Interferon alpha-2a Plus Ribavirin 1,000/1,200 mg versus Interferon alpha-2a Plus Ribavirin 600 mg for Chronic Hepatitis C Infection in Patients on Opiate Maintenance Treatment: An Open-Label Randomized Multicenter Trial

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Abstract

Background: Many intravenous opiate users are infected with hepatitis C virus (HCV) but few are treated. Although this complies with various guidelines, virtually no published evidence supports such a recommendation.

Patients and Methods: In a multicenter study, HCV-infected patients in opiate maintenance treatment programs received interferon plus high- or low-dose ribavirin (1,000/1,200 mg or 600 mg). HIV-coinfected patients were not included. Endpoints were feasibility, efficacy, side effects, and reasons for dropout.

Results: Of the 420 patients who tested positive for HCV, 27 (6%) were enrolled; 393 (94%) either failed to meet the inclusion criteria or refused treatment. Virologic end-of-treatment response was achieved in 12/27 patients, and sustained response in 13/27 (48%). Response depended on viral genotype, not ribavirin dose. The two doses of ribavirin did not differ in their side effects.

Conclusion: In a small fraction of HCV-infected intravenous drug users in an opiate maintenance treatment program, antiviral therapy was feasible, safe, and effective. The success rate was comparable to that achieved in controlled studies that excluded drug users.

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Introduction

Hepatitis C virus (HCV) infection causes chronic hepatitis in approximately 85% of those infected, up to 20% of whom develop cirrhosis as a late sequela [1–3]. Antiviral therapy with standard or pegylated interferon-alpha plus different doses of ribavirin achieves sustained virus elimination in many cases depending on viral genotype [4–8]. HCV infection is particularly common in intravenous drug users. The estimated prevalence is between 60% and near 100%, depending on risk behavior and duration of drug use [9–11]. Yet various national and international guidelines and consensus recommendations have excluded drug users from anti-HCV therapy [12, 13]. The reasons, disputed by some [14], are the following [15]:

- Inadequate compliance by drug users with HCV therapy
- High rate of (mainly psychological) side effects
- High risk of reinfection
- Coinfection with hepatitis B or HIV.
- A proposed alternative is to treat HCV infection only after the drug user has entered successful addiction therapy [16]. To our knowledge, however, only interim data on HCV treatment during opiate maintenance have been published [17].

We conducted a multicenter study of anti-HCV therapy with interferon alpha-2a plus ribavirin in drug users on opiate maintenance treatment in Switzerland. The main objectives were to document the reasons for nontreatment, and to determine the feasibility, efficacy, and safety of HCV

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treatment in an opiate maintenance treatment program. A secondary objective was to compare the side effects and efficacy of high- versus low-dose ribavirin.

Patients and Methods

Centers and Screening

Five centers took part in the study: two Zurich Opiate Consumption Centers (Zürcher Opiat-Konsumlokal [ZOKL]), the ZOKL1 and ZOKL2 drug clinics, operated by the Working Group for Low-Risk Drug Use (Arbeitsgemeinschaft für risikoarmen Umgang mit Drogen [ARUD-Zürich]); Drop-in Zurich; the St. Gallen Cantonal Hospital methadone maintenance unit; and a community practice (PS, Lucerne). The centers offer two forms of opiate maintenance: methadone, with a low threshold for same-day entry (evidence of dependence and claiming two previous withdrawal attempts), and heroin, with high-threshold criteria (maintenance dependent on mandatory weekly consultation). At any one time the five centers maintain some 800 patients on methadone and 100 on heroin.

HCV antibody testing was offered, and in most cases performed, when patients entered the opiate substitution program. Screening for participation in this study was begun not before adherence to opiate mainenance was achieved. None of the patients had signs or symptoms suggesting acute HCV infection during the screening phase.

The study was approved by the local institutional review board and the patients provided their informed written consent.

