

Neurocognitive changes in patients with hepatitis C receiving interferon alfa-2b and ribavirin

Background: During antiviral therapy of chronic hepatitis C, patients frequently report impairment of concentration or memory. Therefore we prospectively investigated neurocognitive performance in patients receiving interferon alfa and ribavirin.

Methods: Repeated computer-based testing of neurocognitive function was performed in 70 patients with chronic hepatitis C receiving interferon alfa-2b (pegylated or conventional) and ribavirin. In addition, depression scores were obtained (Hospital Anxiety and Depression Scale).

Results: Reaction times were significantly increased during treatment (mean reaction time increase after 3 months of therapy: alertness, 46.76 ms [95% confidence interval (CI), 26.86-66.66 ms], $P < .001$; divided attention, 47.04 ms [95% CI, 26.44-67.64 ms], $P < .001$; vigilance, 60.78 ms [95% CI, 29.24-92.32 ms], $P < .001$; and working memory, 38.53 ms [95% CI, 1.22-75.83], $P = .34$). Accuracy measures (number of false reactions) were affected for the working-memory task exclusively. Cognitive performance returned to pre-treatment values after the end of therapy. Cognitive impairment was not significantly correlated with the degree of concomitant depression ($0.04 < r$ [absolute value] < 0.10 , $P > .390$).

Conclusions: Interferon-based combination therapy of chronic hepatitis C causes significant but reversible impairment of neurocognitive performance. Consequences for the requirements of an active life in patients with chronic hepatitis C receiving antiviral therapy need to be assessed. (Clin Pharmacol Ther 2005;77: 90-100.)

Michael R. Kraus, MD, PhD, Arne Schäfer, MPsych, Saskia Wißmann, MD,
Peter Reimer, MD and Michael Scheurlen, MD *Würzburg, Germany*

Chronic hepatitis C is one of the most frequent infectious diseases worldwide and a major cause of chronic liver disease.¹ At diagnosis, approximately 20% of patients with chronic hepatitis C already have liver cirrhosis.² Therapy for hepatitis C is still unsatisfactory, although at present a sustained loss of hepatitis C virus (HCV) will be reached in about 50% of patients treated with a combination of peginterferon alfa and ribavirin for up to 1 year.³

From the Department of Gastroenterology and Hepatology, Medizinische Poliklinik, University of Würzburg.

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Reprint requests: Michael R. Kraus, MD, PhD, Medizinische Poliklinik, University of Würzburg, Klinikstrasse 6-8, D-97070 Würzburg, Germany.

E-mail: kraus_m@klinik.uni-wuerzburg.de

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Psychiatric side effects of interferon alfa are well known and may necessitate dose reduction or even premature discontinuation of therapy.⁴⁻⁷ In addition, patients undergoing interferon treatment frequently report concentration or memory impairment that in some cases interferes considerably with their capacity to manage the requirements of everyday life. This raises the possibility of a deterioration of cognitive functions during antiviral therapy of chronic hepatitis C.

Such side effects of interferons are suggested by very limited data from patients with cancer,⁸⁻¹³ amyotrophic lateral sclerosis,¹⁴ or multiple sclerosis.^{15,16} However, the results available so far are inconsistent, with reports even suggesting that interferon may not have any effect on neurocognitive parameters at all. Hence, an evaluation of potential interferon-induced neurocognitive side effects in a homogeneous study sample with a sufficient sample size has become necessary.

Although chronic hepatitis C is the most frequent indication for interferon therapy, no systematic data are available so far on possible impairment of cognitive

function in these patients. Therefore we prospectively investigated timing, intensity, and specificity of neurocognitive changes induced by therapy with interferon alfa-2b (either pegylated or conventional) and ribavirin in patients with chronic hepatitis C.

METHODS

Patients

The participants were 83 consecutive patients in whom chronic hepatitis C was diagnosed at our institution or who were referred for antiviral therapy of known chronic hepatitis C. All patients had documented antibodies to HCV and circulating HCV ribonucleic acid as measured by reverse-transcription polymerase chain reaction (COBAS AMPLICOR HCV MONITOR Test; Roche Diagnostics, Basel, Switzerland). Patients were recruited from August 1998 to August 2001. The last patient finished the study in August 2002.

Patients were not included if they were aged less than 18 years or more than 65 years or had coinfections (hepatitis B virus or human immunodeficiency virus), severe internal diseases (eg, cancer, ischemic heart disease, and autoimmune disease), psychiatric illness (severe depression or psychosis and so on), active intravenous drug use or alcohol abuse (within the last 6 months before possible study entry), obvious intellectual impairment, or insufficient knowledge of the German language. If liver cirrhosis was already present, it had to be well compensated (Child stage A).

