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Swiss Multicenter Study Evaluating the Efficacy, Feasibility and Safety of Peginterferon-Alfa-2a and Ribavirin in Patients with Chronic Hepatitis C in Official Opiate Substitution Programs

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Key Words
Opiate substitution · Antiviral therapy · Hepatitis C

Abstract
Background: Though patients in opiate substitution programs are commonly infected with HCV, due to safety and efficacy concerns, they are rarely treated with interferon and ribavirin. ***Methods:*** In a multicenter study, HCV-infected patients in opiate maintenance treatment programs received 180 μg pegylated interferon-alfa-2a once weekly, plus daily ribavirin for 24 weeks (genotypes 2, 3), or 48 weeks (genotypes 1, 4). ***Results:*** Of the 67 patients enrolled, 31 (46%) had HCV genotypes 1 or 4, and 36 (54%) had genotypes 2 or 3. Intent-to-treat analysis showed end-of-treatment virologic response in 75% of patients (81% of genotypes 2 or 3; 65% of genotypes 1 or 4), and a sustained virologic response in 61% of patients (72% of genotypes 2 or 3; 48% of genotypes 1 or 4). Fifteen patients (22%) did not complete the study, in 5 (8%) cases because of severe adverse events. ***Conclusions:*** Drug users with chronic HCV infection, regularly attending an opiate maintenance program in which close collaboration between hepatologists/internists and addiction specialists is assured, can be treated effectively and safely with pegylated interferon-alfa-2a and ribavirin. Treatment results are very similar to those in other patient groups, and thus therapy should also be considered for this population.

Introduction

Hepatitis C virus (HCV) infection causes chronic hepatitis in approximately 85% of those infected, and up to 20% of these develop liver cirrhosis as a late sequela [1]. Intravenous drug users (IDU) represent the core of the hepatitis C epidemic in the developed world. The literature cites infection percentages ranging from between 60 and even up to 100% of IDU being chronically infected, depending upon the individual's risk behavior and duration of intravenous drug use [2–8]. Viral transmission is still uncontrolled among IDU [8–12]. Seroprevalence in

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the general population ranges between 0.2 and 2%. For Switzerland, estimates range from 0.5 to 1% of the population [13].

In many cases, depending on viral genotype, antiviral therapy of HCV infection with standard interferon-alfa (SIF) plus ribavirin (RBV) achieves sustained virologic response (SVR). The introduction of pegylated interferons (PEG-IFN) has further improved treatment responses [14–18].

The treatment of chronic hepatitis C in drug users remains controversial. Various national and international guidelines and consensus recommendations have excluded drug users from anti-HCV therapy [19, 20], whereas others have questioned this reasoning [3, 6, 21–23].

It was only in 2002 that the National Institute of Health consensus on medical management of HCV infection changed its recommendation to now consider treatment of IDU on a case-by-case basis [24]. Despite these newer recommendations, IDU still face many obstacles to HCV treatment, few have access to HCV treatment, and they are less frequently treated than other patient groups [25, 26].

The main reasons mentioned for excluding drug users from HCV treatment are the following:

- Presumed inadequate compliance;
- High rate of mainly psychological side effects;
- Risk of re-infection;
- Co-infection with hepatitis B or HIV;
- Treatment of HCV only after successful detoxification;
- Presence of contraindications for HCV treatment.

It has been shown [22, 23, 25, 27–30] that in the setting of opiate maintenance treatment (OMT; with methadone, heroin, buprenorphine or other opiates), HCV treatment with interferon (IFN) and ribavirin is feasible and safe, at least in small, highly selected groups of patients.

We conducted an open-label, phase IIIb multicenter study of HCV treatment with pegylated interferon-alfa-2a plus ribavirin in drug users undergoing opiate maintenance treatment in Switzerland. The primary objective was to evaluate the efficacy of pegylated interferon-alfa-2a in combination with ribavirin in a relatively unselected group of chronic hepatitis C (CHC) patients participating in opiate substitution programs.

