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Effect of Interferon-α on cognitive functioning in patients with chronic hepatitis C

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Abstract

Treatment with interferon-alpha (IFN-α) has been shown to adversely affect cognitive functioning in patients with a variety of medical disorders, but information about the effects of IFN-α on cognitive functioning in patients with chronic hepatitis C (CHC) is limited. The purpose of this study was to examine the effects of IFN-α on neuropsychological test performance in CHC patients. Participants were 30 patients with CHC, 11 who underwent IFN-α therapy and 19 who did not. All participants were tested at baseline (i.e., pretreatment) and approximately 6 months later with the Symbol Digit Modalities Test and Trail Making Test. Results revealed that the treatment group performed significantly worse than untreated CHC patients on Part B of the Trail Making Test after approximately 6 months of treatment. No significant group differences were found on Part A of the Trail Making Test or Symbol Digit Modalities Test. Findings suggest that CHC patients undergoing treatment with IFN-α may experience reduced abilities to benefit from practice but suffer no decrements in performance after 6 months of treatment. Additional research is needed to replicate these findings and to explore risk factors for susceptibility to IFN-α-induced effects. (*JINS*, 2005, *11*, 16–22.)

Keywords: Neuropsychological impairment, HCV, Chronic liver disease

INTRODUCTION

Interferon-alpha (IFN-α) is an endogenous cytokine known to play a key role in the immune response to environmental stressors such as cancerous tumors and viral infections. Under normal conditions, IFN-α is produced by leukocytes and exists in tissue in low concentrations, helping to regulate cell growth and eliminate viruses (de Boer & Breimer, 1998). Under conditions of stress, IFN-α may be produced by astrocytes, and its tissue concentrations increase considerably in an effort by the immune system to reduce abnormal cell growth and inhibit intracellular viral replication. Because of these antiproliferative and antiviral effects of naturally occurring IFN-α, recombinant forms have been developed and approved for use in patients with various forms of malignancies and infections. Currently, the only FDA-approved treatment for chronic hepatitis C (CHC) infection is IFN, and IFN-α alone or in combination with ribavirin is the most commonly used antiviral therapy for CHC.

Treatment with recombinant forms of IFN-α has been reported to affect cognitive functioning and mood adversely (Adams et al., 1984; Fontana, 2000; Renault et al., 1987; Smedley et al., 1983). Cognitive dysfunction appears to be related to dose (i.e., higher doses of IFN-α result in greater cognitive dysfunction) (Mattson et al., 1984; Meyers et al., 1991*b*), duration of treatment (i.e., longer treatment duration results in greater cognitive dysfunction) (Amato et al., 1995; Pavol et al., 1995), and possibly route of administration, with intraventricular administration associated with greater cognitive dysfunction than subcutaneous or intramuscular injection (Meyers et al., 1991*a*). Cognitive difficulties noted on neuropsychological tests include psychomotor slowing, difficulty concentrating, memory problems, reduced visuoconstructional ability, and executive dysfunction (Mattson et al., 1984; Meyers et al., 1991a,

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1991b; Niiranen et al., 1988; Pavol et al., 1995). In general, neuropsychological deficits remit within 2–3 weeks of discontinuation of IFN-α therapy (Mattson et al., 1984; Valentine et al., 1998), although there are reports by Meyers (1999) and Meyers and colleagues (1991*b*) that neuropsychological dysfunction persisted for months and years after therapy discontinuation in a few patients with cancer.

The proposed etiology of cognitive deficits associated with IFN-α therapy is an IFN-α-induced toxic encephalopathy, which primarily interferes with frontal-subcortical connections (Adams et al., 1984; Valentine et al., 1998). This hypothesis is supported by EEG data that showed notable slowing of frontal lobe waveforms in patients receiving high doses of IFN-α (Rohatiner et al., 1983; Smedley et al., 1983; Suter et al., 1984) and by a pattern of neuropsychological deficits of patients undergoing IFN-α therapy (Meyers et al., 1991b; Pavol et al., 1995; Valentine et al., 1998). However, a few studies have failed to find adverse effects of IFN-α on cognitive functioning (Caraceni et al., 1998; Mapou et al., 1996; Panitch et al., 1986), and one study reported improved neuropsychological test performances over the course of IFN-α therapy, which they hypothesized may have been associated with remission of the underlying disorders (Mayr et al., 1999). Discrepant study findings may be attributed to differences in methodology and/or patient samples.