All patients gave written consent to participate in the study before enrollment. The study was approved by the Ethics Committee for Medical Research of Würzburg University, Würzburg, Germany, in accordance with the Declaration of Helsinki.

Study design and procedures

This was a prospective, longitudinal, single-center study. Of 83 patients, 13 (15.7%) could not be included in the final evaluation and statistical analysis; 9 patients terminated therapy prematurely within the first 3 months because of intolerable side effects, and 4 patients withdrew their consent to participate in the study. Of 83 patients, 70 completed the study.

According to the changing recommendations in Germany during the study period, patients were treated with interferon alfa-2b and ribavirin from August 1998 until August 2000 (38/70 patients [54.3%]) or with peginterferon alfa-2b and ribavirin from September 2000 until August 2002 (32/70 patients [45.7%]). In the case of virologic response, 5 MIU of interferon alfa-2b 3 times weekly or 80 to 150 μ g of peginterferon alfa-2b (1.5 μ g/kg) once weekly was given for 12 months

(genotype 1) or 6 months (genotypes 2, 3, and 4). All patients received oral ribavirin (800-1200 mg daily).

In all eligible patients, psychometric scores (depression) and computer-based test results for cognitive functions were obtained before therapy (t1) and after 4 weeks (t2), 3 to 4 months (t3), and 6 to 8 months (t4) of treatment, as well as 4 to 6 weeks (t5) after termination of therapy.

Blood samples were obtained during the patients' medical visits at time points t1 to t5 for measurement of blood count and levels of transaminase, anti-HCV antibodies, and HCV ribonucleic acid. Genotype identification and liver biopsy (staging and grading: inflammation, fibrosis, or cirrhosis) were performed before therapy. The mode of infection was documented.

Psychometric instruments

Hospital Anxiety and Depression Scale. Depression and anxiety were assessed by the well-validated Hospital Anxiety and Depression Scale (HADS, German version, as published by Herrmann et al¹⁷). HADS is a 14-item questionnaire with dimensions of anxiety and depression. All items exclusively refer to the emotional state and do not reflect somatic symptoms.¹⁷

Computer-based testing of neurocognitive functions. Neurocognitive performance was assessed by a set of computer-assisted psychologic tests (Test for Attentional Performance [TAP], version 1.02c, as published by Zimmermann and Fimm^{18,19}).

The core of the procedures comprises reaction-time tasks of low complexity allowing the evaluation of very specific deficiencies. The tasks consist of simple and easily distinguishable stimuli to which the patients react by a simple motor response. Out of a total of 12 subtests, the 4 most relevant computerized tasks were selected to monitor cognitive function during the treatment period in patients with chronic hepatitis C. During each session, the patients performed the tests in the following sequence:

1. Alertness (testing time, 10 minutes): This examination includes a simple and a cued reaction time task (visual test stimulus with and without an additional acoustic cue). The simple reaction time has been shown to be a valid measure of general slowness, whereas the difference between simple and cued reaction time is a measure of phasic alertness. The visual stimulus consists of a white cross on a black background presented approximately every 3 seconds. (A total of 80 stimuli are presented in this subtask.)

2. Divided attention (testing time, 5 minutes): Situations that require divided attention (attention to various aspects) are the rule, not the exception. This performance can be investigated by dual tasks. In this examination this is realized by independent visual and acoustic tasks. The visual task consists of crosses that appear in a random configuration in a 4×4 matrix. The subject has to detect whether the crosses form the corners of a square. The acoustic task comprises a regular sequence of high and low beeps. The subject has to detect an irregularity in the sequence.
3. Vigilance (testing time, 20 minutes): This is a bimodal task (combined visual and acoustic) that assesses sustained attention or vigilance over a time period of 15 minutes. Out of a series of monotonously presented acoustic and visual stimuli (beeps and letters alternately), the patient must press a button if the sequence "high beep followed by E" or "low beep followed by N" occurs.
4. Working memory (testing time, 15 minutes): The test measures the control of a continuous flow of information through short-term memory. Numbers are presented on the screen that must be compared with previously exposed numbers. The repetition of a number within a short interval has to be acknowledged by pressing a key. The frequency of the numbers appearing on the screen is about 1 per second. The key has to be pressed when the presented number equals the last number except 1.

Statistical analysis

Data were registered and analyzed by use of the Statistical Package for Social Sciences (SPSS for Windows, German version 10.0.7²⁰). All tests of significance were 2-tailed. *P* values < .05 were considered statistically significant. Because of the explorative character of the study, we did not consider α adjustment in multiple comparisons.