Inclusion and Exclusion Criteria

The inclusion criteria were age over 18 years, anti-HCV seropositivity, ≥ 50% elevation of transaminases for at least 6 months, positive HCV RNA, written informed consent, hemoglobin > 13 g/dl (women: > 12 g/dl), normal blood glucose or hemoglobin HbA1 ≤ 8.5%, and regular eye examination in diabetics. The exclusion criteria were pregnancy, lactation, intention to become pregnant within 1 year, hemochromatosis, autoimmune hepatitis, hyperthyroidism, life expectancy < 1 year, symptomatic cardiovascular disease, hepatitis B surface antigen positivity, liver disease due to causes other than HCV, other serious disease, HIV infection, creatinine > 150 µmol/l, leukocytes < 2.5×10^3/µl, neutrophils < 1.5×10^3/µl, platelets < 70×10^3/µl, cytostatic chemotherapy, antiviral therapy in the previous 6 months, sexual activity in either sex without adequate contraception, use of a new drug in the previous 6 months, concomitant disease with possible morbidity or mortality during the study, past or ongoing serious neurological disease, uncontrolled psychiatric disease, or any other condition which, in the investigators' opinion, could interfere with analysis of the study endpoints.

Treatment

Antiviral therapy comprised interferon alpha-2a 6 MU sc daily for 28 days, then thrice weekly for another 5 or 11 months (virus genotypes 2 and 3, and 1 and 4, respectively), combined throughout the study with ribavirin, to which patients were randomized at a high or low dose (1,000/1,200 mg depending on body weight, and 600 mg, respectively).

Endpoints

Clinical visits and laboratory investigations were performed 2 and 4 weeks after the start of treatment, then monthly to the end of treatment, with an end of study visit 6 months after completing treatment. Virologic efficacy was assessed at 4 weeks, 28 weeks (end of treatment for virus types 2 and 3), 52 weeks (end of treatment for virus types 1 and 4), and 6 months after completing treatment (also after dropout). Subsidiary endpoints were side effects, which were WHO-graded, dose reductions, treatment interruptions, and dropouts. HCV PCR was measured using COBAS® Amplicor® Monitor HCV RNS 2.0 (Hoffmann-La Roche, Basel, Switzerland), HCV genotyping was performed using INNO-Lipa HCV II (Bayer HealthCare Diagnostika, Fernwald, Germany).

Table 1
Reasons for nonparticipation in the study.

Reasons	N (%)
Patients attending opiate maintenance program	900[a]
Methadone maintenance	800[a]
Heroin maintenance	100[a]
Patients with positive HCV serology	420
Patients asked for study participation	420 (100)
Included	27 (6.4)
Excluded	393 (93.6)
Reasons for exclusion	571 (100)[b]
Protocol exclusion criteria	459 (80.4)
Normal liver enzymes (ALT)	153 (26.8)
HIV coinfection	67 (11.7)
Undetectable HCV (HCV PCR)	57 (10.0)
Poor attendance in opiate treatment program	47 (8.2)
Psychiatric reasons	43 (7.5)
Alcohol consumption > 50 g/d	39 (6.9)
Irregular opiate issue	28 (4.9)
Other (incl. HBs antigen positivity)	25 (4.8)
Patient refusal	112 (19.6)[b]
Afraid of side effects	33 (5.8)
Dislike of blood collection	30 (5.6)
Appointments too frequent	18 (3.6)
Unconvinced by necessity of treatment	11 (1.9)
Dropout from maintenance program	10 (1.8)
Receiving antiviral therapy elsewhere	7 (1.3)
Other (incl. HBs antigen positive)	3 (0.5)

[a] Estimated average (due to fluctuation in the opiate maintenance population); [b] mean 1.45 reasons per patient

Statistics

In the intention-to-treat (ITT) analysis, differences in side effects and efficacy between the high and low doses of ribavirin were assessed using the χ^2 or Fisher's exact test, and those in time on treatment using the log rank test. The 95% confidence intervals (CI) of proportions were calculated as the proportion ± 2 standard errors.

Results

Enrollment and Patient Characteristics

Four centers screened and tested all patients routinely for HCV; of the 420 who were seropositive (seroprevalence: 47%), 27 (6.4%; CI: 3.4%–8.4%) agreed to take part in the study (Table 1). An additional patient was included by the community practice center. Of the total 28 included patients, one female patient was excluded before randomization due to lack of health insurance coverage.

