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Barriers to interferon-α therapy are higher in intravenous drug users than in other patients with acute hepatitis C☆

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***Background/Aims*: Treatment with interferon-α (IFN-α) may eradicate HCV in most acute hepatitis C patients, thus preventing chronic hepatitis and avoiding less efficacious combination therapy.**

***Methods*: In a prospective study, we evaluated the impact of barriers to successful start and completion of treatment of acute and subacute (<12 months from infection) hepatitis C with pegylated IFN-α_{2b}, 1.5 μg/kg, QW, for 24 weeks.**

***Results*: Out of 27 patients (22 were active intravenous drug users [IVDU]), 5 cleared HCV spontaneously. Antiviral treatment was indicated in 22 patients: six refused therapy for fear of side effects, whereas two others were lost to observation. Eight patients completed the treatment or received >80% of the scheduled drug: seven (88%) were sustained virological responders 24 weeks after the end of treatment. Six patients (all IVDU) stopped prematurely due to side effects: only one had a sustained virological response. Based on an intent-to-treat analysis, and considering all 14 patients in whom at least one dose of drug was administered, only 8 (57%) became sustained virological responders.**

***Conclusions*: Treatment of acute hepatitis C with pegylated IFN-α is highly beneficial, but its effectiveness is affected by a poor rate of acceptance and/or adherence to currently available regimens, especially in IVDU and women.**

***Keywords*: Acute hepatitis C; Antiviral treatment; Interferon-α; Substance abuse; Compliance; Adherence**

1. Introduction

Acute hepatitis due to hepatitis C virus (HCV) is rarely severe and its clinical impact is essentially due to the significant propensity to evolve to chronicity [1–6]. Recent studies suggest that treatment of acute hepatitis C with interferon-α (IFN-α) is highly effective, since it may eradicate HCV in 80–100% of cases, thus preventing the development of chronic hepatitis and avoiding more expensive and less tolerated combination therapy [7–11]. Hence, antiviral therapy in this setting should be encouraged, and international guidelines support this attitude [3–6].

Intravenous drug users (IVDU) are a major risk group for infection with HCV [3,4]. In Switzerland, approximately 80% of newly acquired HCV infections are due to sharing of injection equipment among IVDU [12]. Treatment of IVDU with *chronic* hepatitis C has been generally discouraged, for

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presumed non-adherence, increased risk and/or severity of side-effects (especially psychiatric), and risk of reinfection [12]. On the other hand, IVDU often share many factors of good response to therapy, such as young age, short duration of disease, and HCV genotype 3 infection. Moreover, different clinical studies suggest that IVDU can be treated successfully, also when active use of drugs has been withdrawn for only a short period of time [13–16]. Thus, more recent guidelines contain less restrictive recommendations [3,4].

As compared to their more tolerant attitude vis-à-vis chronically infected patients, physicians still seem very reluctant to treat active IVDU with *acute* hepatitis C. Recent studies on treatment of acute hepatitis C with IFN-α monotherapy have included only a minority of IVDU (10–25% of the total treated population) [7–11]. Whether this too cautious attitude should be maintained in the future, given the very high rate of success of treatment, remains to be proven.

The objective of our study was to evaluate the feasibility of pegylated IFN-α monotherapy in acute hepatitis C irrespectively of the risk factor for HCV acquisition.

2. Methods

Patients with acute (<6 months from the estimated date of infection) or subacute (>6 but <12 months from the estimated date of infection) hepatitis C were enrolled in a multicenter prospective trial if they had (1) a documented seroconversion for HCV or (2) a clinical picture compatible with acute hepatitis (symptoms including jaundice and/or fatigue together with serum ALT ≥20 the upper level of the normal, i.e. 50 U/l for males and 42 U/l for females) and a suspected exposure to HCV. Pegylated IFN-α_{2b} monotherapy (PEG-Intron™, Essex Chemie AG, Lucerne, Switzerland), 1.5 μg/kg, QW, for 24 weeks was offered to (1) all symptomatic patients with persisting HCV viral load for at least 5 weeks from onset of symptoms [9,11], and to (2) all asymptomatic patients [8]. All patients were fully informed of the benefits of the treatment and of its potential adverse effects, and simultaneously followed by experienced hepatologists and specialists in substance abuse (albeit at different units). Psychiatric counselling was guaranteed if indicated. Patients had access to a telephone hot line for support.