Descriptive analysis. Results describing quantitative measures are expressed as median or mean \pm SD or SE. Qualitative variables are presented as counts and percentages.

Tests of significance. Comparison of variables representing categorical data was performed with the chi square test. Mean differences of continuous variables between patient subgroups were examined by either *t* tests for independent samples or ANOVA if more than 2 subgroups were included. Group means of dependent samples (eg, time course of continuous variables) were compared by means of repeated-measures ANOVA (general linear model procedure, repeated-measures de-

sign). Corresponding contrasts were analyzed by paired *t* tests. Pearson correlation was used when appropriate (assessment of associations between quantitative variables).

RESULTS

Study population

Table I shows the characteristics of the 70 patients who were included in the final evaluation. There were no significant differences in sociodemographic or biomedical parameters between both subgroups (treatment with conventional or pegylated interferon) with the one exception that patients treated with peginterferon alfa-2b were slightly but significantly older than patients receiving conventional interferon alfa-2b (*P* = .048). Sex, acquisition mode, virus genotype, and liver histologic characteristics did not differ significantly.

A total of 11 of 70 patients (15.7%) received antidepressant medication (selective serotonin reuptake inhibitor [SSRI]) (20 mg paroxetine daily) during the evaluation period, as follows: Two patients were receiving (prophylactic) SSRI medication before the onset of interferon treatment. Another 9 patients received concomitant SSRI therapy subsequent to substance-induced major depression (without suicidal ideation) for the remainder of the antiviral treatment. Subgroup analysis revealed that the factor *SSRI treatment* had no significant effect on the neurocognitive parameters evaluated in our study (data not shown).

Tests of cognitive function

Both reaction times and accuracy measures did not differ significantly between patients treated with conventional or pegylated interferon alfa. Consequently, the results are presented for the study group as a whole.

Fig 1 shows the reaction times for the TAP alertness, divided attention (visual and acoustic subtasks), and vigilance tasks at the different measuring points. During therapy with interferon and ribavirin, reaction times increased for all tasks, with significance failing only for the visual subtask of divided attention (*P* = .060) (reported *P* values refer to repeated-measures ANOVA analysis). The increase in reaction time reached a maximum at either t3 or t4 (3 or 6 months of therapy, respectively). At t4, only 66 of 70 patients were receiving interferon therapy because 4 patients had to stop antiviral treatment prematurely (Fig 1). On average, reactions were delayed between 46.8 ms (alertness) and 65.8 ms (divided attention, acoustic subtask). Observed effect sizes ranged from 0.65 (vigilance) to 0.98 (divided attention, acoustic subtask). Mean relative reaction time increases were between 5.4% (working-

Table I. Pretherapeutic patient characteristics and HADS depression scores

<i>Sociodemographic or biomedical factor</i>	<i>All patients (N = 70)</i>	<i>Peginterferon plus ribavirin (n = 32)</i>	<i>Interferon alfa-2b plus ribavirin (n = 38)</i>	<i>P value</i>
Age (y) (mean ± SD, range)	42.3 ± 9.3 (22-65)	44.7 ± 7.9 (25-63)	40.3 ± 10.0 (22-65)	.048
Women	30 (42.9%)	15 (46.9%)	15 (39.5%)	.533
Men	40 (57.1%)	17 (53.1%)	23 (60.5%)	
Acquisition mode				.277
Unknown	21 (30.0%)	12 (37.5%)	9 (23.7%)	
IVDU	36 (51.4%)	15 (46.9%)	21 (55.3%)	
After transfusion	13 (18.6%)	5 (15.6%)	8 (21.0%)	
Virus genotype				.354
Genotype 1	36 (51.4%)	17 (53.1%)	19 (50.0%)	
Genotype 2	10 (14.3%)	5 (15.6%)	5 (13.2%)	
Genotype 3	22 (31.4%)	8 (25.0%)	14 (36.8%)	
Genotype 4	2 (2.9%)	2 (6.3%)	0 (0.0%)	
Liver biopsy* or liver damage				.184
Hepatitis only	36 (52.2%)	13 (40.6%)	23 (62.2%)	
Fibrosis	18 (26.1%)	11 (34.4%)	7 (18.9%)	
Cirrhosis	15 (21.7%)	8 (25.0%)	7 (18.9%)	
Nonresponder	38 (54.3%)	16 (50.0%)	22 (57.9%)	.509
Responder	32 (45.7%)	16 (50.0%)	16 (42.1%)	
HADS depression score before therapy	4.56 ± 3.42	4.50 ± 3.55	4.61 ± 3.37	.899

HADS, Hospital Anxiety and Depression Scale; IVDU, intravenous drug use.