Secondary objectives were:

- To evaluate the efficacy of PEG-IFN plus RBV on the reduction of HCV viraemia after 4, 12, 24 and 48 weeks;
- To evaluate the efficacy of the combination therapy according to genotype and viral load of hepatitis C;
- To evaluate the efficacy of the combination therapy depending on patient's previous IFN treatment;
- To evaluate the safety of PEG-IFN plus RBV in patients with CHC participating in opiate substitution programs;
- To assess adherence to therapy during treatment with PEG-IFN plus RBV for patients participating in opiate substitution programs.

Patients and Methods

Centers and Screening

Eleven Swiss centers took part in the study. Most centers offer two forms of opiate substitution programs: oral substitution (methadone or buprenorphine) with a low threshold (evidence of dependence and two previous withdrawal attempts), and intravenous diacetylmorphine (heroin) substitution with high threshold criteria [31].

HCV antibody testing is offered, and in most cases performed, at the start of the opiate substitution treatment. Screening for participating in the HCV treatment study started only when adherence to maintenance treatment was achieved and chronic hepatitis was confirmed. During the screening phase, none of the patients had signs or symptoms suggesting acute HCV infection.

The patients provided their written informed consent to participate in the study, which had been previously approved by the local institutional review boards and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Patient Selection

Men and women between 18 and 65 years of age, with serologically proven chronic hepatitis C and participating in an official opiate maintenance treatment program, but not previously treated with interferon-ribavirin combination therapy, were eligible for screening. During the screening phase, within 28 days prior to the first dose of pegylated interferon-alfa-2a and ribavirin, examinations established patient eligibility according to the inclusion/exclusion criteria.

Inclusion criteria were:

- Serum HCV PCR >600 IU/ml (COBAS Amplicor Monitor HCV RNS 2.0; Hoffmann-La Roche);
- Elevated serum ALT documented on at least one occasion within the past 6 months;
- Compensated liver disease (Child Pugh Grade A clinical classification in the case of cirrhosis);
- Ultrasound or MRI with no evidence of hepatocellular carcinoma;
- Serum AFP <100 ng/ml and regular attendance at the treatment center.

A liver biopsy was not required on study entry, and other causes of liver disease were excluded by appropriate laboratory tests (anti-HAV IgM Ab, HBs-Ag, anti-HBc IgM-Ab; coeruloplasmin, ferritin, transferrin saturation; ANA, AMA).

A noninvasive index, the AST to platelet ratio index (APRI), was calculated to estimate the percentage of patients with severe fibrosis or cirrhosis [32].

Patients were excluded from participation if they had:

- Neutropenia (<1,500 neutrophils/mm^3);
- Thrombocytopenia (<90,000 platelets/mm^3);
- Anaemia (<12 g Hg/dl in women and <13 g Hg/dl in men);
- Human immunodeficiency virus (HIV) infection;
- Chronic hepatitis B;
- Decompensated liver disease;
- A serum creatinine level >1.5 times the upper limit of normal;
- Poorly controlled psychiatric disease;
- Substantial coexisting medical conditions;
- Were pregnant or breast feeding, or male partners of a pregnant woman.

Further exclusion criteria were:

- Therapy with any systemic antiviral, antineoplastic or immunomodulatory treatment within 6 months prior to the first dose of study drug, or with any investigational drug within 6 weeks prior to the first dose of study drug;
- Evidence of drug abuse including excessive alcohol consumption outside the official opiate substitution program;
- And inability or unwillingness to provide informed consent or abide by the requirements of this study.

Treatment

In this open-label, phase IIIb multicenter study, patients received once-weekly subcutaneous injections of 180 μg pegylated interferon-alfa-2a, usually administered by a study nurse in the opiate maintenance treatment centers, plus daily ribavirin. In patients with genotype 2 or 3, treatment was given for 24 weeks and the ribavirin dose was 800 mg/day. In patients with genotype 1 and 4, treatment was given for 48 weeks; the ribavirin dose was 1,000 mg/day for patients weighing <75 kg, and 1,200 mg/day for those weighing >75 kg. Clinical visits and laboratory investigations were performed at the screening visit 4 weeks before baseline, at baseline, and at weeks 1, 2, 4, 6, 8 and 12, and then every 6 weeks until 6 months after the end of treatment. Viremia was measured at weeks 4 and 12, at the end of treatment, and 6 months after the end of treatment.

