Treatment of hepatitis C viral infections in substance abusers

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Abstract

Aims : **To examine the evidence for excluding chronic hepatitis C (CHC) patients with substance abuse from treatment with interferon (IFN) and ribavirin.**

Methods : **We reviewed clinical trials focussing on the treatment of chronic hepatitis C of patients with substance abuse between 2001 and 2004. Ten clinical trials concerning antiviral treatment in substance abusers were described of which six were controlled ones. There were no randomised trials. There was one controlled multi-centre trial. One trial used pegylated IFN.**

Results : **In the total group of substance abusers the sustained viral response (SVR) and the adherence was not different from control groups. In former drug users, active drug users and patients taking substitution therapy for opioid dependence the sustained viral response and adherence was not different from control populations. However, non-substituted active drug users seemed more likely to be lost to follow-up. Discontinuation of treatment occurred most frequently during the first 8 weeks of therapy. Neurobehavioural changes leading to depression started in the first 8 weeks of treatment. Although follow-up periods after SVR were short, the currently described re-infection rate occurring in active intravenous drug users remains low.**

Conclusions : **There is no evidence to withhold antiviral treatment against HCV in active substance abusers. It seems important to advise to start substitution therapy in non-substituted active drug users, increase substitution therapy dose in substituted patients and treat depression as early as possible. More prospective controlled trials on HCV treatment in active and difficult-to-reach substance users are needed.** (Acta gastroenterol. belg., **2005**, 68, **55-67**).

Key words : chronic hepatitis C, substance abuse, interferon-alpha, substitution therapy, re-infection hepatitis C-natural history, compliance/adherence, treatment response, liver histology, side effect, discontinuation.

Introduction

Chronic hepatitis C constitutes the largest group of chronic liver diseases at this moment. Most new infections occur in substance users (1). Since those patients will become the most numerous patient group with end stage liver disease and therefore frequently candidate for liver transplantation it is important to reduce the number of infections with hepatitis C in (former) substance users (1). However, guidelines supported the restrictive treatment indication for these patients (2,3). Patients with ongoing substance dependence are in many cases excluded from antiviral treatment. However, the reasons for exclusion are frequently not based on evidence from the literature.

Methods

In order to develop evidence-based practice guidelines for the management of chronic hepatitis C in patients infected after substance use, the literature was reviewed. Searching all available Internet guideline clearinghouses Medline, Pub Med, Cochrane Library, Database of abstracts of Reviews of Effectiveness (DARE) registry both the primary terms and the related Mesh's (Medical Subject Headings) were searched for separately. The following limits were used to restrict the search : Hepatitis viral, human, hepatitis A, hepatitis B, hepatitis C, Chronic, microbiology - virology ; prevention & control, substance abuse, substance dependence, substance use disorders, substance addiction, substance abuse treatment centers, drug therapy, interferons, ribavirin, depression, liver transplantation, vaccination ([MESH] 1985 to 2004).

Results

Ten clinical trials concerning antiviral treatment in substance abusers were described of which six were controlled ones. There were no randomised trials. There was one controlled multi-centre trial. One trial used pegylated IFN.

1. *Characteristics of substance users*

Hepatitis C infection is largely more frequent in substance abusers (33-98%) compared to other patient groups (e.g. patients infected after blood transfusion or community acquired). The infected patients may easily infect and re-infect other intravenous drug users (IVDU) and other people. Since 1991, IVDU has been the principal cause of new infections by the hepatitis C virus (1). In the USA alone, it is estimated that 15 million individuals currently use illicit drugs (4). Of these individuals 1-1.5 million inject their drugs (5). It is further estimated that 80-95% of these IVDUs are infected or will

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become infected with HCV (6,8). Transmission occurs through contact with contaminated blood : this is associated with sharing of injecting material and other paraphernalia. The rate of infection is very fast (a few times sharing of contaminated material is sufficient to infect the recipient with a chance of approximately 80% within 1 year). Other risk behaviour such as sexual intercourse and tattooing increases the chance of infection (1,10).

Those patients are not always well informed about the chance of infection : they are young, they are not aware that sharing of material rapidly can cause infection with the hepatitis C virus. Frequently they belong to lower social classes and have a lower education level. Furthermore, they regularly have a lot of financial difficulties and due to illegal drug use they may have a juridical history with repeated moments of imprisonment, frequently living in the same cell with other HCV infected inmates. They don't live in stable social conditions : they move regularly within the same region or from one region to another (7,9). Some have a history of serious psychiatric conditions.

A lot of patients stop using drugs after several years, others die and some persist using drugs and switch from active to incidental drug use. Substitution programs stabilise the patients and may prepare them for later stopping (8-11).

Their interest to abuse substances is correlated with an increased use of *alcohol and smoking*.

Consumption of high amounts of alcohol (> 80 g/d) is present in 1/3 of IVDUs while alcohol intake fastens the evolution of chronic hepatitis C : patients who used more than 50g of alcohol daily have a 34% increased rate of progression of fibrosis over non-drinkers (12). Women are more susceptible than men (13).