*In 1 patient treated with conventional interferon alfa-2b, liver biopsy was declined by the patient.

memory task) and 17.7% (alertness subtask). After termination of therapy (t5), reaction times returned to the pretreatment values.

Regardless of the increase in reaction times, the “correctness” of the reactions (omissions and false alarms) remained unchanged during interferon-ribavirin therapy as compared with the pretreatment and posttreatment values. Overall, 54 of 70 patients (77.1%) had deterioration in at least 1 of the TAP alertness, divided attention, or vigilance subtasks at t3 (after 3 months of therapy). Patients who experienced worsening could not be characterized by pretherapeutic variables (age, sex, type of interferon, baseline neurocognitive performance, acquisition mode, liver histologic characteristics, or education level) by use of logistic regression analysis.

The TAP working-memory task was available for only 59 of the 70 hepatitis C patients. (As indicated in Fig 2, at t4, 56 of 59 patients were receiving therapy because of premature termination of antiviral medication.) Reasons for the missing data comprise in particular the high task complexity and the sequence of the tests; the memory subtest was the last test presented to the study patients. In our view, however, the evaluation of this test in only some of the patients is justified because the working-memory task covers one impor-

tant aspect of cognitive performance frequently reported as impaired by patients during therapy with interferon alfa plus ribavirin.

Mean reaction times (Fig 2, A) increased significantly over time ($P = .034$) (reported P values refer to repeated-measures ANOVA analysis) with a maximum at t4 (effect size, 0.36). In addition, there was a significant impairment of cognitive performance concerning both the number of correct reactions (Fig 2, B; decline, $P < .001$) and the number of omissions (increase, $P < .001$; data not shown). The frequency of false alarms, however, did not change during the treatment ($P = .578$).

To control these results for potential biasing effects, we compared the 11 patients who were not able to complete the working-memory tasks in our study with the patients without missing data. Subgroup analysis revealed that there was no significant difference between these subgroups with respect to sex, acquisition mode, HADS scores, or neurocognitive performance (both before and during antiviral treatment with interferon alfa-2b). However, the 11 patients without complete working-memory data were slightly but significantly older than the remainder of the study sample (47.7 versus 41.3 years, $P = 0.033$).

Depression

As expected,⁴ depression occurred during the treatment period. HADS depression scores rose significantly to a maximum at t4 ($P < .001$). The interferon-induced increase of HADS depression scores in the study sample is displayed in Fig 1 (with corresponding data and stratified numbers given in Table I). The therapy mode (conventional versus pegylated interferon) had no significant effect on either extent (main effect therapy mode, $P = .752$) or time course (interaction time \times therapy mode, $P = .068$) of depression.

Given that patients with depressive disorders frequently complain about symptoms such as difficulty in concentrating, slowed thinking, or indecisiveness,²¹ we tested whether the cognitive impairment observed in our study patients could be explained by depression. Pearson correlation coefficients revealed that there was neither a statistically significant ($P < .500$) nor a clinically relevant association (r [absolute value] < 0.1) between changes in HADS depression scores and therapy-induced decreases observed in TAP subtasks (changes from t1 to t3).

Anxiety

Confirming the results of previous studies,⁴ HADS anxiety scores increased significantly to maximum values at t4 ($P < .001$). Interferon-induced anxiety was reversible after the end of interferon treatment. Neurocognitive performance was not significantly correlated with the extent of therapy-induced anxiety (data not shown).

Anemia

To assess a potential effect of ribavirin-induced hemolysis and anemia, the changes in hemoglobin levels between t1 and t3 were correlated with the respective changes in reaction times. Hemoglobin values decreased significantly during antiviral therapy. Pearson correlation coefficients ($r = 0.27$ for vigilance, $P = .024$) showed that cognitive impairment during combi-

nation therapy for chronic hepatitis C was weakly but significantly linked to the drop in hemoglobin values.

Severity of liver disease

There was no significant correlation between the degree of liver disease (histologic staging and grading) and the attentional performance in the TAP tasks (data not shown). Liver function or Child stage did not deteriorate in any of our patients during the study period.