The reasons for nonparticipation totaled 571: 459 (80.4%) were dictated by the protocol (inclusion/exclusion criteria), and 112 (19.6%) by patient choice. The major reasons are shown in table 1. The detailed reasons have been published elsewhere [18].

The population, mean age 32 (20–42) years, comprised 20 men (74%) and seven women (26%). The maintenance opiate was methadone in 23 cases, and heroin in the remainder. 12 patients each (44.5%) were infected with virus genotypes 1 and 2/3, and three (11%) with genotype 4. 11 patients were randomized to the high dose of ribavirin, and 16 to the low dose; these groups did not differ significantly in age, gender or viral genotype (Table 2).

17 patients (63%) completed the study, including nine (33.3%) with no protocol violation. Eight patients (30%) experienced intermittent treatment interruptions or changes in dose due to side effects. The ten dropouts (37%) were due primarily to side effects (n = 6) or treatment failure (n = 3) (Table 3).

Table 2
Patient characteristics at baseline[a].

Characteristics	Interferon + ribavirin 1,000/1,200 mg	Interferon + ribavirin 600 mg
Patients (n)	11	16
Males (n)	8	12
Body weight (mean, kg)	71.3	71.5
Opiate maintenance		
Methadone	9	14
Heroin	2	2
HCV genotype		
1 or 4	6	9
2 or 3	5	7

[a] All intergroup comparisons: no significant differences.

Table 3
Treatment results – n (%).

Results	Interferon + ribavirin 1000/1200 mg	Interferon + ribavirin 600 mg	P-value
Treated patients	11 (100)	16 (100)	
Study completers	7 (64)	10 (62)	NS
6-month follow-up[a]	9 (82)	13 (81)	NS
Protocol compliance			
No violation	4 (36)	5 (31)	NS
Violation	7 (64)	11 (69)	NS
Dropout	4 (36)	6 (37)	NS
Virologic failure	2 (18)	1 (6)	NS
Side effects	2 (18)	4 (25)	NS
Patient choice	0	1 (6)	NS
Virologic response (undetectable HCV RNA)			
4 weeks	8 (73)	10 (62)	NS
End of treatment	6 (54.6)	6 (37.5)	NS
Sustained at 6-month follow-up	6 (54.6)	7 (43.7)	NS
Virologic response of HCV genotype 1 or 4[b]			
Total patients, both arms	15 (100)		
4 weeks	10 (67)		
End of treatment (52 weeks)	3 (20)		
Sustained at 6-month follow-up	3 (20)		
Virologic response of HCV genotype 2 or 3[a]			
Total patients, both arms	12 (100)		NS
4 weeks	8 (67)		NS
End of treatment (24 weeks)	9 (75)		0.014[c]
Sustained at 6-month follow-up	10 (83)		< 0.01[c]

[a] Some 6-month values followed dropout; [b] the small group sizes prevented separate high- versus low-dose analysis; [c] versus types 1 and 4.

Side Effects

Frequent WHO grade 2 to 4 side effects were flu-like syndrome (20/27), gastrointestinal disturbances (10/27), alopecia (7/27), anemia (5/27), granulocytopenia (5/27), and depression (4/27). Frequencies of side effects did not differ significantly between the two ribavirin dose groups (Table 4).

The mean of the maximal hemoglobin decline in comparison to baseline levels was 2.33 g/dl in the ribavirin high-dose group, and 2.1 g/dl in the low-dose group, respectively (not significant; 95 % confidence interval of the difference -1.23 to +0.78 g/dl).

Only 4/11 patients in the high-dose group and 5/16 in the low-dose group managed to undergo therapy without a reduction in dose, interruption in treatment, or withdrawal from the study. Of the six dropouts due to side effects, three were due to granulocytopenia, two to psychological reasons, and one to gastrointestinal disturbances. In two of these dropouts, HCV was still undetectable 6 months after discontinuing therapy despite the short treatment period (12 and 31 days).

Table 4
WHO side effects grades 2 to 4.