Subsidiary endpoints were:

- Side effects, which were WHO graded;
- Dose reductions;
- Treatment interruptions;
- And dropouts.

Patients with no early virologic response at 12 weeks (RNA negativity or a drop in viral load by more than two logs) were given the option to discontinue treatment. In case of intolerance to study medication, doses were adjusted according to guidelines. HCV PCR was performed by local and approved laboratories using COBAS Amplicor Monitor HCV RNS 2.0 (Hoffmann-La Roche); HCV genotyping was performed with INNO Lipa HCV II (Bayer).

Most patients received all of their study medication at the same center where they received opiate substitution treatment. Those patients considered reliable enough to administer pegylated interferon-alfa-2a themselves were asked to return all used vials. All patients were asked to return open bottles, and tablet counts were made at each visit. Patients were considered compliant if they had taken at least 80% of the study medication for 80% of the planned treatment period.

Ribavirin was provided by Roche Pharma, Switzerland.

Statistics

The primary end-point of the study was a sustained virologic response to combined therapy, defined as a negative quantitative HCV-RNA determination 24 weeks after the end of treatment. All end-points were evaluated in an intent-to-treat analysis, including all patients who received at least one dose of study medication. Non-parametric tests were used for comparison of groups.

Results

Patient Demographics

Between March 2002 and June 2004, 67 patients from 11 treatment centers were enrolled in the study and received at least one dose of study medications. Of these, 49 were male, 18 were female; the mean age was 34 years. At baseline, 52 of 67 patients were receiving maintenance treatment with methadone alone, 7 used heroin and methadone, 3 only heroin, and 5 other opioids (buprenorphine or oral morphine). The mean duration of intravenous drug addiction was 156.7 ± 59 months. The estimated duration of HCV infection was 132.5 ± 74.9 months. Based on the APRI index (cut-off value >1.5), the estimated percentage of patients with severe fibrosis or cirrhosis was 25%.

Further pretreatment characteristics of the patients are summarized in table 1.

Virologic Response

In the intention-to-treat analysis, 75% of patients had nondetectable HCV RNA at the end of treatment (genotypes 2 and 3: 81%; genotypes 1 and 4: 65%). Some 61% of patients (genotypes 2 and 3: 72%; genotypes 1 and 4: 48%) had a sustained virologic response 24 weeks after the end of treatment. Rapid virologic response at week 4 and early virologic response at week 12 are shown in figure 1. End of treatment response (75%) was lower than early virologic response (84%) because three patients experienced a breakthrough of HCV viremia during treatment and 2 patients dropped out during this phase of the study.

Patients who achieved SVR had been on opiate substitution for a shorter period (139.4 ± 61 vs. 183.9 ± 82 months, $p = 0.0164$) than those with no SVR. This may reflect a shorter duration of HCV infection, which is one of the predictors of response.

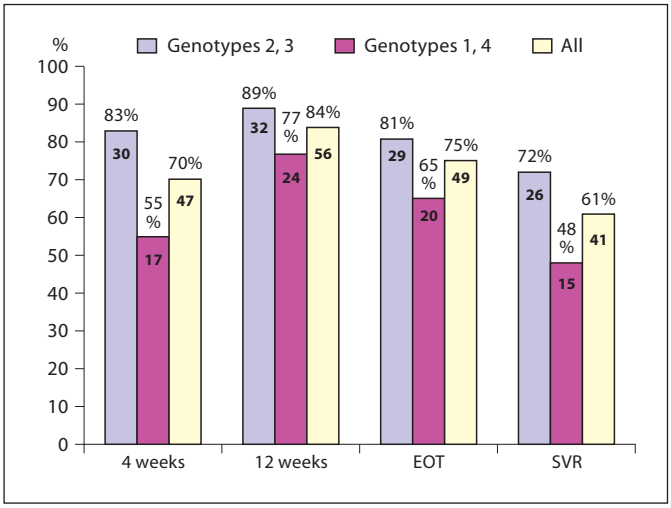

Fig. 1. Viral response rates. Virologic response at weeks 4 and 12, end-of-treatment (EOT) virologic response and sustained virologic response (SVR), according to intention-to-treat analysis. A virologic response was defined as an undetectable level of HCV RNA (<600 IU/ml).