IVDU are frequently *co-infected with other hepatitis viruses such as hepatitis A and B*. This can cause a rapid evolution to fulminant liver disease in cases of acute hepatitis A and rapid evolution to end-stage liver disease in the case of chronic liver disease (14). Administration of hepatitis vaccine to HCV patients who are susceptible to hepatitis A and B infection is therefore recommended (14-16).

Only small numbers of HCV positive substance abusers (17) are infected with *HIV*. On the other hand 60 to 90% of drug users infected by HIV are also infected by HCV (16). The co-infection with HIV increases the progression of HCV-related liver disease. The highly active antiretroviral therapies (HAART) have decreased the numbers of death due to HIV (17), but HCV increases the liver toxicity caused by antiretroviral medications.

Substance users are frequently infected with *hepatitis C genotype 2 and 3* : those genotypes are more sensitive to treatment with interferon and ribavirin than the genotypes 1, 4, 5 such as seen more often in other patient groups (18-21).

Information on the *natural history of intravenous substance users infected with hepatitis C* is scarce : 150 substance users who were infected between 1971-75 and who had a mean age of 19 y were taken in follow-up during 25 years : 54% were HCV-RNA-positive, 69% had increased transaminases and 8% developed cirrhosis. One patient died from liver insufficiency (21). In another study, after 8.8 years 40 of 1667 (2.4%) seropositive users who had a mean duration of infection of 13.7 years developed end stage liver disease. Risk factors were : age at inclusion (> 38 years) and daily alcohol consumption (above 260 g a day) (25). In IVDU, the evolution to end-stage liver disease is estimated to be almost 50 times as frequent as in non- substance users of similar age and sex (21-25).

Since patients infected after intravenous substance use are usually younger, the evolution to end stage liver disease may not be so fast : In younger people the disease does not develop as fast (23-24) as in patients infected after the age of 50 years. They have, however, more remaining time to permit this evolution.

Also *substance-use* itself influences the *life expectancy* of the drug users : In IVDUs without proper follow-up and care, 5 to 35 per 1000 person years will die.

Mortality 24 years after infection has been reported to be 12%. It is due to overdose in 28% of the cases, suicide in 17%, cancers in 17%, cardiovascular diseases in 11%, hepatitis B or C in 11% (25). Mortality sharply drops, however, in patients followed in methadone maintenance programs.

2. *Treatment of substance abusers infected with hepatitis C virus*

Up to now many thousands of patients were reported to be treated after being infected after substance use (26-32). The circumstances concerning substance use in which those patients were treated were not always clearly described.

Since 2001 several studies were performed to estimate *sustained viral response, compliance and characteristics* of substance users, when treated for chronic hepatitis C. Since the population of illicit substance users is not a homogeneous group, it was very important that the different subgroups are studied : former substance users since multiple years, drug users who are in a methadone maintenance program, people who use illicit drugs on a regular basis and active substance users injecting illicit drugs (33-42).

The studies (33-42) mentioned in table 1-4 all dealt with the treatment of patients infected with hepatitis C after IVDU. In total, almost thousand patients were described. However, the study population differed a lot between all the study groups : One study only observed inactive IVDU (34). One study (33) followed patients who recently stopped IVDU and started a detoxification program. Eighty percent of the patients relapsed to IVDU. Thirty percent were admitted to a substitution maintenance program after relapse. Two studies (35,40) followed patients in a methadone maintenance program : the patients seemed to be stable and were excluded when

Table 1. — **General baseline characteristics among patients with substance abuse treated for chronic HCV infection**