	Interferon + ribavirin 1,000/1,200 mg	Interferon + ribavirin 600 mg	P-value
Patients n (%)	11 (100)	16 (100)	
Side effects (n)			
All	40	57	NS
Anemia (< 10 g/dl)*	2	3	NS
Leukopenia (< 800)	1	2	NS
Thrombocytopenia	0	0	NS
Flu-like syndrome	10	11	NS
Pharyngitis	1	1	NS
Dizziness	1	1	NS
Depression	1	3	0.06
Alopecia	3	5	NS

Response Rates

In the ITT analysis, at 4 weeks, 18 patients (67%) were HCV PCR negative; differences in this respect between the high and low doses of ribavirin, and between virus genotypes 2 or 3 and 1 or 4, were nonsignificant. At the end of treatment, 12 patients (44%) had undetectable HCV RNA by PCR (some end-of-treatment PCR missing in cases of early treatment interruption). Six months after completing therapy, this proportion had increased to 13 patients (48%; 95% CI: 29–67%). They comprised 6/11 (54.6%) in the high-dose ribavirin group, and 7/16 (43.8%) in the low-dose group (not significant). Conversely, at this time, the response rates of the group with viral genotype 1 or 4 (3/15 patients; 20%) differed from those with genotype 2 or 3 (9/12 patients; 75%; p = 0.014) (Table 3).

Discussion

This study included only a small fraction, 27/420 (6%), of drug users in opiate maintenance programs who were seropositive for HCV. Nevertheless, in this setting, antiviral therapy with interferon plus ribavirin proved feasible and safe. Efficacy, measured by sustained virus elimination, was 47% across all virus genotypes, i.e. comparable to that achieved using the same therapy in studies requiring cessation of opiate use [5, 7]. Ribavirin dose had no impact on side effect frequency or virologic success. Conversely patients with virus genotypes 2 and 3 had a significantly higher response rate (75%) than those with genotypes 1 and 4 (20%).

Side effects were common in this study, causing dropout in six patients and dose adjustment or treatment interruption in a further eight. The most frequent were flu-like syndrome, gastrointestinal disturbances, alopecia, anemia and granulocytopenia, and depression. Unexpectedly, frequency did not differ between the high and low doses of ribavirin, but the sample size was possibly too small to observe differences.

Side effects were readily differentiated from opiate effects or symptoms associated with opiate withdrawal. The antiviral therapy caused no substantial changes in the opiate maintenance doses. Thus, although blood levels were not measured, pharmacologic interaction appears unlikely.

A strength of the study is that, to our knowledge, it is the first to report HCV treatment of drug users in an opiate maintenance treatment program, along with rates of sustained viral elimination. Antiviral therapy proved feasible, safe, and effective. It achieved a success rate similar to that in nondrug users. The opiate maintenance setting with regular, frequent contact encouraged good compliance in patients normally considered as difficult to treat. Patients received their medication with each opiate issue, namely once to seven times weekly under staff supervision, the rest being take-home doses. Interferon injections were given at the treatment centers on patient request. Concomitant intravenous drug use caused no dropouts from opiate maintenance or antiviral treatment.

The study's main weakness is its small population. Even so, the quality of the data suggests that drug users in a stable opiate maintenance setting can be treated for HCV as successfully as other patient groups, assuming compliance with the inclusion and exclusion criteria. A further weakness is that we did not base the indication for antiviral therapy on liver biopsy.

The study data show that only a tiny fraction of the maintained opiate users qualified for HCV treatment. No HCV serology was available in approximately half the patients attending the opiate treatment centers, for reasons that can only be guessed at. Perhaps blood was not taken because patients did not remain in the opiate substitution program long enough or because their veins were difficult to puncture due to injury associated with their former intravenous drug use. Of the 420 who were seropositive for HCV, only 27 were ultimately treated. Of the reasons for nontreatment, 80% were dictated by the protocol, with physical reasons (HIV coinfection, negative HCV PCR, normal enzymes) far outnumbering psychiatric or addiction-associated reasons (poor attendance, irregular maintenance opiate issue, serious psychiatric comorbidity, alcoholism, benzodiazepine abuse, etc.).