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Table 1. Characteristics of patient population

Mean age, years (range)	34 (21–56)
Male/female, n (%)	49 (73)/18 (27)
Weight, kg	73.6 ± 16.5
BMI	25.0 ± 5.0
ALT, U/l	112 ± 84
Normal ALT	18%
ALT 1-2 ULN	46%
ALT 2–3 ULN	13%
ALT > ULN	22%
Thrombocytes <150,000/μl	12%
APRI score [32]	
>1.5, n (%)	17 (25)
>2.0, n (%)	9 (13)
HCV RNA level, kIU/ml	2,571 ± 5,021
≤500,000 IU/ml	30 (45%)
>500,000 IU/ml	37 (55%)
HCV genotype, n (%)	
Genotype 1	25 (37)
Genotype 2	2 (3)
Genotype 3	34 (51)
Genotype 4	6 (9)

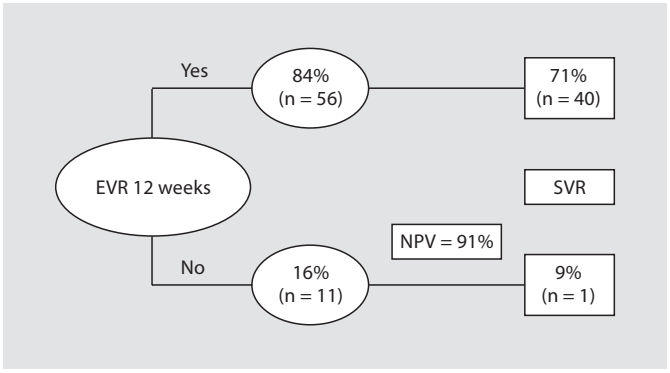

Fig. 2. Predictability of sustained virologic response. At week 12, 84% (56 of 67) of the patients treated with peginterferon-alfa-2a plus ribavirin had an early virologic response (RNA negativity or a drop in viral load by more than two logs). Of these patients, 71% (40 of 56) went on to have a sustained virologic response (SVR). Of the 11 patients who did not have an early virologic response at week 12, 10 (91%) did not have a sustained virologic response.

Patients with a pretreatment HCV RNA level of ≤500,000 IU/ml (n = 30, SVR 77%) had a significantly better treatment response than those with a pretreatment HCV RNA level of >500,000 IU/ml (n = 37, SVR 49%, p = 0.02).

Of the 67 patients, four (three genotype 1, one genotype 2) had previously been treated unsuccessfully with interferon monotherapy. None of these patients achieved SVR.

Predictive Value of Early Virologic Response

By week 12, 84% (56/67) of the patients treated with peginterferon-alfa-2a plus ribavirin showed an early virologic response, defined as no detectable serum HCV RNA or a drop in viral load by more than two logs (fig. 2). Of those with early virologic response, 71% subsequently had a sustained virologic response. In contrast, among the 11 patients who did not have an early virologic response, 10 (negative predictive value, NPV = 91%) did not have a sustained virologic response.

Safety

From the 67 patients entering the study, 83% (6 discontinuations) with genotype 2 or 3, and 69% (9 discontinuations) of those with genotype 1 or 4, completed the study as planned. Premature study termination due to adverse events was observed in 5 (8%) of the patients (table 2).

Dose modifications due to adverse events were frequently necessary (not all data shown). Only 37% of patients continued full treatment doses of pegylated interferon-alfa-2a and ribavirin. The need for ribavirin dose reduction was significantly more frequent in patients

Table 2. Reasons for premature study withdrawal

	Genotype 2, 3	Genotype 1, 4	All
Adverse events	2	3	5
Lost to follow-up	2	0	2
Withdrawn consent	2	1	3
Other	0	3	3
NR after week 12	–	2	2
Total	6	9	15

Table 3. Incidence of adverse events (occurring in more than 5%)

