Adherence and Mental Side Effects During Hepatitis C Treatment With Interferon Alfa and Ribavirin in Psychiatric Risk Groups

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Psychiatric disorders or drug addiction are often regarded as contraindications against the use of interferon alfa (IFN-α) in patients with chronic hepatitis C. Our aim was to obtain prospective data on adherence to as well as efficacy and mental side effects of treatment with IFN-α in different psychiatric risk groups compared with controls. In a prospective trial, 81 patients with chronic hepatitis C (positive hepatitis C virus [HCV] RNA and elevated alanine aminotransferase [ALT] level) and psychiatric disorders (n = 16), methadone substitution (n = 21), former drug addiction (n = 21), or controls without a psychiatric history or drug addiction (n = 23) were treated with a combination of IFN-α-2a 3 MU 3 times weekly and ribavirin (1,000-1,200 mg/d). Sustained virologic response (overall, 37%) did not differ significantly between subgroups. No significant differences between groups were detected with respect to IFN-α–related development of depressions during treatment. However, in the psychiatric group, significantly more patients received antidepressants before and during treatment with IFN-α ($P < .001$). Most of those who dropped out of the study were patients with former drug addiction (43%; $P = .04$) compared with 14% in the methadone group, 13% in the control group, and 18% in the psychiatric group. No patient in the psychiatric group had to discontinue treatment because of psychiatric deterioration. In conclusion, our data do not confirm the supposed increased risk for IFN-α–induced mental side effects and dropouts in psychiatric patients if interdisciplinary care and antidepressant treatment are available. Preexisting psychiatric disorders or present methadone substitution should no longer be regarded as contraindications to treatment of chronic hepatitis C with IFN-α and ribavirin in an interdisciplinary setting. (HEPATOLOGY 2003;37:443-451.)

Worldwide, 170 million people are estimated to be chronically infected with hepatitis C virus (HCV). The prevalence in the United States and western Europe ranges between 1% and 2.4%.[1,2]

Chronic HCV infection is the leading cause of chronic liver disease, including cirrhosis and cancer, and the most common indication for liver transplantation.[3] Interferon alfa (IFN-α) was the first effective treatment of this disease, and the combination with ribavirin increased sustained virologic response rates from 10% to more than 40%.[4,5]

The most frequent routes of HCV infection are contaminated human blood products and needle-sharing by individuals with an intravenous drug addiction.[1] Between 36% and 95% of intravenous drug users are infected with HCV before 40 years of age, mostly with genotype 2 and 3.[6-8] Young age and genotype 2 or 3 are regarded as positive predictors of response to IFN-α therapy,[4] but former or current drug use as well as mental disorders are considered risk factors for IFN-α–induced severe psychiatric side effects such as depression, suicidality, or relapse in drug use.[9-12] In particular, reports of suicide attempts during IFN-α therapy and the risk of reinfection led to the

opinion that the use of IFN-α is contraindicated in cases of a preexisting mental disorder, ongoing opiate abuse, and methadone substitution.[3] Consequently, almost 50% of these patients remain untreated even though they fulfill the medical criteria for antiviral treatment of chronic hepatitis C.[13] Paradoxically, the high prevalence of depression in the general population and in former drug users makes it likely that a substantial number of patients with undiagnosed psychiatric disorders receive treatment with IFN-α without psychiatric care.[14-16]

Combination treatment with IFN-α and ribavirin has not yet been evaluated in a controlled manner in psychiatric patients and those with a former drug addiction. We studied compliance with treatment, side effects, response rates, and dropout rates during combination treatment of chronic hepatitis C in patients with psychiatric disorders, former drug addiction, or ongoing methadone substitution compared with controls without a psychiatric history or drug addiction.