Further factors possibly influencing neurocognitive symptoms

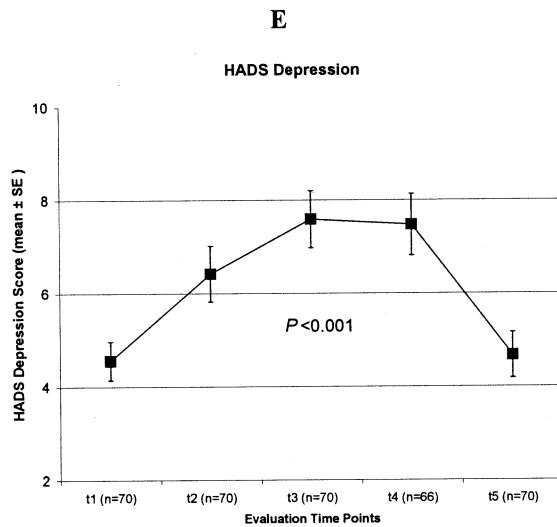
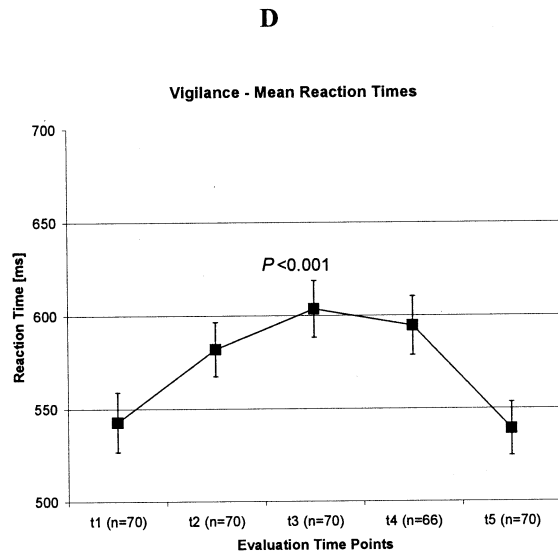
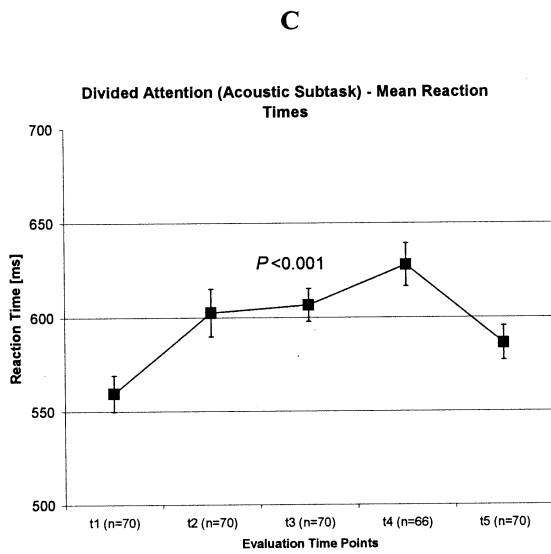
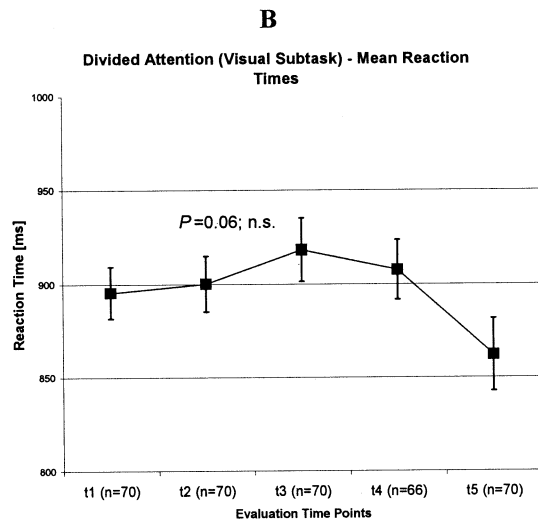
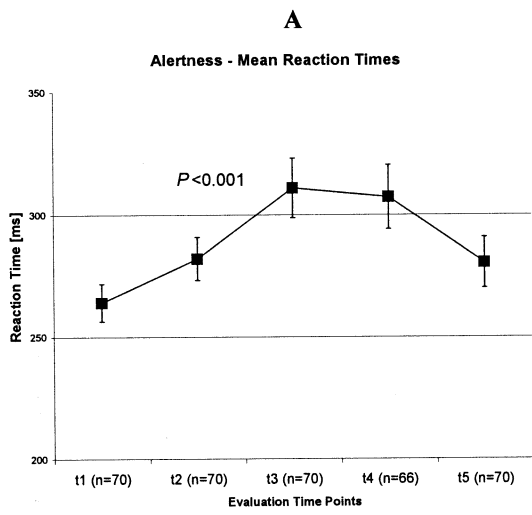
Age and education level are well-known factors that may have an impact on neuropsychologic tasks; therefore we correlated these variables with measures of interferon-induced cognitive changes. However, we were not able to find any statistically or clinically relevant associations of the extent of neurocognitive decline with age or education level (data not shown; correlation coefficients were all below 0.3).