Blood system disorders overall[1]	12 (19%)
Neutropenia/granulocytopenia	6
Thrombocytopenia	5
Anemia	5
Eye disorders overall[1] (various)	6 (9%)
Gastrointestinal disorders overall[1]	28 (42%)
Nausea	12
Vomiting	8
Abdominal pain	5
Upper abdominal pain	5
Dyspepsia	4
Nervous system disorders overall[1]	27 (40%)
Headache	21
Psychiatric disorders[1]	31 (46%)
Depression	20
Insomnia	14
Thoracic disorders[1]	9
Skin disorders overall[1]	28 (42%)
Alopecia	10
Pruritus	10
Dry skin	5
General disorders[1]	42 (63%)
Fatigue	29
Flu-like symptoms	27
Irritability	8
Injection site erythema	5
Concomitant infections	18
Anorexia	9
Musculoskeletal pain	9

[1] Patients with at least one AE.

treated for 48 weeks (i.e. with genotypes 1 or 4) than in those treated for 24 weeks (69% vs. 40%, p = 0.039), whereas the need for dose reduction of pegylated interferon-alfa-2a did not significantly differ between the groups (overall 55%, p = 0.09). Though adverse events were seen in most patients, the most common reasons leading to dose reductions were granulocytopenia (6), thrombocytopenia (5), anemia (5), and a flu-like syndrome (2) (table 3).

Most adverse events were those commonly associated with interferon-based treatment (table 3). There were 188 events that occurred in the 36 patients treated for 24 weeks (genotypes 2 or 3), and 171 events were reported in the 31 patients treated for 48 weeks (genotypes 1 or 4). Severe adverse events (WHO grade 3 or 4) being reported more than once were neutropenia (3), thrombopenia (2), fatigue (3), anorexia (2), and headache (2). Psychiatric side effects grades 3 or 4 were rare. One severe episode of depression, one panic attack and one psychotic disorder were recorded. Rarely did serious adverse events lead to termination of the study (5 patients).

Concomitant Medications

Concomitant medications were prescribed for 77% of all patients at some point during the study. In particular, 10 patients (15%) were taking antidepressants at entry and a further 15 patients (23%) received antidepressants during the study for treatment of side effects. Two patients (3%) took benzodiazepines at entry and a further 10 patients (15%) received benzodiazepines during the course of the study.

Discussion

The treatment of HCV-infected patients who continue to take opiates, even in the setting of an opiate maintenance treatment program, is still a matter of debate. In this study, we report the results of treatment with pegylated interferon-alfa-2a plus ribavirin. As was observed in earlier studies, only a selected group of patients in opiate maintenance treatment were included. Among approximately 1,700 substituted patients at eleven Swiss treatment centers, 67 started treatment with pegylated interferon-alfa-2a plus ribavirin. Recruitment was slow and took longer than expected. The reasons for non-treatment were not assessed in the actual study, but were, in general, either patient- and/or physician-related. Nevertheless, in this setting, antiviral treatment with pegylated interferon-alfa-2a plus ribavirin proved feasible and safe. Efficacy, measured as SVR, was 61% across all virus genotypes. Compared to an overall sustained viral response of 47% in an earlier study with standard interferon and ribavirin in the same setting [30], the treatment response rate with pegylated interferon-alfa-2a was clear-

ly higher, as has been shown in studies using the same therapies but requiring cessation of opiate use [18]. Patients with genotype 2 or 3 had a sustained virologic response rate of 72%; those with genotype 1 or 4 had an SVR of 48%. These response rates are very similar to those from previous studies requiring cessation of opiate use [15, 18].

A reappearance of HCV after early virologic response was observed in five patients. Most likely, this was due to a breakthrough and not to reinfection. No patient relapsed to i.v. drug use for the duration of the study. Even if individual patients had been injecting drugs during the course of the study, they most likely would have used clean needles and syringes, which are easily available in Switzerland.

Early prediction of virologic response to interferon-based therapy can help identify patients unlikely to have a sustained response, and allow clinicians the option to discontinue treatment, thereby saving patients side effects and cost of additional therapy. There is now a consensus that treatment should be discontinued in patients who do not achieve early virologic response by week 12 [33]. The current study suggests that this also holds true for opiate substituted patients: 91% of our patients who did not have an early virologic response by week 12 did not achieve a sustained virologic response. These results are very similar to those in larger studies involving non-IDU patients.