Cognitive dysfunction has been reported by as many as 10-20% of CHC patients undergoing IFN-α therapy (Davis et al., 1998; Fontana, 2000; McHutchison et al., 1998). Little is known, however, about whether changes in cognitive functioning during IFN-α therapy for CHC are evident on objective neuropsychological tests. This is an important question for patients with CHC, because data suggest that persons with a history of neurologic compromise may be more susceptible to IFN-α neurotoxicity (Adams et al., 1988; Meyers et al., 1991a; Renault et al., 1987), and a significant percentage of CHC patients have been shown to exhibit cognitive deficits (Forton et al., 2002b; Hilsabeck et al., 2002, 2003). Further, investigation of the effects of IFN-α therapy on cognitive functioning may contribute to knowledge of the neuropathological correlates of IFN-α in neuropsychiatric disorders, which can aid in identifying possible risk factors and inform development of prevention strategies.

Review of the literature revealed only one reported investigation of cognitive dysfunction associated with IFN-α therapy in CHC patients using objective measures of cognitive functioning. Juengling and colleagues (2000) described significant decreases in cerebral glucose metabolism, predominantly in the prefrontal cortex, and reduced ability to learn a word list in their sample of 11 CHC patients tested at baseline and after 3 months of IFN-α therapy. Acknowledging the lack of a suitable comparison sample owing to legal and ethical concerns, these researchers pointed out that there was the possibility that findings may have been affected by variables such as participant maturation (i.e., within-subject variables not related to the research) and history (i.e., extraneous variables affecting participants such as increased disease activity or illness), as well as instrumentation (i.e., variability associated with measurement devices, such as when examinees gain experience with tests and/or test procedures). The purpose of the present study was to examine the effects of IFN-α on cognitive functioning in CHC patients using objective neuropsychological tests and a comparison group of CHC patients not undergoing IFN-α therapy, thus controlling for maturation, history, and instrumentation. Given previous findings that IFN-α therapy resulted in neuropsychological deficits in patients with other types of chronic medical conditions, it was hypothesized that CHC patients undergoing IFN-α therapy would experience decreased performances on neuropsychological tests over time compared to a group of CHC patients not undergoing treatment.

METHODS

Research Participants

Participants were CHC patients seen in an outpatient liver clinic at the University of California, San Diego (UCSD) Medical Center. Participants were selected from a larger group of CHC patients who had provided written informed consent as approved by the Institutional Review Board at UCSD to participate in a study examining the impact of chronic liver disease on quality of life (see Hilsabeck et al., 2002). Thus, this was a retrospective analysis of participants selected from a prospective cohort of CHC patients receiving care at the UCSD Liver Clinic. Participants were selected if they met the following criteria: (1) had undergone neuropsychological testing on two occasions; (2) were not receiving IFN-α therapy at the time of the initial assessment; and (3) had received at least 2 months of IFN-α therapy at the time of the second assessment (if in the treatment group). A total of 39 patients had undergone neuropsychological testing on two occasions, but seven were receiving IFN-α therapy at the time of the initial assessment and two had not been treated with IFN-α for at least 2 months at the time of the second assessment (one had been on treatment 1 week and the other had been on treatment 3 weeks). Thus, a total 30 patients met selection criteria and were included in the analysis.