The increase in reaction time in the single subtasks did not show any significant correlation with pretherapeutic performance (r [absolute value] < 0.01). However, there was a correlation between absolute performances before and during interferon treatment (eg, for alertness subtask, $r = 0.6$).

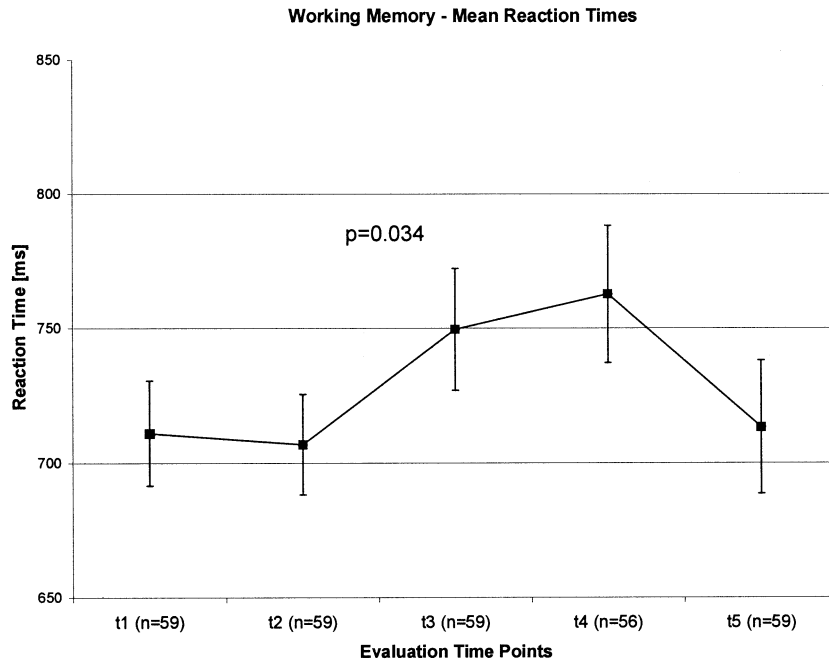
Some studies have suggested a direct association between hepatitis C infection (presence of HCV) and cognitive impairment.²² Therefore we compared the subgroups with ($n = 32$ [45.7%]) and without ($n = 38$ [54.3%]) virologic response with respect to their post-treatment cognitive performance. Neither reaction times nor measures of accuracy differed significantly between both subgroups ($.10 < P < .80$, t tests for independent samples).

Likewise, in our patients (both total study sample and responders), no significant improvement was found between pretreatment and posttreatment levels of neurocognitive performance (time points t1 and t5; $P > .05$, paired t tests).

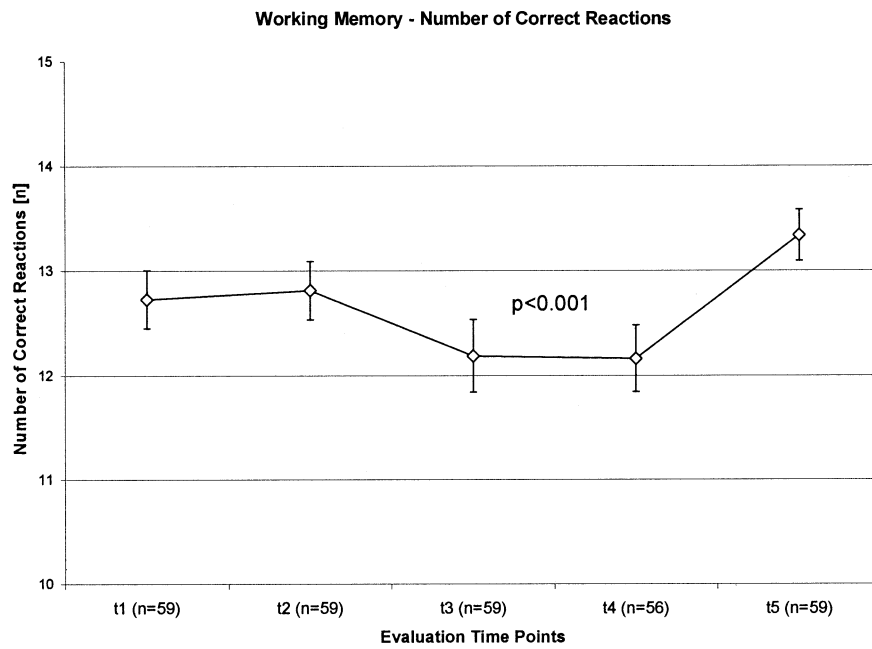
Fig. 1. Time course of mean Test for Attentional Performance (TAP) reaction times (in milliseconds) (\pm SEM) in 70 patients before, during, and after interferon alfa therapy for alertness subtask (A); divided attention, visual subtask (B); divided attention, acoustic subtask (C); and vigilance subtask (D) (measure of variation, SEM) and time course of mean Hospital Anxiety and Depression Scale (HADS) depression scores (\pm SEM) (E) in 70 hepatitis C patients before, during, and after interferon alfa therapy. n.s., Not significant; t1, before therapy; t2, after 4 weeks of treatment; t3, after 3 to 4 months of treatment; t4, after 6 to 8 months of treatment; t5, 4 to 6 weeks after termination of therapy.