Clinical and laboratory data were gathered on standardized study forms. The primary endpoint was a sustained virological response at the end of a 24 weeks period of follow up after the end of treatment, and was defined by undetectable levels of HCV RNA in serum by a qualitative PCR (Roche Amplicor Monitor™, Roche Diagnostics, Rotkreuz, Switzerland). Additional data were collected on factors that could potentially influence acceptance of antiviral therapy and/or its completion (age, gender, active IVDU at the time of enrolment, presence of symptoms, ongoing psychiatric therapy, hospitalisation at a psychiatric institution during the 6 months preceding therapy, ongoing methadone therapy, as well as housing, household and professional status). The time from diagnosis to start of therapy was also considered, as well as the number of missed appointments during treatment. HCV RNA was measured by quantitative PCR (Amplicor Monitor, Roche Diagnostics, Rotkreuz, Switzerland). HCV genotyping was performed with a second-generation reverse-hybridisation line probe assay (Inno-Lipa HCV II, Innogenetics, Zwijndrecht, Belgium). Differences between groups were evaluated by the Fisher's exact test.

This study was sponsored by the Swiss Association for the Study of the Liver (SASL 18). It was approved by all local Ethical Committees and conducted in conformity with the Helsinki declaration. All patients consented to participate.

3. Results

Between May 2002 and September 2003, 27 cases (20 males) fulfilling the criteria for acute ($n=24$) or subacute ($n=3$) hepatitis C were referred. A total of 26 patients had a documented seroconversion against HCV, whereas only one patient had anti-HCV already at presentation, together with a recent acute post-transfusion hepatitis contracted in a developing country, and no prior history of liver disease.

Risk factors for HCV infection were active IVDU (22 cases, or 81.5%), accidental needle-stick with HCV-containing blood (two cases, both healthcare workers [HCW]), sexual contact with an HCV-infected partner (1 case), transfusion with HCV-contaminated blood (1 case) whereas for one patient, in spite of a documented seroconversion against HCV, no overt risk factors for HCV infection were identified.

The date of exposure to HCV was estimated based on the self-reported date of risk behaviour (for IVDU) or on the exact date of exposure in case of accidental needle-stick, sexual intercourse or blood transfusion. For the patient in whom no risk factors were identified—but for whom a HCV-negative serology was available 6 months before seroconversion—we estimated that he had been infected with HCV 3 months before seroconversion. HCV genotype was assessed in 21 cases and was 1a in 5 cases, 1b in 4, 2 in one, and 3a in 11.

Sixteen patients (59.3%) had symptomatic acute hepatitis, the most prevailing symptoms being jaundice (in 7 cases) and fatigue (all 16 patients). Symptoms occurred 64±46 days from the estimated date of infection.

Of the 27 patients, five (three symptomatic) presented spontaneous HCV clearance upon HCV RNA retesting and had no indication for further treatment (Fig. 1). Patients with spontaneous HCV clearance were comparable to the remaining patients in terms of serum HCV RNA levels at presentation (400,830±894,000 IU/ml vs. 3,560,000±8,740,000 IU/ml, P=NS), peak ALT levels (1316±1143 U/l vs. 661±635 U/l, $P=0.09$), occurrence of symptoms (3/5 vs. 13/22, P=NS), and HCV genotype distribution (1/2 vs. 10/18 with genotype 3a, P=NS).

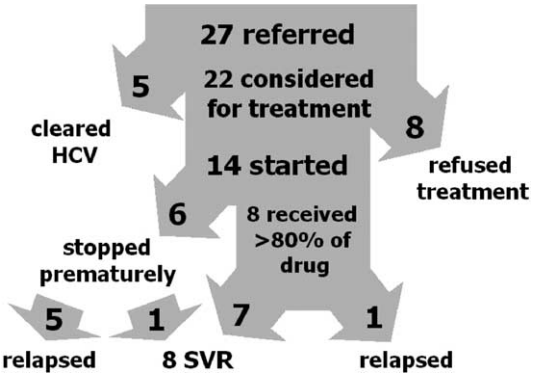

Fig. 1. Schematic representation of the outcome of 27 acute hepatitis C patients considered in the present study.