The sample consisted of 21 men and 9 women with an average age of 47.8 years ($SD = 8.4$). Mean education of the sample was 13.3 years ($SD = 2.1$), and mean estimated IQ as measured by the Shipley Institute of Living Scale (Zachary, 1986) was 101.9 (SD = 13.2), which is in the average range. Seventy-three percent of patients were White, 17% were Hispanic, 7% were Asian American, and 3% were African American. About half of the sample was cirrhotic (i.e., 53%), and most were genotype 1 (i.e., 70%). Four patients (13%) were co-infected with human immunodeficiency virus (HIV), 1 patient (3%) was co-infected with hepatitis B, and 3 patients (10%) had history of significant alcohol use evidenced by alcoholic hepatitis suggested on liver biopsy.

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One-third of patients ($n = 10$) were taking psychiatric medication at the time of the study. Eight were taking antidepressants and 2 were taking atypical antipsychotic medications. The number of patients characterized by current psychiatric conditions (i.e., 33%) is similar to that reported by Dwight and colleagues (2000), who found that 28% of their sample was currently depressed according to self-reports during a structured clinical interview. Most of the present sample (70%) admitted to a history of illicit drug abuse, with 2 patients reporting drug abuse in the past month (i.e., marijuana), and the remaining patients reporting abstinence from illicit substances for 11 months or longer. The majority of participants, or 63%, denied current alcohol use, and another 23% reported alcohol use less than once a month. The remaining patients (13%) described alcohol use 2–4 times a month.

The Medical Outcomes Study Short Form–36 (SF–36) was administered to assess perceptions of health-related quality of life (Ware & Sherbourne, 1992). The SF–36 has been well validated and widely used in several patient populations, including CHC (Bonkovsky et al., 1999; Foster et al., 1998; McHorney et al., 1993, 1994). It consists of eight subscales, which can be summarized into two global indices, the Physical and Mental Composite Scores (PCS and MCS), which are *T*-scores with a mean of 50 and a standard deviation of 10. The average SF–36 PCS and MSC scores for this sample were 38.7 ($SD = 12.1$) and 43.2 ($SD = 11.7$), respectively. Depressive and anxious symptoms were assessed using two well-known self-report measures, the Beck Depression Inventory–II (Beck et al., 1996) and Beck Anxiety Inventory (Beck & Steer, 1990), respectively. Scores on these measures range from zero to 63 with higher scores indicating greater distress. The average depression score in this sample was 15.2 ($SD = 9.9$), and the average anxiety score was 11.5 ($SD = 10.1$), both of which are in the mild range of severity. Fatigue was measured with the Multidimensional Assessment of Fatigue (MAF) scale (Belza et al., 1993). The MAF has demonstrated adequate psychometric properties and has been used successfully with CHC patients (Belza, 1995; Dwight et al., 2000). Scores on the MAF range from 1 to 50, with higher scores indicating greater fatigue. The average level of fatigue reported by this sample was 25.6 ($SD = 13.8$), a level similar to that reported in a previous study of CHC patients recruited from a large university hospital setting (Dwight et al., 2000).

Of the 30 study participants, 11 received IFN-α therapy. Seven of the 11 patients received PEG intron 1.5–5 MU once a week, and 5 of these also took 400–1200 mg of ribavirin daily (2 patients could not take ribavirin due to medical contraindications). The remaining patients received PEGASYS 180 μg once a week in combination with 1200 mg of ribavirin. None were receiving IFN-α therapy at the time of the initial assessment. At retest, 9 patients had been receiving IFN-α therapy for 6 months, one for 4 months, and one for 2 months ($M = 5.6$ months; $SD = 1.4$ months). Seven had nondetectable viral loads at the time of retest, but only three of these eventually achieved a sustained viral response (i.e., nondetectable viral load 6 months after treatment completion). One patient with nondetectable viral load at retest was lost to follow-up after 30 weeks of treatment; thus, his sustained response status is unknown. Patients who underwent IFN-α therapy did not differ significantly from patients who did not undergo IFN-α therapy on any of the following variables: age, education, estimated IQ, sex, ethnicity, level of fibrosis, genotype, comorbid disease (i.e., any chronic medical condition requiring continued care), coinfection with HIV ($N = 2$ per group), current psychiatric medication use (i.e., 5 patients per group with 4 in each group on antidepressants and 1 in each group on atypical antipsychotic medications), history of drug use, months post last drug use, drinking frequency, global physical and mental quality of life, depression, anxiety, or fatigue (see Table 1).