Patients and Methods

A total of 93 patients with chronic hepatitis C and a medical indication for combination therapy with IFN-α and ribavirin were considered for this study between 1998 and 2000. Patients from the outpatient Department of Psychiatry or Gastroenterology of the University of Munich as well as inpatients with elevated transaminase levels were tested for HCV infection and considered for our trial to avoid a positive or negative selection. Medical inclusion criteria were a detectable serum HCV RNA level in a polymerase chain reaction–based assay (AMPLICOR; Roche Diagnostics, Branchburg, NJ) for more than 6 months and an elevated alanine aminotransferase level (ALT >30 U/L; normal, <24 U/L). General exclusion criteria were the presence of other liver disease, Child B or C cirrhosis, severe cardiac or neurologic disease, coinfection with hepatitis B or human immunodeficiency virus, hepatocellular carcinoma evaluated by ultrasonography and α-fetoprotein level, autoimmune disorders, a neutrophil count less than 1,500/mm^3, and a platelet count less than 75,000/mm^3.

After informed consent was obtained, patients were stratified into 4 groups. The first group included patients without a psychiatric history, present psychiatric disorders, or addiction (control group). The second group included patients with a current or preexisting psychiatric disorder. The third group included patients in a methadone substitution program; comorbidity with chronic psychiatric disorders (affective, bipolar, schizoaffective, or schizophrenic disorders) had been excluded. The fourth group included patients with former intravenous drug addiction; exclusion criteria for this group were schizophrenic, schizoaffective, or chronic affective disorder and the abuse of alcohol or drugs within 3 months before the start of treatment.

Psychiatric history and diagnosis was assessed by a structured clinical interview. A present psychiatric illness and the development of depression during treatment were diagnosed by using a semistructured diagnostic interview according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[17,18] Patients were monitored for drug or alcohol abuse for 3 months before treatment was started. Before and during the observation period, urinary drug controls were performed every 4 weeks for heroin, methadone, cocaine, amphetamines, and benzodiazepines. A liver biopsy was recommended when indicated but was not required for inclusion in the study. A total of 47% of the patients agreed to a liver biopsy. The study protocol was approved by the Ethics Committee of the University of Munich, and all patients gave written informed consent.

All patients received IFN-α-2a (Hoffmann-La Roche, Basel, Switzerland) 3 MU 3 times weekly and ribavirin (MEDUNA GmbH, Hanover, Germany) 1,000 to 1,200 mg daily depending on body weight (<75 kg = 1,000 mg). Patients with genotypes 2 and 3 and patients with genotypes 1 or 4 not responding to combination therapy until 6 months of therapy stopped treatment at this time, whereas genotype 1 and 4 responders continued treatment for a total of 1 year. The dosage of ribavirin was adapted when required by anemia and clinical symptoms (minimum dose, 600 mg/d). Patients were trained for subcutaneous self-injection of IFN-α. All patients who discontinued treatment because of somatic or psychiatric reasons or because of noncompliance were considered "dropouts."

All patients were seen by hepatologists and psychiatrists biweekly during the first 8 weeks of treatment and then monthly on an outpatient basis. Mental status was monitored and changes were diagnosed according to DSM-IV criteria. Depressive state before treatment was evaluated to allow differentiation from new depressive episodes or a significant worsening during treatment with IFN-α. According to the number of depressive symptoms, the severity of depressive episodes was classified as mild, moderate, or severe. At each visit, patients were screened by the psychiatrist for suicidal thoughts, irritability, sleeping disturbances, lack of concentration, and craving for drugs or alcohol. These items were evaluated by patient self-reports and clinical interview. Antidepres-