Among the remaining 22 patients to whom the antiviral therapy was proposed, 8 never started therapy: 6 (5 active IVDU) refused because of fear of side-effects, while 2 IVDU never showed up for the first treatment dose and were lost to follow-up.

Thus, antiviral treatment was started in 14 of the 22 patients to whom it was proposed (63.6%) (see Table 1 for baseline features). In 8 symptomatic patients, treatment began 100 ± 82 days from the start of symptoms. In the remaining 6 asymptomatic cases, therapy was started 63 ± 53 days from the first HCV-positive assay.

Of the 14 patients who received at least one dose of the drug, 6 completed the full course of therapy (3 IVDU). Two additional patients (both IVDU) stopped treatment at week 22 from the start due to fatigue (1 case) and severe depression (1 case).

Thus, among the 22 patients to whom therapy was proposed, 8 (36.4%) accepted it and received $>80\%$ of the scheduled drug. Of the 18 IVDU to whom PEG-Intron™ was proposed, only 5 (27.8%) accepted it and received $>80\%$ of the drug, vs. 3 of 4 non-IVDU ($P=0.15$). Of the 5 females to whom PEG-Intron™ was proposed, only 1 (20%) accepted to be enrolled and received $>80\%$ of treatment, vs. 7 of 17 males ($P=0.017$). Considering the 14 patients who started therapy, 5/11 IVDU (45.5%) received $>80\%$ of treatment, vs. 3 of 3 non-IVDU ($P=0.15$), whereas 1/2 females (50%) received $>80\%$ of treatment as compared to 7/12 males ($P=0.53$) (Table 2).

A dose reduction was necessary at week 4 in only one patient due to severe fatigue and intolerance. There were no dose reductions due to significant bone marrow toxicity: in five patients, however, a lymphopenia <0.5 G/l was observed.

Overall, 6 patients (all IVDU) stopped treatment before having received $>80\%$ of the scheduled drug due to side effects (4 cases of severe depression, one case of violent behaviour, one of severe intolerance). In two of them, a sudden, major change in personal entourage (sentimental break-up) was identified, triggering a severe depression in one occasion (12 weeks from start), and an episode of violent behaviour (leading to imprisonment) in another (9 weeks from start) (this patient had a history of personality disorder with occasional bouts of violent behaviour in the past). Another patient developed a major depression 2 weeks after becoming aware of a loss of biochemical and virological response (10 weeks from start): this patient was self-injecting the pegylated IFN-α_{2b}, and denied having missed a single injection. A fourth patient developed a depression while setting to live alone, apart from his family, and against our advice: he abandoned treatment 4 weeks after start but, despite all odds, became a SVR (see below). No external, triggering factor was identified for the last case

Table 1
Baseline features of 14 acute hepatitis treated in the present study

#	Mode of infection	Sex	Age	HCV genotype	Peak ALT (U/l)[a]	Jaundice	Symptoms[b]	Weeks between 1st proof of HCV infection and start of treatment	Treatment duration (weeks)	Treatment outcome
1	IVDU	M	35	3a	190	No	Yes	1	22	SVR
2	IVDU	M	21	3a	615	No	No	8	24	SVR
3	IVDU	M	21	3a	343	No	Yes	2	4	SVR
4	IVDU	M	18	3a	2303	Yes	Yes	6	24	SVR
5	IVDU	M	39	3a	924	No	Yes	50	22	SVR
6	IVDU	M	25	1a	1429	No	No	10	24	SVR
7	IVDU	M	29	3a	940	No	No	8	12	EOTR[c]/ relapser
8	IVDU	M	20	3a	84	No	No	4	9	EOTR/ relapser
9	IVDU	M	31	3a	300	No	Yes	6	12	EOTR/ relapser
10	IVDU	F	34	1b	660	No	Yes	4	1	Relapser
11	IVDU	M	49	1b		No	Yes	6	12	Loss of on-therapy response
12	Transfusion	M	51	2a	796	No	No	25	24	EOTR/ relapser
13	Unknown	M	47	1b	1949	Yes	Yes	3	24	SVR
14	HCW	F	25	1a	64	no	No	3	24	SVR

[a] Normal ranges: 12–50 U/l (males), 9–42 U/l (females).
[b] Mainly consisting of fatigue, abdominal discomfort.
[c] EOTR, end of treatment response.

