2). Nine of 11 patients received pegylated interferons, five of them in combination with ribavirin. Two patients were treated with standard interferon alone, both receiving intensified regimens with daily injections for the first 14 and 30 days respectively. HCV-RNA was undetectable in eight of 11 patients at week 12. One patient showed a 2 $\log_{10}$ reduction in HCV-RNA, whilst two patients maintained unchanged persistent viraemia. At week 12, ALT had normalized in nine patients, but in the other two patients elevated ALT persisted at 61 IU/L and 752 IU/L respectively. Duration of treatment ranged from 21 to 27 weeks in nine of the 11 patients. Treatment was discontinued at week 11 in one patient because of severe psychosis, while treatment was prolonged to 48 weeks in the other patient as HCV-RNA was still detectable at week 12. Post-treatment virological responses (undetectable HCV-RNA at the end of treatment) were observed in 10 of 11 patients, while one patient with HCV-genotype 1 infection showed persistent viraemia (Table 2). This response was sustained (undetectable HCV-RNA 24 weeks after end of treatment) in all responders. Post-treatment, ALT had normalized in eight patients, while three patients (two virological responders, one nonresponder) showed persistent mild ALT elevation (<1.5 the upper limit of normal). Adverse events under interferon ± ribavirin treatment were reported in nine of 11 patients. Severe or life-threatening adverse events [World Health Organization

**Table 1** Demographic and baseline data of patients

| Patient | Sex | Age (years) | $ALT_{max}$ (IU/mL) | $ALT_{Tx}$ (IU/mL) | HCV-RNA (IU/mL) | HCV-GT | Symptoms of hepatitis | CDC class | CD4 cells (/μL) | HIV-RNA (copies/mL) | HAART |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Responder | | | | | | | | | | | |
| 1 | Male | 41 | 396 | 347 | 785 000 | 2b | None | C3 | 1157 | <50 | d4T, EFV, IDV |
| 2 | Female | 32 | 344 | 344 | 124 444 | 1a | Diarrhoea, asthenia, jaundice | A1 | 531 | 18 000 | None |
| 3 | Male | 60 | 601 | 106 | >800 000 | 1b | Jaundice | A2 | 448 | <50 | LPV/r, NVP[1] |
| 4 | Male | 28 | 534 | 68 | 225 000 | 1b | Nausea, vomitting, abdominal pain, asthenia | A2 | 496 | 6000 | d4T, 3TC, NVP[2] |
| 6 | Male | 36 | 1128 | 948 | >400 000 | 1b | Asthenia, dark urine, arthralgia, heart-burn, jaundice | A1 | 676 | <200 | AZT, 3TC, LPV/r[3,*] |
| 7 | Male | 31 | 384 | 304 | 1 250 000 | 4c/4d | Clay-coloured stool | A2 | 630 | <400 | AZT, 3TC, ABC, LPV/r |
| 8 | Male | 51 | 408 | 234 | 226 000 | 4c/4d | None | A2 | 445 | 84 000 | None |
| 9 | Male | 36 | 1436 | 390 | 1028 | 1a | Dark urine | A2 | 507 | 140 000 | None |
| 10 | Male | 41 | 1689 | 1586 | >800 000 | 1a | Jaundice, flu-like symptoms, asthenia | B2 | 716 | 19 700 | ddI, d4T, NFV† |
| 11 | Male | 39 | 122 | 122 | 4 359 410 | 1a/1b | Diarrhoea, loss of appetite, weight-loss, depression | B3 | 150 | 36 762 | AZT, 3TC, LPV/r‡ |
| Nonresponder | | | | | | | | | | | |
| 5 | Male | 26 | 978 | 390 | 1 840 000 | 1b | GI symptoms, jaundice | A2 | 404 | 52 000 | AZT, 3TC, ABC[4] |

$ALT_{max}$, maximum ALT elevation observed before start of interferon therapy; $ALT_{Tx}$, last available ALT prior to interferon therapy; HCV-GT, hepatitis C virus genotype; CDC class, classification according to the Centers of Disease Control and Prevention 1993; d4T, stavudine; EFV, efavirenz; IDV, indinavir 800 mg t.i.d; LPV/r, boosted lopinavir; NVP, nevirapine; 3TC, lamivudine; AZT, zidovudine; ABC, abacavir; ddI, didanosine; NFV, nelfinavir. [1–4]HAART was stopped at the beginning of acute hepatitis [2] and reinitiated at week 2 [1], 21 [2], and 4 [3] after the start of interferon-therapy. *Patient switched from AZT to d4T at week 20. †Patient switched to ABC, 3TC and LPV/r at week 9. ‡Patient switched to ABC, 3TC, AZT at week 12.