Table 1. Patient Characteristics at Baseline

	Patient Groups					
	All (n = 81)	Control (I) (n = 23)	Psychiatric (II) (n = 16)	Methadone (III) (n = 21)	Former Addiction (IV) (n = 21)	P
Male sex (%)	49 (61)	14 (61)	5 (31)†	14 (67)	16 (76)	.042†
Age (yr)	40 ± 12	48 ± 13	41 ± 13	34 ± 9‡	36 ± 7‡	<.001‡
Naive to IFN-α (%)	68 (84)	19 (83)	13 (81)	18 (86)	18 (86)	NS
Relapse (%)	3 (4)	1 (4)	0	1 (5)	1 (5)	
Nonresponder (%)	10 (12)	3 (13)	3 (19)	2 (10)	2 (10)	
ALT level before treatment (U/L)	74.0 ± 49.1	63.5 ± 42.3	60.3 ± 41.6	78.9 ± 52.2	91.2 ± 55.1	NS
HCV RNA (mio IU/mL)	3.3 ± 6.3	2.4 ± 3.5	1.7 ± 2.5	5.9 ± 9.6	2.9 ± 6.1	NS
HCV genotype (%)						
1	41 (50)	15 (66)	11 (69)	6 (28)§	9 (43)§	.049§
2	7 (9)	3 (13)	0	2 (10)	2 (10)	
3	30 (37)	4 (17)	4 (25)	13 (62)§	9 (43)§	
4	3 (4)	1 (4)	1 (6)	0	1 (4)	
Cirrhosis (Child A) (%)	13 (16)	3 (13)	5 (31)	2 (10)	3 (14)	NS
Unknown* (%)	43 (53)	13 (43)	9 (56)	11 (52)	10 (48)	
Mode of infection (%)						<.001‖
Transfusion	11 (14)	7 (30)‖	4 (25)‖	0 (0)	0 (0)	
Intravenous drugs	43 (53)	0 (0)‖	7 (44)	16 (76)	20 (95)	
Other	8 (10)	4 (17)	2 (13)	2 (10)	0 (0)	
Unknown	19 (23)	12 (52)	3 (18)	3 (14)	1 (5)	

NOTE. Data expressed as n ± SD unless otherwise indicated.
*Patients refused liver puncture.
†Significantly different from the methadone and former addiction groups.
‡Significantly different from controls.
§Significantly different from the control and psychiatric groups.
‖Significant differences between group 1 compared with 2, 3, and 4 and 2 compared with 4.

sant treatment was allowed at any time of treatment for any side effects (anxiety, depression, sleeping disturbance, irritability). Patients who were on psychiatric medication, especially antidepressants, were kept stable on this medication. In case of psychiatric deterioration, patients were seen on demand with the option of admission to a psychiatric ward or a change of psychiatric medication according to clinical need.

Statistical Analysis. For nonparametric data, the Kruskal-Wallis one-way ANOVA test was used. ANOVA or *t* test (2-tailed), respectively, were analyzed for parametric data comparing the treatment groups. Post-hoc testing was performed by the Bonferroni procedure. For categorized data, χ^2 test or Fisher's exact test (2 × 2 tables) were used. All data were evaluated on an intention-to-treat and per-protocol basis. Data on dropouts were included as last observation carried forward. The influence of alcohol before or during treatment on ALT levels during and after treatment was calculated using multiway tables with the log-linear model. *P* values less than .05 were considered significant.

Results

From 93 screened patients, 81 fulfilled the inclusion criteria. Eight patients had no elevated liver enzyme levels,

and 4 patients (2 controls, 1 psychiatric patient, and 1 patient with a former drug addiction) denied participation in the trial. A total of 23 patients were included in the control group, 16 in the psychiatric group, 21 in the methadone group, and 21 in the former addiction group. Six patients in the psychiatric group had major depression, one had a general anxiety disorder, 2 had schizoaffective disorder, 4 had chronic schizophrenia, and 3 had severe borderline personality disorder combined with a major depression. Five patients in this group also had a history of former drug abuse, and 2 patients with schizophrenic disorders additionally received methadone.