Procedure

All patients completed baseline neuropsychological assessment and underwent a second testing session approximately 6 to 9 months later (i.e., an average of 8.5 and 6.4 months for the untreated and treated groups, respectively; $t = 3.19$, $p = .004$). No patient had undergone neuropsychological testing at any time prior to this study. Selection of neuropsychological tests was based primarily on the necessity for assessment of relevant cognitive functions in a short amount of time. Since prior research indicated that attention, working memory, and psychomotor speed were the most significantly impaired functions in patients with CHC (Forton et al., 2002b; Hilsabeck et al., 2002, 2003), the Symbol Digit Modalities Test (SDMT; Smith, 1982) and the Trail Making Test (TMT; Reitan & Wolfson, 1993) were selected. Both of these measures are brief and easy to administer and score, have age- and education-corrected norms, are highly sensitive to brain dysfunction, and have been used successfully with CHC patients (Hilsabeck et al., 2002, 2003). The SDMT has demonstrated a 1-month test–retest reliability of .80 and a 1-year test–retest reliability of .78 (Lezak, 1995). Test–retest reliabilities for the TMT have been much more variable. Six-month test–retest reliabilities for Parts A and B were .78 and .67, respectively, while 1-year test-retest reliabilities ranged from .69–.94 for Part A and from .39–.86 for Part B, depending on the population studied (Lezak, 1995). Both measures were administered and scored according to standardized instructions. Normative data from the manual were used for the SDMT, and normative data from Heaton et al. (1991) were used for the TMT. Scores more than 1 *SD* below the normative mean were considered impaired, as this criterion is often considered clinically meaningful when using demographically corrected norms (Taylor & Heaton, 2001).

Data analyses

Descriptive statistics, including means, standard deviations, and frequency distributions, were used to characterize scores on neuropsychological measures and the

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Table 1. Demographic characteristics by group

Characteristic	No IFN-α	IFN-α	*p*
Age (years)	45.8 (*SD* =7.7)	51.2 (*SD* = 8.9)	.10
Education (years)	12.8 (*SD* = 2.0)	14.2 (*SD* = 1.9)	.08
Estimated IQ	100.4 (*SD* = 11.2)	104.2 (*SD* = 16.3)	.49
Sex (% Male)	68%	73%	.80
Ethnicity (% Caucasian)	74%	73%	.48
Fibrosis (% severe to cirrhotic)	74%	55%	.28
Genotype (% genotype 1)	68%	73%	.46
Comorbid disease (% positive)	26%	26%	.83
Psychiatric medication (% taking)	26%	46%	.28
History of drug use (% positive)	68%	73%	.80
Months since last drug use	108.1 (*SD* = 104.4)	122.2 (*SD* = 111.3)	.79
Drinking (% abstinent)	68%	55%	.73
SF–36 PCS	38.3 (*SD* = 12.0)	39.6 (*SD* = 12.8)	.78
SF–36 MCS	44.0 (*SD* = 13.5)	42.0 (*SD* = 8.3)	.61
BDI–II	16.1 (*SD* = 11.1)	13.3 (*SD* = 7.8)	.58
BAI	11.4 (*SD* = 10.0)	11.7 (*SD* = 16.7)	.93
MAF	23.6 (*SD* = 14.7)	29.3 (*SD* = 11.5)	.30

Note. SF–36 = Short Form–36; PCS = Physical Composite Score; MCS = Mental Composite Score; BDI–II = Beck Depression Inventory–II; BAI = Beck Anxiety Inventory; MAF = Multidimensional Assessment of Fatigue scale.

percentage of patients scoring in the impaired range. Chi-square analyses were conducted to investigate differences in the proportion of impaired test performances at baseline between CHC patients who were and were not undergoing IFN-α therapy. A repeated measures multivariate analysis was employed to examine group differences in neuropsychological test scores over time. Alpha was set at .05 for all analyses.