	Study design	*Population*	*N total(m/f)*	*Age(y)*	*ALAT (IU/l)*	*Fibrosis*	*Viral* (Genotype) (%)	*Duration of infection (y)*
Backmund, 2001 (33)	open, uncontrolled, prospective	Opiate-dependent patients admitted to a detoxification unit.	50 (33/17)	32.5 (19-48)	68.4	No data	genotype 1 : 27 genotype 2/3 : 23	No data
Jowett, 2001 (34)	retrospective	Non-active IVDU	50			9% of the screened patients : cirrhosis	No data	No data
Sylvestre, 2002 (35)	open, uncontrolled, prospective	Included in a MMT program (no active drug use and/ or alcohol abuse)	50 (26/24)	50 (32-66)	55	38% fibrosis (liver biopsy) 22% cirrhosis (baseline platelet count of less than 100 000)	Genotype1 :52% Genotype non-1 : 48%	30 (4 to 50)
Dalgard, 2002 (36)	Controlled with 5 years follow-up	IVDU vs controls	69 (49/20) 47 (34/13)	32 35	No data	1% had cirrhosis 6% had cirrhosis	genotype 1 : 29 genotype 2 :12 genotype 3 : 49 genotype 4 : 1 unknown : 9 genotype 1 : 38 genotype 2 : 11 genotype 3 : 40 genotype 4 : 0 unknown : 11	
Neri, 2002 (37)	open, controlled, prospective	Heroin users vs. controls	47 (47/0) 30 (30/0)	26 ± 3 27 ± 2	94 ± 6 114 ± 4	< 2 according to Knodell's numerical score < 2	genotype 1b : 100 genotype 1b : 100	
Schaefer, 2003 (38)	open, controlled, prospective	methadone vs. former IVDU *vs. controls* *vs. psychiatric disorders*	21 (14/7) 21 (16/5)	34 ± 9 36 ± 7	79 ± 52 91 ± 55	10% 14%	genotype 1 : 28 genotype 2 : 10 genotype 3 : 62 genotype 4 : 0 genotype 1 : 43 genotype 2 : 10 genotype 3 : 43 genotype 4 : 4	
Van Thiel, 2003 (39)	open, controlled, retrospective	IVDU : History of recent (within 6 months) or current i.v. drug abuse (defined as the use of illegal drugs), Matched control group (without a history of IVDU)	120 (79/41) vs. 120 (79/41)	43 ± 6.7 vs. 43 ± 7.1	96.6 ± 76.6 vs. 92.4 ± 90.1	24% had cirrhosis vs. 16% had cirrhosis	Genotype 1a or 1b :86% Other genotype : 14% vs. Genotype 1a or 1b : 84% Other genotype : 16%	No data
Mauss, 2004 (40)	prospective	On stable MMT. Vs. Control group (no history of IVDU, illicit drug use, or opioid maintenance	50 (44/6)	35 (22-50)	ALAT 39 IU/L	No data	Genotype 1 or 4 : 58% Genotype 2 or 3 : 42%	No data

Table 1. — **Continuation**

		therapy for ≤ 5 years)	50 (44/6)	40 (23-53)	ALAT 48 IU/L		Genotype 1 or 4 : 58% Genotype 2 or 3 : 42%	
Cournot, 2004 (41)	open, controlled, prospective	IVDU (27% active IVDU followed for 2.5 ± 1 years) ; *non IVDU control group*	NS-AIVDU :41 S-AIVDU :75 EX-AIVDU : 109 NON-AIVDU : 210	NS-AIVDU :29 S-AIVDU :30 EX-AIVDU :34 NON-AIVDU : 53	81% elevated transaminases	7.4% F4 score in IVDU 22.6% in non IVDU	genotype 1 : 56 genotype 2 : 2 genotype 3 : 40 genotype 4 : 3	NS-AIVDU :9 S-AIVDU :10 EX-AIVDU :13 NON-AIVDU : 15
Robaeys, 2003 (42)	open, controlled, retrospective, multi centre	former IVDU, MMT IVDU, active IVDU ; *non IVDU Control group*	98 (81/17)	37.8 ± 9.3		8,4% had cirrhosis (no difference between subgroups) Controls : 12.8%	IVDU genotype 1 : 45 genotype 3 : 44 controls : genotype 1 : 77 genotype 3 : 8	No data

MMT = methadone maintenance therapy

NS-AIVDU : non substituted active intravenous drug user
S-AIVDU : substituted active intravenous drug user
EX-AIVDU : ex active intravenous drug user
NON-AIVDU : non active intravenous drug user.

actively using drugs. Mauss *et al.* (40), made a comparison with a non drug using group. Van Thiel *et al.* (39) studied substance users with a history of recent (within 6 months) or current i.v. substance abuse (defined as the use of illegal drugs). Robaeys *et al.* (42) compared the compliance and effect of treatment in different substance user populations [former IVDU, IVDU in a Methadone Maintenance Treatment (MMT), active IVDU] with a control group consisting of non IVDU. Cournot (41) did not exclude substance users actively abusing drugs from the start and treated a lot of patients not substituted for opioid dependence. Schaefer compared IVDU with patients with a psychiatric history (38).

The drugs most frequently used by the IVDU were heroin and cocaine (table 2). In most studies about 25% of the patients were active substance users. The amount used seemed rather low (36% cocaine on a weekly basis). Other drugs (particularly amphetamines) were occasionally used. Sixty-two percent had a benzodiazepine dependency. In at least three studies non-active substance users were included (34-36). About 20-80% of the patients (ab-) used a large amount of *alcohol* (table 2). Twenty to 65% of the patients who were using substances were treated in a *substitution program* (methadone, buprenorphine or another opioid maintenance program). Subjects followed in a MMT used a mean dose of 55 to 60 mg of methadone (33,35,37,38, 39,41 and 42). Thirty-seven to 62% reported a history of psychiatric disorder (mostly depression : 46% on average) (35,38,39).

Patients were *aged* from 26 to 40 years at the start of antiviral treatment (table 1). In one study concerning patients who were stable in a MMT the age was higher (50 years) (35).

The Metavir activity scores in *liver biopsies* of substance abusers were comparable to activity scores in patients contaminated by another transmission mode (41,42). In studies with a higher mean age of the patients, cirrhosis was more frequent (35,39). In other studies the prevalence of cirrhosis was lower : 7-14% (34,38,41,42). The prevalence was similar to the non substance users (42) or lower (41).