Baseline characteristics of the study population are shown in Table 1. The mean age was 40 ± 12 years. Forty-nine men and 32 women were included. Patients in the former addiction and methadone groups were significantly younger than those in the control group (*P* < .01 and *P* < .001, respectively), as expected from the epidemiology of addiction. There were more women in the psychiatric group compared with the methadone and former addiction groups (*P* < .05), which might be explained by the higher incidence of major depression and borderline personality in women. Pretreatment with IFN-α, baseline ALT levels, virus load, the frequency of histologically proven cirrhosis, body weight (mean,

Table 2. Biochemical and Virologic Response (Intention to Treat)

	Patient Groups					
	All (n = 81)	Control (n = 23)	Psychiatric (n = 16)	Methadone (n = 21)	Former Addiction (n = 21)	P
ALT (U/L) at end of treatment	24.2 ± 24.0	24.3 ± 21.9	20.3 ± 17.2	23.0 ± 23.6	28.5 ± 31.0	NS
ALT (U/L) 6 months after end of treatment	24.8 ± 23.9	22.5 ± 20.8	23.6 ± 19.6	23.2 ± 23.3	30.0 ± 30.7	NS
Virologic response (end of treatment) (%)	38 (47)	9 (39)	8 (50)	13 (62)	8 (38)	NS
Genotype 1	14 (34)*	4 (31)*	4 (36)*	3 (50)*	3 (33)*	
Genotype 2	5 (71)	2 (67)		1 (50)	2 (100)	
Genotype 3	18 (60)	3 (75)	3 (75)	9 (69)	3 (33)	
Genotype 4	1 (33)	0	1		0	
Sustained virologic response (6 months after end of treatment) (%)	30 (37)	8 (35)	6 (38)	10 (48)	6 (28)	NS
Genotype 1	9 (22)*	4 (31)*	2 (18)*	0 (0)*	3 (33)*	
Genotype 2	5 (71)	2 (67)		1 (50)	2 (100)	
Genotype 3	15 (50)	2 (50)	3 (75)	9 (69)	1 (11)	
Genotype 4	1 (33)	0	1		0	
Relapse (%)	9 (11)	1 (4)	2 (12)	3 (14)	2 (10)	NS
Dropout (%)	18 (22)	3 (13)	3 (18)	3 (14)	9 (43)†	.04†
Somatic side effects	4 (5)	1 (4)	2 (12)		2 (10)	
Psychiatric side effects	2 (2)				2 (10)	
Noncompliance	10 (13)	2 (9)	1 (6)	3 (14)	3 (13)	
Drug relapse	2 (2)				2 (10)	
Ribavirin reduction (%)	31 (38)	9 (39)	7 (44)	8 (38)	7 (33)	NS

NOTE. Data expressed as n ± SD unless otherwise indicated. Virologic response was indicated by undetectable HCV RNA in the qualitative assay.

*The percentage of response depending on the number of patients with this genotype in Table 1.

†Significantly different from the control, psychiatric, and methadone groups.

73.3 ± 12.2 kg), and height (mean, 173.6 ± 8.1 cm) did not significantly differ between groups.

The most frequent genotypes were 1 and 3 compared with genotypes 2 and 4. Genotype 1 was more frequent in patients in the control and psychiatric groups, whereas genotype 3 ($P = .01$ vs. controls) was predominant in the drug addiction groups.

Response. In the intention-to-treat analysis, at the end of treatment, 47% of all patients were HCV RNA negative (virologic response): 34% with genotype 1, 71% with genotype 2, 60% with genotype 3, and 33% with genotype 4 (Table 2). During the 6 months after the end of therapy, 11% (only genotypes 1 and 3) of all patients experienced a relapse without significant differences between treatment groups. Overall, 37% of the patients showed a sustained virologic response: 35% in the control group, 38% in the psychiatric group, 43% in the methadone group, and 28% in the former addiction group. Group differences were not significant. A sustained response was shown in 22% of the patients with genotype 1, 71% with genotype 2, 47% with genotype 3, and 33% with genotype 4.

Dropouts. Therapy was discontinued early in 22% of the patients; reasons were somatic (5%) or psychiatric (2%) side effects, relapse in drug and alcohol abuse (2%), and noncompliance (13%). A total of 13% in the control group and 14% in the methadone group dropped out, mostly because of noncompliance. A total of 18% of the psychiatric group discontinued treatment because of somatic complications or noncompliance. No patients in the psychiatric group had to stop treatment because of psychiatric side effects. 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 noncompliance (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.