RESULTS

At baseline, there was no significant difference in the percentage of impaired performances on Part A of the TMT between CHC patients not undergoing IFN-α therapy and those about to undergo IFN-α therapy [i.e., 26% in each group; $\chi^2(1) = .003$, $p = .95$]. On Part B of the TMT, 27% of each group was impaired at baseline, resulting in no significant group difference [$\chi^2(1) = .003$, $p = .95$]. In addition, no significant group difference in the proportion of impaired performances at baseline was found on the SDMT [i.e., 42% for the no IFN-α therapy group and 36% for the IFN-α therapy group; $\chi^2(1) = .096$, $p = .76$]. Because some of the cells included fewer than 5 data points, Fisher's Exact Tests were conducted and confirmed no significant group differences on any variable at baseline.

A repeated measures multivariate analysis of variance revealed no main effects for treatment group [$F(3,26) = 1.40$, $p = .27$, partial eta-squared = .139] or time [$F(3,26) = .82$, $p = .49$, partial eta-squared = .087], but the interaction was significant [$F(3,26) = 3.45$, $p = .03$, partial eta-squared = .285]. Follow-up analyses showed that CHC patients who had received IFN-α therapy were significantly slower on Part B of the TMT at retest than patients who had not received IFN-α therapy. Performances on Part A of the TMT and on SDMT were not significantly different between groups at retest. These results suggest that taking IFN-α for at least 2 months may interfere with one's ability to benefit from practice on Part B of the TMT. Means and standard deviations of test scores by group over time are presented in Table 2. Due to trends for the treatment group to be slightly older and more educated, we examined whether there were significant associations between age and education and change scores on each neuropsychological measure, and no significant relationships were found (data not shown).

DISCUSSION

This study examined the effect of IFN-α on cognitive functioning in patients with CHC using two sensitive neuropsychological tests (i.e., the TMT and the SDMT). It was hypothesized that CHC patients undergoing IFN-α therapy would perform significantly worse on these measures than CHC patients not undergoing IFN-α therapy. Results partially supported this hypothesis, revealing that CHC patients in the treatment group performed significantly worse than untreated CHC patients on Part B of the TMT after approximately 6 months of IFN-α therapy. Using the standard error of prediction method to estimate reliable change (Basso et al., 1999; Lineweaver & Chelune, 2003), the 90% confidence interval for untreated and treated CHC patients on Part B of the TMT is ±9.5 and ±8.8 s, respectively. Therefore, the average improvement of approximately 20 seconds from baseline to retest in the untreated group can be

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Table 2. Test means and standard deviations by group over time

	No IFN-α				IFN-α					
	Baseline		Follow-up		Baseline		Follow-up			
	M	(*SD*)	*M*	(*SD*)	*M*	(*SD*)	*M*	(*SD*)	*p	Partial eta^2
TMT–A	35.3	(15.0)	34.3	(14.1)	32.4	(10.2)	30.4	(8.1)	.82	.002
TMT–B	84.3	(41.4)	64.4	(27.3)	84.5	(50.6)	89.1	(62.3)	.02	.170
SDMT	43.0	(9.5)	42.8	(10.4)	42.7	(12.3)	44.8	(11.8)	.51	.016

Note. TMT–A = Trail Making Test, Part A; TMT–B = Trail Making Test, Part B; SDMT = Symbol Digit Modalities Test.
*Univariate *F* tests of within-subjects effects.

considered a reliable change, whereas the average decline of almost 5 s in the treated group cannot. While absence of a practice effect in the treatment group is not synonymous with impairment, the significant improvement of the untreated CHC group at retest suggests that administration of IFN-α may interfere with CHC patients' abilities to benefit from practice. As noted by Dikmen and colleagues (1999), "more cognitively able people . . . tend to benefit more from practice" (p. 353). In the present study, it is possible that the untreated group was "more cognitively able" than the treated group due to effects of IFN-α therapy. This explanation seems most likely given the preponderance of prior studies suggesting adverse effects of IFN-α on cognitive functioning in other patient samples and the lack of baseline (i.e., pretreatment) group differences on any other variable that may account for this finding in the current study.