Table 2
Factors associated with completion of treatment and SVR in acute hepatitis C

	n	Accepted therapy and received >80% of the scheduled drug		Started therapy and became SVR	
		n	*P*	*n*	*P*
All 22 patients in whom therapy was indicated:					
Active IVDU	18	5	NS	6	NS
Females	5	1	0.017	1	0.012
		Received >80% of the scheduled drug		Became SVR	
		n	*P*	*n*	*P*
All 14 patients who actually started therapy:					
Active IVDU	11	5	NS	6	<0.001
Females	2	1	NS	1	NS

of depression that occurred 12 weeks from start. Finally, one additional patient (a female IVDU) abandoned after her first injection, for severe intolerance (fatigue, flu-like symptoms).

Among the 8 patients who received >80% of the scheduled drug, 7 (87.5%) became sustained virological responders (SVR) 24 weeks after the end of therapy. Conversely, among the 6 who received less than 80% of the scheduled therapy, only one had a sustained virological response (even though he had received only 4 weeks of treatment). Of the other 5, three had a virological response at the end of therapy but underwent a relapse thereafter, one received only one injection of the drug and was still HCV RNA-positive in her serum tested 1 year later, and one had had a loss of response during treatment. Based on an intent-to-treat analysis, and considering all 14 patients in whom at least one dose of drug was administered, only 8 patients (57%) became SVR.

We then evaluated factors that could influence acceptance or completion of therapy, and how these affected the odds of achieving a sustained virological response.

We first analysed the impact of factors on the odds of becoming a SVR considering all 22 patients to whom antiviral treatment was proposed. The rate of SVR was low among females: among the 5 to whom treatment was proposed, 3 refused and only 1 completed according to the schedule, later to become SVR (1/5 vs. 7/17, $P=0.012$ vs. male patients). On the contrary, the fact of being active IVDU did not result in a significantly lower rate of SVR as compared to non-IVDU, considering the 22 patients in whom treatment was indicated (6/18 vs. 2/4, $P=0.34$) (Table 2).

When considering only the 14 patients who actually started therapy, female sex was not associated with lack of SVR (1/2 vs. 7/12, $P=$NS when considering only patients who started therapy). Eleven IVDU patients received antiviral treatment. The odds of achieving a SVR were affected by the fact of being active IVDU at enrollment (6/11 vs. 2/3 non-IVDU, $P<0.001$) (Table 2). It has to be pointed out that only one of the active IVDU at enrolment completely discontinued use of illicit substances I.V. during the participation into the trial (later to become a SVR after completing therapy), whereas the remaining 10 admitted to still occasionally abuse of I.V. drugs while receiving the antiviral therapy.

The fact of having received >80% of the scheduled drug was significantly associated with the chances of becoming ($P=0.016$), but other factors, as lack of methadone substitution therapy ($n=2$), recent hospitalisation at a psychiatric institution ($n=2$), lack of fixed housing ($n=1$), or time from diagnosis (acute vs. subacute) were not (data not shown). In addition, there were no differences between SVR and non-SVR as to baseline serum HCV RNA level (819,000 + 1,083,000 IU/ml vs. 354,000 + 232,000 IU/ml, respectively, $P=$NS), peak ALT level (977 + 836 U/l vs. 452 + 404, $P=$NS) or HCV genotype (5/7 vs. 3/5 had genotype 3a, $P=$NS).

4. Discussion

Our study shows that treatment of acute/subacute hepatitis C with pegylated IFN-α monotherapy for 24 weeks is highly effective, provided that patients receive at least >80% of the scheduled drug, in agreement with previous studies using standard IFN-α [7–11]. However, of the 22 patients to whom treatment was offered, only 14 started and, among these, only 8 received >80% of the scheduled drug. Refusal of therapy for fear of side effects, abandon and premature withdrawal due to side effects were frequent, since they involved two thirds of patients. Treatment refusal and/or premature interruption were especially high among females and IVDU. Thus, the therapeutic effectiveness in the setting of acute hepatitis C is rather an issue of access/adherence to treatment than of drug efficacy.