We could not answer some important questions which need to be addressed in future studies, e.g. how often antiviral therapy might be recommended in HCV-infected drug users based on the biopsy histology, how frequent is HCV reinfection, and how education after treatment impacts reinfection risk behavior. Future studies will need to determine whether the pegylated interferons improve results in these patients too.

In summary, the study shows that HCV infection can be treated in a small proportion of drug users, irrespective of possible concomitant intravenous drug use, provided they regularly attend an opiate maintenance program and restrict their alcohol consumption, and provided the drug center possess the requisite know-how. Provided also that the contraindications are complied with, it appears unjustified to withhold HCV therapy on principle from drug users who are not yet fully abstinent. Further studies are required in larger populations using pegylated interferons and ribavirin doses adjusted to body weight. The inclusion and exclusion criteria could also be relaxed, in particular to incorporate the HIV-coinfected patients who were excluded in the present study.

References

1. Marcellin P, Asselah T, Boyer N: Fibrosis and disease progression in hepatitis C. Hepatology 2002; 36: S47–S56.
2. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, Nolt K, Nelson KE, Strathdee SA, Johnson L, Laeyendecker O, Boitnott J, Wilson LE, Vlahov D: The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA 2000; 284; 450–456.
3. Freeman AJ, Dore GJ, Law MG, Thorpe M, Von Overbeck J, Lloyd AR, Marinos G, Kaldor JM: Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology 2001; 34: 809–816.

4. Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, O'Grady J, Reichen J, Diago M, Lin A, Hoffman J, Brunda MJ: Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med 2000; 343; 1666–1672.
5. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK: Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001; 358: 958–965.
6. Lauer GM, Walker BD: Hepatitis C virus infection. N Engl J Med 2001; 345; 41–52.
7. Chander G,Sulkowski MS, Jenckes MW, Torbenson MS, Herlong HF, Bass EB, Gebo KA: Treatment of chronic hepatitis C: a systematic review. Hepatology 2002; 36 (Suppl. 1): S135–S144.
8. Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, Bain V, Heathcote J, Zeuzem S, Trepo C, Albrecht J: Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet 1998; 352: 1426–1432.
9. Broers B, Junet C, Bourquin M, Deglon JJ, Perrin L, Hirschel B: Prevalence and incidence rate of HIV, hepatitis B and C among drug users on methadone maintenance treatment in Geneva between 1988 and 1995. AIDS 1998; 12: 2059–2066.
10. Edlin BR: Prevention and treatment of hepatitis C in injection drug users. Hepatology 2002; 36 (Suppl. 1): S210–S219.
11. Steffen T, Gutzwiller F: [Hepatitis B and C in intravenous drug abusers in Switzerland]. Schweiz Rundsch Med Prax 1999; 88: 1937–1944.
12. EASL International Consensus Conference on hepatitis C. Paris, 26–27 February 1999. Consensus Statement. J Hepatol 1999; 31 (Suppl. 1): 3–8.
13. Management of hepatitis C. National Institutes of Health Consensus Statement. Bethesda: Md. 1997 Mar 24–26; 15: 1–41.
14. Davis GL, Rodrigue JR: Treatment of chronic hepatitis C in active drug users. N Engl J Med 2001; 345: 215–217.
15. Edlin BR, Seal KH, Lorvick J, Kral AH, Ciccarone DH, Moore LD, Lo B: Is it justifiable to withhold treatment for hepatitis C from illicit-drug users? N Engl J Med 2001; 345; 211–215.
16. Backmund M, Meyer K, von Zielonka M, Eichenlaub D: Treatment of hepatitis C infection in injection drug users. Hepatology 2001; 34: 188–193.
17. Sylvestre DL: Treating hepatitis C in methadone maintenance patients: an interim analysis. Drug Alcohol Depend 2002; 67: 117–123.
18. Huber M, Schmid P, Vernazza P, Meili D: Gründe für die ausbleibende Hepatitis C Behandlung bei Drogenabhängigen in Opiatsubstitution. Suchttherapie 2002; 3 (Suppl.): 27–30.