Eight to 56 percent of the patients received psychiatric medication at the start of treatment (35,38,40).

Patients were treated with the *treatment schedule* which was appropriate at that moment : interferon monotherapy in early years (32,33,34,37,39), the combination of interferon and ribavirin (33,34,35,42) or peginterferon in combination with ribavirin (40) (table 3).

Compliance was high : 78 (35) to more than 90% (42) of the patients completed the study. In one study seventy-eight percent missed none of the interferon injections up to the end of treatment (33). Seventy-six to 93% came to more than two thirds of all appointments (33,42). Active substance use itself did not decrease compliance (38,41,42). However, active substance users non-substituted for opioid dependence were significantly more frequently lost to follow-up during antiviral therapy (41). One third of the patients were lost to follow-up during the first 8 weeks of treatment. This occurred especially in the patient group infected after substance abuse (37).

The *sustained viral response (SVR)* to interferon therapy in substance users varied in the different studies from 24 tot 48% (table 3). In the peginterferon treated patients SVR was 42% (40). In the controlled studies there was no difference in SVR versus the control groups (36,39,40,41,42). The numbers are comparable

Table 2. — **Characteristics concerning substance use and psychiatric history of patients with substance abuse treated for chronic HCV infection**

	Drug use	*Methadone use*	*Alcohol consumption*	*History of psychiatric diagnosis*	*Receiving psychiatric medications at the start*
Backmund, 2001 (33)	Opiate dependent-36% cocaine on a weekly basis, 62% benzodiazepine dependency	Inpatient detoxification lasted on average 28 days.	44% drank alcohol daily ; of these, 26% met the current lCD-I0 criteria for alcohol dependency. 65% consumed no alcohol at all ;	No data	No data
Jowett, 2001 (34)	Relapse in intravenous drug misuse before treatment was an exclusion criterion	At presentation, before referral for treatment 43% was on MMT	No data	No data	No data
Sylvestre, 2002 (35)	Drug-free 2 y (6 months-11 years)	60 mg (20-100 mg).	Heavy alcohol consumption : 0-43 years (median : 5 years)	62% reporting : 46% depression, 12% anxiety, 2% obsessive compulsive disease, 2% schizophrenia	56% were receiving psychiatric medications at the start of treatment (SSRI's : 29%, benzodiazepines : 25%).
Dalgard, 2002 (36)	All IVDUs had stated discontinuation of illicit drug use at least 6 months before initiation of IFN-α treatment	No data	No data	No data	No data
Neri, 2002 (37)	47 patients with heroin abuse. HCV treatment was initiated shortly after detoxification treatment over 2-4 weeks with methadone	No data	No history of alcoholism and/or addictions to other substances (benzodiazepines, cocaine)	No data	No data
Schaefer, 2003 (38)	Drugs most frequently used : heroin cocaine, Drugs occasionally used : amphetamines.	 Methadone 1 (5%) Mean dosage before treatment was 57 m/d (6-160) mg/d) Former : 0 (0%)	 Methadone : 8 (38%) Former : 7 (33%)	History of depression Methadone : 3 (10%) Former : 0	 Methadone : 1 (5%) Former : 0
Van Thiel, 2003 (39)	Recent or current i.v. drug abuse	20% using methadone	85% of alcohol use	37% had a history of psychiatric disorder	
Mauss, 2004 (40)	27% active IVDU followed for 2.5 ± 1 years	Duration : 21 m ; daily dose : 55 (6-140)	No data	No data	treated with antidepressants At baseline, 8% methadone patients and 4% control patients : (p = .68).
Cournot, 2004 (41)	During treatment : 76% non-active IVDU 24% active IVDU	65% substitution therapy : buprenorohine : 78%, methadone : 15%, another opioid : 7%	Before treatment : daily intake >= 40 g : 40% (two-fold higher versus non IVDU) ; during treatment : 10% in different subgroups (substituted non-substituted active, non-active IVDU)	No data	No data
Robaeys, 2003 (42)	24% active IVDU during therapy	24% in MMT during therapy	19%	No data	No data

Table 3. — **Treatment modalities and response among patients with substance abuse and chronic hepatitis C**