Depression and Psychiatric Side Effects. The incidence of depression before and during treatment with IFN-α is shown in Table 3. More patients in the psychiatric group were in a depressed mood when entering the study ($P < .001$ vs. all other subgroups). A total of 16% of all patients developed a new depression during treatment with IFN-α. We found no significant differences in frequency and severity of new depressions during treatment between the groups. However, patients with drug addiction tended to have more often but milder depressions, whereas the severity of depressive episodes in patients in the control and psychiatric groups tended to be moderate or severe. Suicidal thoughts were reported in 4% to 6% of patients, without significant differences between the subgroups. Only 2 patients (3%) dropped out because of a worsening of preexisting depression or development of

Table 3. Psychiatric History and Psychiatric Side Effects

	Patient Groups					
	All (n = 81)	Controls (n = 23)	Psychiatric (n = 16)	Methadone (n = 21)	Former Addiction (n = 21)	P
History of depression	13 (16)	0	12 (75)*	0	1 (5)	<.001
Depression at baseline	8 (10)	0	6 (38)*	2 (10)	0	<.001
New depressive episodes during treatment with IFN-α	13 (16)	3 (12)	1 (6)	3 (14)	6 (29)	NS
Depression during treatment†	21 (26)	3 (12)	7 (44)	5 (24)	6 (29)	NS
Mild	11 (15)	1 (4)	4 (25)	3 (14)	3 (14)	NS
Moderate	6 (7)	1 (4)	1 (6)	2 (10)	2 (10)	NS
Severe	4 (5)	1 (4)	2 (13)		1 (5)	NS
Use of antidepressants before treatment	4 (5)	0	3 (19)*	1 (5)	0	<.05
Use of antidepressants during treatment	13 (16)	1 (4)	10 (62)*	5 (24)	2 (10)	<.0001
Suicidal thoughts	4 (5)	1 (4)	1 (6)	1 (5)	1 (5)	NS
Sleeping disturbance	55 (68)	16 (70)	11 (69)	14 (67)	14 (67)	NS
Sleep medication	23 (28)	4 (17)	6 (38)	9 (43)	4 (19)	NS
Irritability	62 (77)	15 (65)	13 (81)	18 (86)	16 (76)	NS
Lack of concentration	46 (57)	12 (52)	12 (75)	11 (52)	11 (52)	NS
Craving	35 (43)	0‡	6 (38)§	16 (76)	13 (62)	<.001

NOTE. Data expressed as n (%).
*Significantly different from the control, methadone, and former addiction groups.
†According to DSM-IV criteria.
‡Significantly different from the psychiatric, methadone, and former addiction groups.
§Significantly different from the methadone group.

suicidal thoughts. However, none of these patients had to stop treatment from the psychiatric point of view and suicidal thoughts disappeared under psychiatric care in all cases. Depression before or during treatment had no statistically significant influence on therapeutic outcome (sustained response) or dropout rate. In addition, patients with depression had significantly less problems with alcohol consumption during treatment ($P = .046$).

As expected, craving for drugs or alcohol was reported less frequently in controls compared with patients in the psychiatric group ($P = .02$), methadone group ($P < .001$), and former addiction group ($P < .001$). The most frequent psychiatric side effect was irritability. The frequency of sleeping disturbances, concentration difficulties, and irritability did not differ significantly between groups (Table 3). Sleeping disturbances were treated with benzodiazepines (zolpidem or zopiclone) in 28%. Admission to the psychiatric ward was necessary for 3 patients in the psychiatric group and 2 patients in the methadone and former addiction groups but for none of the controls. It could not be determined in any case that admission was caused by a direct association with psychiatric side effects of treatment with IFN-α.