A



B



DISCUSSION

Data from small studies suggest that, among the central nervous side effects of interferon, an impairment of neurocognitive performance may also occur.^{8,9,12-16} However, these observations have been challenged by some reports rejecting the hypothesis of cytokine-induced neurocognitive deficits.^{10,11,23}

Systematic data on the extent and spectrum of deficiencies induced by this drug, especially as part of the combination therapy of chronic hepatitis C, are not available so far. Neurocognitive impairment has only been systematically studied in untreated hepatitis C patients.^{22,24-26}

Therefore this study was performed prospectively in a homogeneous group of hepatitis C patients in a longitudinal design. Because there may be a possible discrepancy between patients' complaints and actual neurocognitive performance, as may occur in depression (a major side effect of interferon therapy^{4,5}), a standardized and objective computer-based neurocognitive test battery was used. Furthermore, we designed the study to control changes in neurocognitive performance for potentially confounding variables such as interferon-induced depressive symptoms and ribavirin-induced hemolysis, which had not been done in previous studies.

In contrast to hepatic encephalopathy, for example,^{24,26} no specific psychometric tests to measure interferon-induced neurocognitive symptoms have been validated so far.

Standardized data for the TAP subtasks, as well as information concerning learning effects in healthy control subjects, are available.^{18,19} Performance in the TAP subtasks used in our study has been shown not to be influenced by significant learning effects when administered repeatedly. Therefore a control group without antiviral therapy was considered unnecessary in our study design.

The results of our study demonstrate a marked and significant decline of important aspects of cognitive performance. This is basically consistent with the results of Poutiainen et al¹⁴ in patients with amyotrophic lateral sclerosis undergoing high-dose interferon alfa therapy or Capuron et al^{8,9} (interferon alfa/interleukin [IL] 2 in cancer patients) as far as cytokine-induced cognitive effects in general are concerned. However, our specific findings for the combination therapy with

interferon alfa and ribavirin in patients with chronic hepatitis C comprise additional and more detailed aspects of quality and time course of cognitive impairment.

With regard to the alertness, divided-attention, and vigilance tasks, the respective reaction times are markedly and significantly increased during therapy with peginterferon alfa. On the other hand, accuracy measures such as the number of correct answers or omissions are not significantly changed in these subtests. Therefore cognitive functions were slowed down but did not become less accurate during antiviral therapy of chronic hepatitis C.

However, this is not the case for the working-memory task: Both reaction time and accuracy are impaired during therapy with peginterferon alfa and ribavirin. This finding is in contrast to the results of Capuron et al,⁸ who did not observe any impairment in measures of memory performance accuracy. However, their study focused exclusively on short-term cognitive effects of cytokine immunotherapy (IL-2, interferon alfa) during a treatment period of only 1 month in cancer patients. In our study a significant impairment of both reaction time latency and accuracy in the working-memory task did not occur before 3 months after initiation of antiviral therapy (t3).

In general, by means of TAP testing, we were able to monitor transient and reversible signs of cognitive deficits. In all of the 4 tested domains of cognitive performance, both reaction time and accuracy levels reached pretreatment values after termination of interferon therapy. These results are not consistent with the findings of Meyers et al,¹² who suggested persistent neurotoxicity in some cases even after termination of interferon alfa therapy in cancer patients.

In addition, we found no evidence that pegylated interferon alfa, because of the higher dose applied, causes significantly more or stronger neurocognitive deficits than conventional interferon alfa. Both therapies were similar in quality and intensity of the cognitive changes they produced in patients with chronic hepatitis C.

As shown here, interferon alfa adversely affects cognition, attention, and memory. Several pathophysiologic mechanisms of immune-to-brain communication can be discussed in this context.²⁷⁻²⁹

←
Fig. 2. Mean reaction times (A) and number of correct reactions (B) for TAP working-memory task before, during, and after therapy with interferon alfa and ribavirin (measure of variation, SEM).