	Treatment	Compliance	EOT	SVR	Genotype	Inpatient program – Drug free at home
Backmund, 2001 (33)	68% patients : interferon alfa-2a alone, 32% patients : interferon alfa-2a and ribavirin	78% patients missed none of the interferon injections up to the end of treatment 76% came more than two thirds of all appointments	No data	36%	SVR : 26% of patients with genotype la or 1b and 48% of patients with genotype 2 or 3, and 26% of patients with genotype la or 1b, had cleared HCV RNA 24 weeks after the end of treatment.	The inpatient detoxification lasted on average 28 days -11 patients underwent inpatient treatment for 14 days or less -9 patients for more than 40 days.
Jowett, 2001 (34)	multiple treatment regimens : alpha-IFN monotherapy, combination treatment alpha-IFN and ribavirin, alpha-IFN and amantadine ; peg-IFN	Patients did not attend in 30% of appointments. Six percent of new referrals did never attend any clinic.	No data	36%	No data	SVR : - Patients predominantly treated in an inpatient abstinence program : 20% - - living drug free at home 60%.
Sylvestre,2002 (35)	IFN + ribavirin genotype non1 : 24W genotype 1 : 46W	78% completed treatment	54%	No data	EOT : -36% of patients with genotype 1 -70% of non-genotype 1 patients.	
Dalgard, 2002 (36)	IFN-alpha- 2a 6 MU t.i.w. for 3 months followed by 3 MU 3TIW for 6 months ; non responders were offered a second treatment (IFN-A 4.5M TIW for 6 months alone or in combination with ribavirin ; 9 patients received a third treatment (IFN-A and ribavirin)	83%	No data	39%	No data	No data
Neri, 2002 (37)	Standard IFN-alpha-2b (5mU daily) over a period of 8 weeks. In the case of virological clearance (HCV PCR negative), treatment was continued for another 48 weeks with 5mU IFN-alpha-2b three times a week (tiw).	adherence : 64%	*virological clearance at week 8* analysed per protocol -heroin users : 90% -controls : 83.3% time to viral relapse (weeks) -heroin users 53 -controls 26	No data	No data	

Table 3. — **Continuation**

Schaefer, 2003 (38)	IFN-alpha-2a 3mU t.i.w. plus ribavirin 1000-1200 mg daily	Non compliance Methadone : 14% former IVDUs : 13% controls : 9%	No data	Methadone : 48% former IVDUs : 24% controls : 35%	Data in reference	
Van Thiel, 2003 (39)	5 million units of IFN/day for a minimum of 1 yr (nonresponders) or until 15 consecutive months of HCV-RNA indetectability in the serum had elapsed (responders)	Compliance with the study : > 90% ; 85% completed the study	No data	IVDU : 33% vs. controls : 37%	No data	No data
Mauss, 2004 (40)	Pegylated interferon a-2b (1.5 mg/kg body weight) + ribavirin dosed at 1000mg (< 75 kg body weight) and 1200 mg (> 75 kg body weight) during : 48 weeks for patients with HCV genotypes 1 and 4 and 24 weeks for HCV genotypes 2 and 3.	-methadone group : 25 or 50 (50%) prematurely discontinued interferon-based -control group : 12 of 50 (24%) (p = 0.01).	-methadone arm : 25/ 50 (50%) ; - Control group : 38/50 (76%) (p = 0.01)	- Methadone arm : 21/ 50 (42%) - Controls : 28 of 50 (56%) (p = 0.16)	SVR : -methadone arm : genotype 1 or 4 : 38% genotype 2 or 3 : 48% - controls : genotype 1 or 4 : 55% genotype 2 or 3 : 57%	No data
Cournot, 2004 (41)	No data	Lost to follow-up : NS-AIVDU : 26% S-AIVDU : 6.5% EX-AIVDU : 14 % NON-AIVDU : 6%	No data	NS-AIVDU : 16% S-AIVDU : 35% EX-IVDU : 6.5% NON-IVDU : 14.4%	Genotype is associated with SVR	No data
Robaeys, 2003 (42)	During 8 weeks (group A) as compared to interferon alpha 2b at 5MU SC thrice weekly (group B) followed by the standard dose of interferon alpha 2b (3MU thrice a week) in previously untreated chronic hepatitis C patients. In both groups, ribavirin was added at week 5, twice daily at a total dose of 1000 or 1200 mg for patients whose weight was less or more than 75 kg, respectively.	IVDU : 93,8% active IVDU : 100% ; non-IVDU : 93,2%	IVDU : 61.1% active IVDU : 48.0% non-IVDU : 48.4% IVDU : 46.6% active IVDU : 31% non-IVDU : 34.6%	IVDU : 46.6% active IVDU : 31% non-IVDU : 34.6% 33% in MMT program and 43% in patients not using methadone 14% in patients abusing alcohol and 52% in patients not abusing alcohol	IVDU -Genotype 1 : 29.4 -genotype non-1 : 65.6 Controls -Genotype 1 : 28.6 -genotype non-1 : 53.8	No data

Table 4. — **Side effects and secondary effects during interferon treatment among patients with substance abuse en chronic hepatitis C viral infection**