Use of Antidepressants. Overall, 4 of the 81 patients (5%) were on antidepressants before and 13 of 81 patients (16%) received antidepressants during treatment with IFN-α for hepatitis C (Table 3). For 6 of the patients in the psychiatric group, an additional antidepressant treatment was initiated during the first 2 weeks of treatment

because of preexisting depression. The following antidepressants were used: citalopram (10 times), mirtazapine (3 times), nefazodone (one time), paroxetine (2 times), fluoxetine (one time), and amitriptyline (one time). We found significant group differences in use of antidepressants before ($P = .0322$) and highly significant differences ($P < .0001$) at the end of the treatment with IFN-α, with the most frequent use in the psychiatric group. Regarding the influence on liver function, antidepressant treatment did not influence ALT levels during or after treatment compared with patients not taking antidepressants. Relapse after treatment was also not related to antidepressants.

Alcohol. Seven of 23 patients in the control group (30%), 4 of 16 patients in the psychiatric group (25%), 8 of 21 patients in the methadone group (38%), and 7 of 21 patients in the former addiction group (33%) reported occasional alcohol consumption before hepatitis treatment. During treatment, 3 patients in the control group, 3 patients in the psychiatric group, 6 patients in the methadone group, and 9 patients in the former addiction group reported alcohol intake. Two patients in the methadone group and 4 patients in the former addiction group had to be treated for alcohol abuse. However, only one patient in the former addiction group dropped out after 8 weeks; all other patients could be stabilized by inpatient treatment over 8 to 14 days.

Alcohol abuse before treatment was associated with increased ALT levels after 6 months ($P = .038$) and 12

Table 4. Somatic Side Effects

| | Patient Groups | | | | | |
	All (n = 81)	Controls (n = 23)	Psychiatric (n = 16)	Methadone (n = 21)	Former Addiction (n = 21)	P
Diarrhea	24 (30)	2 (9)	5 (31)	13 (62)*	4 (19)	.001*
Pruritus	24 (30)	11 (48)	4 (25)	8 (38)	1 (5)†	.013†
Cough	18 (22)	2 (9)	0	5 (24)	11 (53)‡	<.001‡
Fatigue	53 (65)	16 (69)	11 (69)	18 (86)	8 (38)§	.012§
Dyspnea	56 (69)	15 (65)	11 (69)	19 (90)	11 (53)	NS
Anorexia	30 (37)	4 (17)	6 (38)	12 (57)	8 (38)	NS

NOTE. Data expressed as n (%).
*Significantly different from the control and former addiction groups.
†Significantly different from controls.
‡Significantly different from the control and psychiatric groups.
§Significantly different from the methadone group.

months ($P = .039$) of treatment but not with the mean ALT level 6 months after treatment ($P = .302$). No differences were found between treatment groups. Alcohol consumption during treatment had no influence on the mean ALT levels at 6 months ($P = .226$) and 12 months ($P = .147$) during and 6 months after treatment ($P = .151$), respectively. Furthermore, patients who reported occasional alcohol consumption before or during hepatitis treatment showed no significant differences with respect to a virologic relapse with positive polymerase chain reaction.

In summary, we could not find differences in alcohol intake between treatment groups. Furthermore, alcohol use before or during treatment did not influence the therapeutic outcome and ALT levels after treatment.

History of Addiction and Methadone Substitution. Patients in the former addiction group reported a duration of drug abuse between 11 months and 22 years (mean, 8.9 years) and patients in the methadone group reported a duration between 7 months and 24 years (mean, 11.6 years). Patients were in methadone substitution between 5 months and 13 years (mean, 3.4 years). The mean dosage of methadone before treatment was 57 mg/d (6-160 mg/d) and increased slightly to 59 mg/d (0-170 mg/d) at the end point of treatment with IFN-α. Eight of 21 patients (38%) were kept on a stable dosage. The dosage was increased in 38% and decreased in 24%. Thus, we found no statistically significant differences between methadone dosage before and during treatment with IFN-α.