**Table 2** Treatment regime, duration and outcome for the individual patients

| Patient | Body weight (kg) | Time to Tx ALT (weeks) | Time to Tx diagnosis (weeks) | Interferon/ribavirin | Duration (weeks) | ETR | STR |
|---|---|---|---|---|---|---|---|
| Responder | | | | | | | |
| 1 | 73 | 25 | 10 | Pegylated IFN α-2b 100 μg q.w. + RBV 800 mg/day | 23 | Yes | Yes |
| 2 | 70 | 10 | 2 | IFN α-2a 14 days 9 MIU/day, then 6 MIU t.i.w. | 26 | Yes | Yes |
| 3 | 72 | 8 | 2 | Pegylated IFN α-2b 120 μg q.w. + RBV 1200 mg/day | 11 | Yes | Yes |
| 4 | 69 | 21 | 3 | Pegylated IFN α-2b 100 μg q.w. + RBV 800 mg/day | 21 | Yes | Yes |
| 6 | 76 | 19 | 1 | Pegylated IFN α-2a 180 μg q.w. | 25 | Yes | Yes |
| 7 | 98 | 17 | 9 | Pegylated IFN α-2b 150 μg q.w. + RBV 800 mg/day* | 48 | Yes | Yes |
| 8 | 63 | 23 | 2 | Pegylated IFN α-2b 100 μg q.w. | 23 | Yes | Yes |
| 9 | 81 | 18 | 2 | Pegylated IFN α-2a 180 μg q.w. | 27 | Yes | Yes |
| 10 | 71 | 8 | 2 | Pegylated IFN α-2b 100 μg q.w. | 24 | Yes | Yes |
| 11 | 68 | 16 | 7 | IFN α-2a 30 days 4.5 MIU/day, then 4.5 MIU t.i.w. | 27 | Yes | Yes |
| Nonresponder | | | | | | | |
| 5 | 64 | 8 | 2 | Pegylated IFN α-2b 100 μg q.w. + RBV 800 mg/day† | 30 | No | No |

Time to Tx ALT, time from the last available normal laboratory value (ALT or negative HCV test) to beginning of interferon therapy; Time to Tx diagnosis, time from diagnosis (positive HCV test) to beginning of interferon therapy; Duration, duration of interferon therapy; ETR, end of treatment response (undetectable HCV-RNA at the end of treatment); STR, sustained treatment response (undetectable HCV-RNA 24 weeks after the end of interferon therapy); IFN, interferon; RBV, ribavirin; t.i.w., three times per week; q.w., once weekly. *RBV was started at week 15. †Interferon-type was switched to peg-IFN-α-2a at week 19.

(WHO) grade 3–4] were reported only in one patient, in whom interferon therapy had to be discontinued because of acute psychosis. Adverse events in eight patients were mild to moderate (WHO grade 1–2) and comprised flu-like symptoms ($n = 5$), general asthenia ($n = 4$), depression ($n = 3$), gastrointestinal symptoms ($n = 1$), dry skin ($n = 2$), transient hyperthyroidism ($n = 1$) and haemolytic anaemia ($n = 1$).

## DISCUSSION

Hepatitis C virus infection constitutes a therapeutic problem in HIV-infected patients. Circumstantial evidence suggests that with prolonged survival under HAART, HCV infection might become a leading cause of death in HIV-coinfected patients [7,8]. Once in the chronic state of HCV infection, the efficacy of interferon therapy in HIV-infected patients is poor compared with immunocompetent patients, with overall sustained virological response rates between 25 and 40% [9–11], clearly highlighting the need for a more efficacious treatment. Here we show that interferon therapy in the acute phase of HCV infection achieved sustained virological response rates in 91% of our HIV-infected patients. This finding is particularly remarkable, because 10 of the 11 patients had unfavourable HCV-genotype 1 or 4 infections and were treated for a median of 25 weeks only. The safety data obtained from our 11 patients suggest a good tolerability of interferon therapy in the treatment of acute hepatitis C. In addition, because of the shorter and less intense treatment regimens, fewer treatment discontinuations were observed compared with pegylated interferon ribavirin combination therapy over 48 weeks [10,11].

This study was carried out as a retrospective survey and thus has its methodological limitations. Nine of the 11 patients presented with symptomatic hepatitis C, a circumstance associated with spontaneous clearance rates of 50% in patients without HIV infection. Whether higher clearance rates in symptomatic hepatitis also apply to HIV-infected patients remain to be elucidated, as the overall rates of progression to chronic hepatitis C are increased in HIV-coinfected patients [1]. Furthermore, six of the 11 patients had high CD4+ cell counts above 500 cells/μL, so that the effect of acquired immune deficiency on the course of HCV infection may have been small.

Nevertheless, our data suggests that HIV-infected patients may substantially benefit from interferon therapy early after acute HCV infection and provide a rationale basis for prospective studies to determine the optimal time interval and antiviral regimen to sucessfully treat acute hepatitis C in HIV-infected patients.

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