	Side effects	Relapse in substance use	Methadone dose	Psychiatric medications	Discontinuation of treatment	Reinfection
Backmund, 2001 (33)	2% hair loss, 4% severe depression, 2% pancreatitis, 2% weight loss of 20%. 92% flu-like syndrome after the first injection which, after the third injection, was no longer deemed so severe. 10% : light to moderately depressive moods. 18% : flu-like syndrome persisting for more than 5 days. 4% : ribavirin treatment had to be interrupted when haemoglobin levels fell to less than 8 g/l.	After leaving inpatient detoxification treatment, 80% of patients had one or more drug relapses : 30% were admitted to a substitution maintenance program after relapse, with a sustained response in 53%. Of the 50% who were injecting drugs again (predominantly heroin), 24% showed a sustained response.	No data	No data	The therapy was terminated in 10% patients because of the magnitude of side effects.	None of the patients became re-infected although 56% (10/18) patients had relapsed and injected heroin intravenously for periods ranging from 4-140 days.
Jowett, 2001 (34)	82% : minor side-effects : lethargy, myalgia, headache and weight loss,	No data	No data	No data	18% who initially responded at 3 months stopped treatment prematurely : side-effects : profound neutropenia and depression	No data
Sylvestre,2002 (35)	-78% : Fatigue -70% : depression/ irritability -54% : nausea -38%. : flu-like symptoms Side effects were generally mild and conservatively managed	No data	42% of subjects raised their methadone dose by a median of 10 mg during therapy	88% of treated patients were taking antidepressants by the end of treatment period. 62% received a new psychiatric medication during treatment ; 32% had not been taking psychiatric medications at the start of treatment. SSRI's were the most commonly prescribed medication during treatment, in 68% of patients. Overall, 88% were taking a psychiatric medication by the end of treatment	27% : due to medication side effects 27% due to worsening of psychiatric disease 27% due to decompensating liver disease 9% due to alcohol abuse. 73% discontinuing treatment had a pre-existing psychiatric diagnosis, a disease rate not significantly different from that in the total sample.	No data
Dalgard, 2002 (36)		After treatment : return to injecting drug use in 33% of IVDUs ; 50% in IVDUs who had injected more than 100 times before treatment as compared to 9% who had injected less than 100 times ($p = 0.049$)	No data	No data	Early cessation of treatment was seen in 17% of IVDUs and 6% of non IVDUs ($p = 0.08$)	In 1/27 IVDU (3.7%) before genotype 1a and after genotype 1b

Table 4. — **Continuation**

Neri, 2002 (37)	11% flu-like symptoms 6% severe depression	No data	No data	No data	31% discontinued treatment early (Non-compliance, side effects).	No data
Schaefer, 2003 (38)	Diarrhea was significantly more frequent in the methadone group compared with the former addiction group and control group. In those with former addiction, itching.was rare but coughing was frequent vs. patients in the psychiatric group). Fatigue differed significantly only between patients in the methadone and former addiction groups. Hyperthyroidism in patients in the psychiatric group and pneumonia in one patient in the methadone group were treated successfully.	- methadone 0% - former IVDUs 10%	Methadone dosage increased slightly to 59 mg/d (0-170 mg/d) at the end of treatment. 38% of patients were kept on stable dosage. The dosage was increased in 38% and decreased in 24%. Methadone : 5 (24%) Former 2 (10%)	- methadone 62% - former IVDUs 24%	In 43% of patients in the former addiction group *(P* < .01 vs. patients in the control and psychiatric groups), treatment was terminated prematurely because of non-compliance (13%), depression (5%), suicidal thoughts (5%), relapse in alcohol or drug abuse (10%), or somatic side effects (10%). The dropout rate was highest during the first 2 months of therapy.	
Van Thiel, 2003 (39)	The type and frequency of IFN associated side effects were similar for the two groups. The major side effect was fatigue, a lack of psychic energy or inertia. Weight loss : common (often amounted to 10–15% of the subjects' initial weight).	No data	Several more patients started methadone use while on IFN therapy in an effort to combat the side effects. Most patients either did not change their dose of actually had it increased by 10-15 mg/day.	No data	No data	No data
Mauss, 2004 (40)		no patients in the methadone group returned to using intravenous drugs	Methadone patients who completed interferon-based therapy did not increase the median daily methadone dose during interferon-based therapy (55 mg/day vs.50 mg/ day). In these patients, 24 weeks post-therapy, the median methadone dose (20 mg/day) was lower compared to baseline (55 mg/ day).	treated with antidepressants At baseline, 8% methadone patients and 4% control patients : (P = .68). During interferon-based therapy, 30% methadone patients and 20% control patients (p = 0.36). At the end of follow-up, 6% methadone patients and 8% control patients (p = 1.00).	50% prematurely discontinued interferon-based therapy in the methadone group. Vs. 24% in the control group (P = .01).	No data

Table 4. — **Continuation**

Cournot, 2004 (41)	Interruption for adverse effect : NS-AIVDU : 0% S-AIVDU : 3% EX-AIVDU : 2% NON-AIVDU : 9%	No data	No data	No data	lost to follow-up -NS-IVDU : 26.3% -SA-IVDU : 6.5% -EX-IVDU : 14.% -non IVDU : 5.8%	in 1 patient (7%) after SVR
Robaeys, 2003 (42)	No data	No data	46% increased methadone dosage during therapy	No data		No data

to SVR measured in the reference trials for treatment of chronic hepatitis C (27-30,32).

SVR was significantly lower in the genotype 1 group in comparison with patients with genotype 2 or 3 (33,35,38,40,41,42). SVR was also lower in cirrhotic patients (35,39,41). This was not confirmed in the Benelux population (42) (table 3).