Somatic Side Effects. The frequency of somatic side effects is shown in Table 4. The dosage of ribavirin had to be reduced in 38% (Table 2). Diarrhea was significantly more frequent in the methadone group compared with the former addiction group ($P = .011$) and control group ($P < .001$). In those with former addiction, itching was

rare ($P = .002$ compared with controls) but coughing was frequent ($P = .002$ vs. controls, $P = .001$ vs. patients in the psychiatric group). Fatigue differed significantly only between patients in the methadone and former addiction groups ($P = .004$). Hyperthyroidism in 2 patients in the psychiatric group and pneumonia in one patient in the methadone group were treated successfully. Other frequent somatic side effects, such as headache, myalgia, pyrexia, alopecia, nausea, exanthema, and pharyngitis, did not differ between subgroups. Differences in cough, diarrhea, and itching might be explained by long-term effects of methadone and opiates on the nervous system of the skin and the abdominal and pulmonary organs.

Discussion

IFN-α has been therapeutically used for more than 15 years in patients with chronic hepatitis, but there only are few psychiatric investigations about the incidence and severity of psychological side effects, especially in patients with predisposing conditions. In a prospective study using internationally standardized psychiatric diagnostic criteria, depression during treatment of hepatitis with IFN-α occurred in 38% of nonpsychiatric patients after 12 weeks.[12] In 2 multicenter studies, in which DSM criteria were not used, the incidence of depression ranged between 11% and 37%.[4,19] Several cases of IFN-α–related suicide attempts or severe psychosis have been reported, but most of these patients had no psychiatric history.[20,21] Furthermore, a prior individual or family history of psychiatric illness does not seem to predict depression or anxiety during IFN-α therapy.[9] Suicide attempts during IFN-α therapy have been reported mainly in patients with organic personality changes or delirious syndromes.[22] These patients and their families did not attribute thought and behavioral changes to IFN-α be-

cause they had no experience with psychiatric symptoms and therefore did not seek psychiatric help. Taken together, the assumption of a generally increased risk for psychiatric side effects in psychiatric patients has been deduced from reports about complications in nonpsychiatric patients admitted to clinical trials.

We therefore studied psychiatric symptoms during IFN-α therapy in patients believed to be at increased risk. In the present trial, patients in all subgroups developed psychiatric side effects that were systematically evaluated by standardized diagnostic criteria (DSM-IV), but no significant differences in the frequency and severity of psychiatric side effects between subgroups were noted. Psychiatric patients had more depressive symptoms before and during treatment compared with the other groups, with an increased need for treatment with antidepressants. However, these differences also seem to reflect their psychiatric condition before IFN-α therapy and cannot be completely ascribed to IFN-α–induced mood changes. This is supported by the observation that psychiatric patients had the best compliance and a low dropout rate. In our trial, depression and suicidal thoughts occurred in most cases independently of a preexisting psychiatric disorder. These results are in line with 2 recent studies reporting that psychiatric patients with chronic hepatitis C can be safely treated with IFN-α monotherapy.[22,23]

It has been suggested that schizophrenic and schizoaffective patients as well as patients with depression or anxiety disorders show no worsening during IFN-α therapy.[24-26] In our study, even patients with a severe borderline personality disorder and some patients with drug addiction tended to be more stable and therapeutically reliable during treatment. The awareness of the risk of liver damage and the opportunity to receive a potentially successful treatment seemed to support cooperative behavior.

In all patients who had depression during treatment with IFN-α, improvement was possible with psychiatric and psychopharmacologic support. Novel antidepressants with less sedation (selective serotonin reuptake inhibitors) and benzodiazepines were especially effective in treating sleeping disturbances, irritability, and depression. The successful use of selective serotonin reuptake inhibitors for the management of IFN-α–related psychiatric effects has been described in several case reports.[27-30] Most patients in the psychiatric group continued treatment with antidepressants because of a preexisting depression. Only one patient developed a new major depressive episode, although he received treatment with antidepressants. The earlier use of antidepressants in the psychiatric

group may explain the low incidence of major depressive episodes and suicidal syndromes. Recently, Musselman et al. showed that pretreatment with paroxetine as an antidepressant was highly effective in preventing depression and reducing the dropout rate during adjuvant treatment of melanoma with IFN-α.[31] In addition, Kraus et al. reported high efficacy in treating acute IFN-α–associated depressive symptoms.[28] Thus, our data extend the efficacy of antidepressants in preventing and treating IFN-α–associated depressive episodes, especially in psychiatric patients and patients with methadone substitution and chronic hepatitis C. Overall, the low rate of dropouts due to psychiatric side effects may be in part the result of the timely use of antidepressants in all groups. Moreover, the high dropout rate of patients with former drug addiction may also be explained by the significantly less frequent use of antidepressants in this group.