One of the reasons for the reluctance of hepatologists to treat IDU with HCV infection is a supposed noncompliance and a higher rate of dropouts from treatment programs. In a previous treatment study with pegylated interferon-alfa-2b plus ribavirin in patients on methadone maintenance, sustained virologic response was 42% in the methadone group, and thus lower, though not statistically significantly so, than the 56% in the control group ($p = 0.16$). The main reason for this difference appeared to be a higher rate of early treatment discontinuation within the first 8 weeks due to non-compliance or patient request [34]. In a recent paper, Guadagnino et al. [35] showed that patients treated in a multidisciplinary management model had treatment responses not different from those achieved in non-IDU patients. Other, retrospective studies found similar compliance rates and responses to therapy among IDU and non-IDU patients [36]. Treatment compliance rates for IDU in other chronic diseases, such as tuberculosis or HIV [37], are similar to cohorts of non-IDU, and healthcare providers cannot reliably predict patients who are likely to be compliant with the prescribed regimen. Previous studies have indicated that active IDU with CHC infection can achieve an SVR, particularly if they comply with at least two-thirds of their scheduled clinic visits, and are attending a multidisciplinary clinic that includes both hepatologists/internists and specialists in addiction medicine [27–29]. In our study, patients were treated at the same center where they also received opiate maintenance treatment, further assuring compliance with scheduled visits.

Side effects of treatment were common in this study; however, serious side effects leading to premature withdrawal occurred in less than 10% of patients (5 of 67). The side effects did not differ in character or frequency from those of earlier published studies with treatment using pegylated interferon and ribavirin. Serious psychiatric side effects were very rare. This may be due to the fact that patients received antidepressants and/or benzodiazepines as deemed necessary by the treating physician. Overall, at some point during the study, 38% of patients were prescribed antidepressants and 18% benzodiazepines.

Some limitations apply to the results of this study. Although our findings are encouraging, the number of treated patients was small and we did not include a control group of non-IDU patients. We also did not assess why more patients in opiate maintenance treatment programs did not receive HCV treatment. Clearly, there is a selection bias, although the same can be said for treatment studies in non-IDU patients [38]. In a previous screening study among Swiss patients on opiate maintenance treatment, the type and distribution of reasons for nonparticipation of hepatitis C seropositive candidates were assessed using a semistructured questionnaire [39]. In less than half of all candidates, a decision for or against treatment was actually made. The rest had either a negative hepatitis C serology, or other reasons were given for nonparticipation. Some 80% of the reasons for nonparticipation in the treatment study were based on protocol issues. The three most frequent were normal liver values, co-infection with HIV, and negative HCV RNA. These together accounted for nearly half of all protocol-based refusals.

In our earlier study [30], only 6% of all infected patients were eligible for treatment; indeed, a recently published study cited an even lower percentage [6]. Our study is therefore not able to answer the important question of whether treating a larger proportion of HCV infected IDU and using less stringent selection criteria would still be effective and safe. Also, we cannot answer the question as to which elements of addiction treatment programs, which patient characteristics, or what type of collabora-

tion model between hepatologists and physicians prescribing opiates are critical for success. In this context, we should not forget that in Switzerland and several other countries, many patients receive their opiate maintenance treatment through primary care physicians, and that thoughts about collaboration models should include these groups. As do others, we believe that the need for such research is urgent in the view of the high prevalence of HCV infection among this population.

In summary, our results indicate that HCV therapy of patients treated in opiate treatment programs with pegylated interferon-alfa-2a plus ribavirin is feasible, safe and efficacious, with SVR rates similar to those from previous studies in non-IDU patients. Close collaboration between hepatologists/internists and specialists in the treatment of addiction seems to be important, and patients should preferably be treated in a setting where they also receive opiate maintenance treatment. Further community-based studies are required to better define the natural history of the disease, and to determine the safest and most effective treatment regimen for this group of patients. Better strategies should be developed to include more IDU patients in HCV treatment programs. Enhanced collaboration between hepatologists and specialists in treatment of addiction should be encouraged. For that purpose, the allocation of more resources in terms of funding and manpower is an imperative and would allow treatment of larger numbers of IDU patients. Indeed, IDU patients now constitute a large part of the HCV-infected population in most countries of the developed world.

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