The SVR in patients on substitution therapy (table 3) was not different from control patients. (38,40,41,42). However, SVR was significantly lower in non-substituted active substance users (41) in comparison with substituted drug users. Substitution therapy stabilises the patient and may increase adherence to therapy. Former substance users had a similar SVR in comparison to other patients groups (37,41,42) although this was not found in all studies (38).

SVR was not significantly different in patients who relapsed to drug use and subsequently returned to treatment (53%), from those who relapsed and did not return to treatment (24%), or did not relapse (40%) (33). Patients with a history of drug use had a similar SVR rate (41). Of those patients, 20% were using methadone at study entry (39).

According to Sylvestre (43) the use of drugs possibly influences the response to treatment : The impact of sobriety length (43) on treatment outcomes showed that even minimal periods of sobriety were protective. Patients with sobriety lengths of less than six months exhibited virological responses similar to those with lengthier sobriety, 37% vs. 30%, respectively. This similarity in treatment outcome is confirmed in other studies (37). However, patients without pretreatment drug sobriety at all showed a decrement in treatment outcome, with an overall SVR of 17% (43).

Patients using heroin, cocaine and / or methamphetamines during HCV treatment, showed a SVR of 20%, compared with 32% in abstinent patients. When analyzed by quantity of drug use, a stepwise decrement in treatment outcome was seen, with the most dramatic effect of this behavior seen in those using drugs regularly. None of those patients had a virological response, whereas 20% to 29% of those using drugs less frequently showed a sustained virological response (43).

Employed patients, patients in inpatient programs or who are living drug-free at home have significantly higher SVR (respectively 67% vs. 29% and 60% vs. 20%) (33).

Side effects are frequent during treatment with interferon and ribavirin (27-31). Most frequently flu-like symptoms (fatigue, myalgia in around 60%), weight decrease (in around 30%), gastrointestinal symptoms, psychiatric symptoms (depression in around 30% of the patients), respiratory symptoms and dermatological symptoms are noticed. In IVDU the same side effects were noticed (33,34,35,38,40). No difference in type or frequency of interferon-associated side effects was seen in comparison with non-IVDUs (39). The major side effect was fatigue, followed closely by a lack of psychic energy or inertia. Weight loss was common and often amounted to 10-15% of the subjects' initial weight (39). Side effects were generally mild and conservatively managed (35). The alanine aminotransferase profile did not differ between methadone patients and controls. The decrease in leukocytes, platelets, and haemoglobin was comparable in both groups (40).

During interferon treatment, depression and suicidal ideation occurred independently from pre-existing psychiatric disorders or drug dependence (38). Psychiatric co morbidity did not influence response to treatment (39). No significant differences in the frequency and severity of psychiatric side-effects were noted between methadone substitution and patients with psychiatric disorders. Most drug relapses occurred during the first two treatment months (38). Also Wichers *et al.* (44,45) found no difference in depression between substance abusers and non-substance abusers. Moreover, depression scores as Montgomery Asberg Depression Rating Scale showed a first sharp increase which attenuated approximately after 8 weeks of treatment. Furthermore, first week increase in vegetative-depressive symptoms was predictive of cognitive-depressive symptoms at week 8 and week 24 (44,45). When antidepressants were started effectively during interferon therapy no patient in the methadone group returned to using intravenous drugs or did increase the median daily methadone dose (40).

Discontinuation rate of treatment was low in several studies (10-27%) (33,34,35,36). However, it was high in a MMT study with subjects not using drugs anymore (40) : In total 50% discontinued prematurely their

interferon-based therapy in the methadone group, compared to 24% in the control group (a value similar to that reported by the registration trials for interferon and ribavirin trials). This difference was driven by the discontinuation rate - mainly due to non compliance or patient request - during the first 8 weeks of therapy : 22% in the methadone group versus 4% in the control group. Methadone patients who discontinued during the first 8 weeks of therapy showed no specific HCV-genotype pattern. After the first 8 weeks of therapy, there was no significant difference in discontinuation rate due to non-compliance or patient request.

Discontinuation as a consequence of adverse treatment effects or viral treatment failure did not differ between the treatment groups : MMT patients (20%) versus control (10%). In the methadone group, 4 patients discontinued the treatment due to adverse weight loss, impaired renal clearance, anaemia, and alcohol abuse. In the control group, 2 patients had to discontinue treatment because of adverse events (hypothyroidism, first manifestation of multiple sclerosis) (40). The overall dropout rate was reported similar to that reported by the registration trials for interferon and ribavirin trials (24%).

In a first study on MMT patients without IVDU 56% were receiving *psychiatric* medications at the start of treatment ; of these, the most commonly prescribed medications were SSRI's (29%) and benzodiazepines (25%) (35). Sixty-two percent received a new psychiatric medication during treatment ; 32% had not been taking psychiatric medications at the start of treatment. SSRI's were the most commonly prescribed medication during treatment, in 68% of patients. Overall, 88% were taking a psychiatric medication by the end of treatment (35). According to a second MMT study (40), there was no difference between MMT and a control group in consumption of psychiatric medication. However, the number of patients treated with psychiatric medications was clearly lower. In the first study methadone dosis was increased during antiviral therapy. This was not the case in the second study, in which there was a high rate of discontinuation. On the other hand, there was no relapse in drug use. It can be suggested from this that it is important to treat psychiatric changes carefully in order to prevent discontinuation of treatment. Neurobehavioural changes leading to depression start in the first weeks of treatment (44,45).