Interestingly, we could not find differences in ALT levels during and after treatment with IFN-α in patients who received treatment with antidepressants compared with others. Thus, antidepressants did not affect liver function during treatment of hepatitis C. However, controlled studies focusing on the efficacy of antidepressants in preventing psychiatric side effects of IFN-α and interactions with response and liver enzymes during and after treatment of hepatitis C are needed.

We are aware that our results have to be interpreted cautiously because of the heterogeneity in psychiatric diagnoses, the lack of psychiatric controls without IFN-α therapy, and the limited number of patients. Final conclusions about the incidence of psychiatric side effects for special diagnostic subgroups during IFN-α therapy and a causal relationship between the necessity of hospitalization of psychiatric patients cannot be drawn. Hyperthyroidism led to hospitalization in at least one patient. Hyperthyroidism should be closely monitored, particularly in psychiatric patients, because of its relevance for the mental state.[32,33]

Study of the virologic response was not the main purpose of this investigation, but some comments seem appropriate. The somewhat-low sustained response may be explained by the inclusion of IFN-α relapsers and nonresponders and the high number of patients with genotype 1. The better response in the methadone group can be ascribed to the higher prevalence of genotypes 2 and 3, whereas the low rate of sustained response by intention-to-treat analysis in the former addiction group was due to the high dropout rate in this group. With better adherence, higher response rates will be possible in both methadone-substituted patients and in patients with former drug addiction.

Methadone-substituted patients are often classified as active drug users and excluded from treatment of hepatitis. Although a recent study on treatment of hepatitis C in injection drug users showed encouraging sustained response rates,[6] no controlled studies regarding methadone-substituted patients are available thus far. In our trial, methadone-substituted patients finished treatment without relevant differences in psychiatric side effects compared with controls. In contrast to patients with former drug abuse, no patient dropped out because of drug relapse during treatment, although most patients reported craving. Cannabis abuse or occasional intake of benzodiazepines and even a single intravenous drug abuse using sterile needles were not regarded as a reason for cessation of therapy because of the small risk of reinfection. This is in line with the current discussion about treatment of HCV in active drug users.[6,34,35] Patients with former addiction had the highest dropout rate and mental instability, although severe psychiatric comorbidity was excluded. Time of abstinence, ranging from 3 months to several years, did not seem to influence the number of dropouts due to a drug relapse. However, more patients are necessary to answer this question. The increased dropout rate of patients with former addiction in our study is in line with the results of Renault and Hoofnagle.[9,36] Therefore, treatment results, especially in those with a former drug addiction and methadone-substituted patients, depend on their motivation, compliance, and toleration of side effects.[6,34,35] However, former drug users with known personality and behavioral problems are the main "difficult to treat" group and will need special interdisciplinary management concepts in future clinical hepatitis C treatment trials to minimize the dropout rate and increase response to treatment with IFN-α.

In conclusion, our prospective controlled study evaluating IFN-α therapy in various psychiatric risk groups with chronic hepatitis C should encourage physicians to offer this effective therapy to these patients. Although psychiatric-risk patients need special psychiatric care, this can be achieved in an interdisciplinary setting. Because of the frequent psychiatric changes during treatment with IFN-α, we recommend close cooperation with a psychiatrist starting before treatment. Our results add objective psychiatric data to the present discussion concerning the tenability of psychiatric contraindications to IFN-α and the practicability of IFN-α during methadone substitution.

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