Barriers to access to treatment have been described in HIV-infected IVDU [17–22]: they tend to come under care later in the course of their disease and are less likely to receive antiviral treatment. Recognized barriers are female gender, young age, psychiatric illnesses, and lack of methadone substitution therapy. Interestingly, in our study, of the five women in whom antiviral therapy was indicated (four of them were IVDU), three refused to undergo it for fear of side effects and another abandoned after the first injection due to intolerance. Thus, gender may

significantly affect the acceptance of antiviral treatment, especially among IVDU, as observed also in chronic hepatitis C (Mauss S and Berger F, personal communication). Once started, also adherence to treatment may be reduced, especially by continuing drug use, depression, psychosocial stress, unstable housing, unstable sentimental relationships (like in two patients of the present series), lack of social support and factors related to the medical care, such as poor quality of clinician–patient relationship, treatment regimen and side effects [23,24].

The few studies on IFN-α treatment of recent IVDU with chronic hepatitis C show the existence of relevant barriers [25,26]. Access is limited due to presumed non-adherence, but also to fear of re-infection of and fear of psychiatric side effects of therapy. However, a study of HCV-reinfection after successful therapy for chronic HCV suggests that the rate may be as low as 7% [27]. The prevalence of psychiatric disease(s) among IVDU prior to commencement of antiviral therapy is significant [28,29], but a recent review suggests that psychiatric comorbidity did not negatively influence adherence or treatment outcome [30]. Studies on psychiatric side effects during IFN-α administration show conflicting results: one study showed a rate of premature withdrawal due to psychiatric side effects of 44.5% [31], whereas another study found no serious psychiatric events among methadone-receiving maintained IVDU [32]. Factors related to successful completion of therapy of chronic hepatitis C include access to methadone maintenance treatment, close supervision by physicians specialized in both hepatology and addiction medicine, and relative abstinence from alcohol [33,34]. Several studies suggests that treatment dropout among IVDU due to non-compliance or patient request occurs in general in an early phase [30,32], as was the case for six patients in our study.

Results from studies on chronic hepatitis treatment cannot be simply extrapolated to acute hepatitis C. In the case of chronic hepatitis the decision to treat is taken over a long period of time, patients and caregivers can be well prepared and a certain level of control over substance use can be a condition for treatment. Acute hepatitis C frequently means that the person is in a period of recent and/or active substance abuse, the decision to treat has to be taken within a short period, and it is possible that patients and caregivers are less well prepared. In our series, however, the time from diagnosis to start of therapy did not influence the subsequent adherence rate.

In the present study, we proposed antiviral treatment to all patients suffering from acute hepatitis, regardless of personal background. Notwithstanding this theoretically easy access to treatment, acceptance of and adherence to treatment were low, especially among IVDU and females. Reasons for not starting treatment were especially patient's fear of side effects. Two patients did not even show up after having been fully informed of the treatment procedure. In our study, psychiatric side effects were responsible for premature withdrawal from therapy in at least 5 patients. We think that once treatment has started, IFN-α may destabilize precarious situations even further, suggesting that management should be individualized, based on the specific and thorough knowledge of each patient's personal background. In spite of preventive measures, premature termination of antiviral therapy is frequent, especially due to psychiatric side effects. Active IVDU are a fragile patients' population, for whom destabilising factors (e.g. changes in sentimental entourage and/or household, as in some of our patients) may lead to dramatic consequences.

Despite all of the above difficulties, we support an aggressive management of acute hepatitis C in active IVDU, not only to prevent these patients from progressing to chronically evolving liver disease, but also to curb the HCV spread within the IVDU community. Our results suggest that treatment of acute hepatitis C with 24 weeks pegylated IFN-α monotherapy is highly efficient, but this efficacy is significantly reduced by multiple barriers, especially among IVDU. It is also noteworthy that a shorter therapy, albeit more acceptable, may not be sufficient for most patients: three of our patients interrupted treatment after 12 weeks, and all had a hepatitis relapse thereafter.

Although the rate of SVR among these patients, analysed on an intent-to-treat basis, was relatively high ($>50\%$), it was (1) significantly lower than that obtained among non-IVDU and as reported in other trials, and (2) associated with severe side-effects and premature termination in a significant proportion of patients. Therefore, we suggest that specific support measures be carefully evaluated and implemented in future trials: they should include an individualized management and an improved education of gastroenterologists in addiction medicine (and of addiction specialists in hepatology), possibly via the integration of HCV treatment within substance abuse treatment. Thus, future management of acute hepatitis C patients should preferably be carried out in an integrated way at highly specialized, multidisciplinary units.

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