Some patients raised *methadone dose* during therapy whereas others did not (35,38,39,40,42). As usual, also during antiviral therapy methadone should be titrated according to the complaints of the patients : this stabilizes the patients. It prevents psychiatric side effects. The drop out ratio is four times higher in non-substituted active IVDUs, decreasing the SVR in those patients (41).

Alcohol might influence the response to treatment. Ongoing alcohol consumption decreases the rate of treatment response in hepatitis C. Twenty-one percent of treated patients consumed alcohol of any quantity during HCV therapy, and SVR were similar, 29% in the abstinent group and 25% in those using alcohol. Because of the low number of patients in the alcohol group, a sub analysis of the effect of alcohol quantity could not be undertaken (35). Alcohol abuse seemed to decrease the proportion of patients who develop a SVR : only 14% in patients abusing alcohol while 52% in patients not abusing alcohol (42). However, a combined weaning for alcohol and substances decreased the use of alcohol during antiviral therapy to a level not different anymore from the control group (43).

The studies differ quite markedly according to the *ethnic mix of patients* included in each study. The Baltimore (39) group was predominantly African American ; the San Francisco group (35) was more evenly distributed between white and African American populations ; and the Chicago group was predominantly white (39). Only the German (33) and Benelux (42) study included a homogenous population. There were no data on this in the UK (34) and another German study (40). African Americans develop a lower SVR.

Re-infection after SVR in active IVDU ?

Backmund *et al.* (33) saw no re-infections during a 24-wk follow-up period (after 4-140 days) in 18 patients they followed after successful viral clearance, although 56% (10/18) of the patients returned to intravenously injected heroin. Also, after a median of 64 (13-82) months Dalgard *et al.* (36) saw only 1 case (3%) of probable re-infection on 27 former IVDUs who had been successfully treated for chronic hepatitis C. This probably resulted from re-infection since originally the patient was infected with a genotype 1b before treatment and at follow-up a genotype 1a was present. A return to injecting drug use occurred in 9/27 (33%) of IVDUs. They frequently shared needles. Also Cournot saw only in one patient (7%) re-infection after sustained viral response (41).

Asselah *et al.* (46) described the first patient who was re-infected by another genotype of hepatitis C virus during interferon therapy. The patient did not develop chronic hepatitis. This may be due to protection from the first infection or result from the treatment of interferon.

The risk of developing chronic hepatitis by re-infection after SVR seems to be lower. This may be caused by safer injection routines in experienced IVDU or due to a partial protective immunity (47,48).

3. *Methods to raise the effect of treatment in IVDU*

Only 35% of the patients develop sustained viral response. Therefore, it is very important to increase the prevention, to decrease the chance of re-infection. It is not clear either that the information we have from trials is representative for the clearance of the virus in patients not included in trials.

At this moment the available information comes from patients included in trials. Only a small part of the patients present themselves for treatment. In England only 50 out of 100 (50%) patients in whom antiviral therapy was indicated, started treatment (49). In Poitou-Charentes only 13% of illegible IVDUs have received a treatment in the 6 months following diagnosis. In a recent study in France (50) a small proportion of patients were effectively treated : of the illegible 404 patients only 66% could be screened with serology. Of those 225 less than 60% could be screened for HCV-RNA. Out of 120 patients who had an indication for liver biopsy, 88 accepted to perform a liver biopsy. Out of the 47 patients who were suitable for therapy (fibrosis scale more than F2) 27 really started therapy, 15 patients ended the therapy, 5 patients had a sustained viral response.

To increase the availability of treatment a lot of effective strategies for improving adherence are available : information about intended effects and side effects of medication, attention to perceived side effects, respectful and nurturing provider-patient relationship, devices (pager reminders, pill organizer boxes), treatment of depression when appropriate, multidisciplinary collaboration between all professionals in caring for the patient.

It is also very important to warn about hepatitis C infection risks by drug use, the chance of co-infection with other viruses, the “terrible” effect of alcohol and drug intake, the chance of re-infection by needle sharing. Patients should be encouraged to reduce injection drug use (1,7,9-11).

Conclusions

For patients in stable, long-term recovery, including those receiving methadone maintenance therapies, there is no reason to withhold hepatitis C treatment because of a past history of illicit drug use. For active drug users, adherence, psychological side effects, and the possibility of re-infection may present challenges to effective treatment. Those patients have to be advised and referred to start a substitution therapy. Their social situation needs to be stabilised as well before interferon treatment can be started. Decisions about antiviral treatment should be made by a multidisciplinary treatment team together with the patient based on individualized risk-benefit assessments.

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