Performances on the other two measures investigated in this study (i.e., Part A of the TMT and SDMT) were not significantly different between the two groups at baseline or follow-up and did not show significant changes over the study period. It is unclear why group differences were evident on Part B of the TMT and not on these other two measures. Given that psychomotor and complex processing demands are relatively equivalent across these tests, it is possible that Part B of the TMT places a higher cognitive load on working memory and mental flexibility, making it more vulnerable to the effects of IFN-α.

Findings of the present study are consistent with those of Juengling and colleagues (2000), suggesting that frontal-subcortical systems may be affected by IFN-α in patients with CHC. In general, results also are consistent with the preponderance of investigations on the effects of IFN-α therapy on neuropsychological test performance in other patient populations, where frontal–subcortical functions were affected (Adams et al., 1984; Mattson et al., 1984; Pavol et al., 1995; Meyers et al., 1991a). In those studies failing to find adverse effects of IFN-α on cognitive functioning (Caraceni et al., 1998; Mapou et al., 1996; Mayr et al., 1999; Panitch et al., 1986), differences in the influences of the underlying disease process on the central nervous system (CNS) may be important. For example, in CHC, preliminary evidence suggests that variants of the hepatitis C virus specific to the brain may replicate within the CNS, which can activate microglia and possibly induce excitotoxicity (Forton et al., 2002*a*), resulting in greater susceptibility of CHC patients to IFN-α neurotoxicity.

Multiple mechanisms for neurotoxicity associated with IFN-α have been proposed, including direct effects on the brain (Akwa et al., 1998; Calvert & Gresser, 1979; Crow et al., 2003; Shibata & Blatteis, 1991; Smith et al., 1985; Yamada & Yamnaka, 1995) and indirect effects via changes in neuroendocrine systems, neurotransmitter function, and/or secondary cytokines (Daniels et al., 1990; Gisslinger et al., 1993; Licinio et al., 1998; Shuto et al., 1997). Understanding of these possible mechanisms is rudimentary at this time. However, the epidemic of CHC and the associated demand for treatment can provide a fruitful backdrop for investigating both the etiology and management of IFN-α-induced neurotoxicity.

In conclusion, the data collected in this study are consistent with previous reports that neuropsychological performances may be affected by administration of IFN-α. However, several limitations to the study deserve comment, particularly the small sample size, which may have reduced the likelihood of detecting additional group differences (i.e., Type II errors) and prohibited analyses of intragroup differences, such as whether the two types of pegylated IFN-α utilized in this study produced different performance patterns on objective cognitive measures, whether there was a dose–response relationship, and whether cognitive performances at retest differed according to virologic status (i.e., detectable or nondetectable viral load). Although we attempted to account for factors that may have contributed to group differences (see Table 1), the sample was one of convenience, and baseline characteristics contributing to the decision to undergo treatment may have influenced the findings. Reasons to forego treatment are varied, ranging from medical contraindications to low levels of inflammation and fibrosis to preference and timing, and these variables were not noted systematically in this study. The strengths of this study include the use of objective measures of cognitive dysfunction and an appropriate comparison group of nontreated CHC patients. Future research using larger sample sizes is needed to confirm these findings, to examine the effect of IFN-α on a broader range of neuropsychological test performances, and to clarify functional

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implications, if any. Results of this study suggest that the TMT may provide a feasible means to monitor objectively changes in prefrontal lobe functioning of CHC patients over time.

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