It has been demonstrated by several groups that cytokines present in the circulation outside the blood-brain barrier may exert effects on the central nervous system either directly or indirectly.^{30,31} In particular, activation of IL-1 by interferon alfa and the interaction of IL-1 with specific neurohormones and neurotransmitters in the brain might play an important role in this context.^{28,32} IL-1 α crosses the blood-brain barrier by a saturable transport system.³³ With regard to the localization of cytokine pathways within the brain, IL-1, especially IL-1 α , has been found in several brain regions, including the hippocampus.³⁴ Nevertheless, the mapping of the various cytokine pathways and their receptors and the precise pathophysiologic mechanisms of the observed cognitive impairment in the brain remain unclear.

Our findings suggest that the observed cognitive impairment is not substantially linked to depression or decline of hemoglobin values. Both factors are potential candidates in models of attentional and memory-related deficits during interferon-based antiviral therapy. However, in the case of depression, our study clearly indicates that the observed deterioration of cognitive or attentional performance is not significantly related to the occurrence or aggravation of affective or mood disorders.

Regarding the decline in hemoglobin values, we found a weak association with measures of neurocognitive impairment. Although the correlation was statistically significant ($P < .03$), it cannot, to a substantial degree, account for the variation of attentional and memory-related deficits ($r < 0.30$). Therefore ribavirin-induced hemolysis may be an aggravating factor with respect to attentional performance but does not represent the major cause for it. This finding is in accordance with results of other studies reporting on cognitive or neuropsychologic impairment in patients receiving interferon monotherapy.^{8,9,14}

In addition, reduced performance was not correlated with HCV positivity per se. After treatment, no difference was found between responders and nonresponders to therapy. Similar results have been reported by Cordoba et al,³⁵ who found no direct effect of HCV on neurocognitive function. We are, however, aware that this evaluation of possible effects of mere HCV presence on neurocognitive function is a preliminary one, because this was not a primary aim of our investigation. Studies with the main focus on this issue must be designed with a longitudinal analysis, as well as higher sample sizes, to detect possible differences based on smaller effect sizes.

In conclusion, the decline of neurocognitive functions induced by interferon-based antiviral therapy is marked and significant and can be measured by means of the TAP test battery. The observed cognitive impairment is transient (ie, fully reversible after termination of therapy). According to our findings, accuracy was exclusively affected in the working-memory task whereas a deterioration of reaction time was a characteristic of all tests.

The magnitude of reaction time increases found in our study (mean values between 5.4% in the working-memory task and 17.7% in the alertness subtask) may be put in perspective by a comparison with side effects of other drugs in therapeutic doses.

At least the latter result (TAP alertness subtask) lies within the dimension of what has been found for antihistamines. Theunissen et al³⁶ reported a 15.4% increase in reaction time subsequent to mequitazine administration. The effects of this drug are similar to those of other second-generation antihistamines in that it causes mild driving impairment.

With regard to benzodiazepines, Kelly et al³⁷ found a significant increase in reaction time (audiologic reaction times, 10 dB) of 12% (500 ms at baseline versus 560 ms after application) in 15 subjects receiving midazolam (0.04 mg/kg; clinical, sedating dose).

To summarize, the interferon-induced prolongation of reaction times observed in our study is within the range of prolonged reaction times observed for other drugs known to impair cognitive performance. We are, however, aware of the fact that the comparisons described have to be interpreted with caution because the applied tests were different in the respective studies and the percentage of reaction time changes can only be a clue for clinical significance. Finally, only a subgroup of the patients in our study was particularly affected by interferon-induced reaction time prolongation.

The implication of our findings with regard to the patients' performance in their daily activities or work is not clear. However, it cannot be excluded that an increase in reaction time as observed in our study may affect performance, at least in certain specialized professions. Our data raise some important questions with regard to interferon-induced neurocognitive deterioration; implications and consequences for clinical practice, however, can only be derived from specific tests (eg, driving performance tests with regard to the issue of driving safety). In addition, the effect of interferon on reaction times varied considerably between single individuals. Whereas in the alertness (simple reaction time) subtask reaction time increased by a mean of about 47 ms, in 12 of 70 patients a prolongation of

reaction time between 100 and 380 ms was found. A car with a speed of 120 km/h will cover a distance of 1.6 m in 47 ms but 12.6 m in 380 ms. In the divided-attention test (acoustic subtask), 19 of 70 patients even had an increase in reaction time by more than 100 ms. Because complex tasks are the rule rather than the exception in real life, the latter test may better simulate reality.

Given the considerable number of patients with chronic hepatitis C treated during an active phase of their lives for up to 1 year, further systematic evaluations of interferon-induced neurocognitive side effects with respect to their significance, especially with regard to sophisticated tasks and quality of life, are necessary.

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