Cognitive Function Does Not Worsen During Pegylated Interferon and Ribavirin Retreatment of Chronic Hepatitis C

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Treatment of chronic hepatitis C with pegylated interferon (peginterferon) and ribavirin can cause or exacerbate depression but its effects on cognitive function are largely unknown. The aim of this study was to determine whether treatment with peginterferon and ribavirin adversely impacts cognitive function in patients with chronic hepatitis C. Prior nonresponders to interferon were retreated with peginterferon alfa-2a and ribavirin for 24 (n = 177) or 48 weeks (n = 57) in the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis trial. Cognitive function was prospectively assessed using a battery of 10 standardized neuropsychological tests at weeks 0, 24, 48, and 72. Cognitive impairment was defined based upon a global deficit score. The Beck Depression Inventory and Brief Symptom Inventory were used to assess mood status. The 57 subjects who completed 48 weeks of antiviral therapy reported significant increases in difficulty concentrating, emotional distress, and symptoms of depression, all of which improved after cessation of therapy [$P < 0.0001$, analysis of variance (ANOVA)]. Nonetheless, the frequency of cognitive impairment did not increase during the first 24 weeks of treatment in 177 patients (34% versus 32%, $P = 0.64$) nor in the 57 patients completing 48 weeks of treatment ($P = 0.48$, ANOVA). *Conclusion:* Retreatment of prior non-responders with peginterferon and ribavirin was not associated with objective evidence of cognitive impairment as measured by a comprehensive battery of neuropsychological tests. The lack of cognitive impairment is reassuring and suggests that self-reported symptoms of cognitive dysfunction are more likely related to the systemic and psychiatric side effects of antiviral treatment rather than measurable changes in cognition. (HEPATOLOGY 2007;45:1154-1163.)

Abbreviations: ANOVA, analysis of variance; BDI, Beck Depression Inventory; CVMT, continuous visual memory test; GDS, global deficit score; GSI, global severity index; HALT-C, Hepatitis C Antiviral Long-term Treatment against Cirrhosis; IFN, interferon; peg IFN, pegylated interferon; SS, standard score; WCST, Wisconsin card sorting test.

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Received October 10, 2006; accepted December 22, 2006.

Supported by the National Institute of Allergy and Infectious Diseases (NIAID); the National Cancer Institute; the National Center for Minority Health and Health Disparities; General Clinical Research Center grants from the National Center for Research Resources; National Institutes of Health; Hoffmann-La Roche, Inc.; Cooperative Research and Development Agreement (CRADA) with the National Institutes of Health; National Institute of Diabetes and Digestive and Kidney Diseases, Division of Digestive Diseases and Nutrition; University of Southern California, Los Angeles, CA (Contract N01-DK-9-2325, Grant M01RR-00043); University of Michigan Medical Center, Ann Arbor, MI (Contract N01-DK-9-2323, Grant M01RR-00042); New England Research Institutes, Watertown, MA (Contract N01-DK-9-2328).

This is publication number 22 from the HALT-C Trial Group.

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.21633

Potential conflict of interest: Dr. Fontana is in the speakers' bureau of Roche Pharmaceutical and Bristol-Myers Squibb. Dr. Lindsay received grants from and advises for Hoffmann-LaRoche, Inc., and Valeant Pharmaceuticals. She also received grants Schering-Plough Corp., Scripps Clinic Liver Research Consortium, and Idenix Pharmaceuticals, Inc. She advises for Gilead Sciences, Roche Diagnostics, Quest Lab., Amgen Corporation, Invesek, Bristol Myers Squibb, Charles River Lab., iMedOptions, Zymogenetics, Inc., Peregrine Pharmaceuticals, Inc., and Kendle International. She is a consultant for Fujisawa Research Institute of America, Inc., GlaxoSmithKline, Wellpoint Pharmacy Management, Aventix Pharmaceuticals, Inc., and Medtronics.

The combination of pegylated interferon (peginterferon) and ribavirin is now considered the optimal therapy for chronic hepatitis C.[1,2] A 48-week course of this combination results in sustained eradication of hepatitis C virus (HCV) RNA from serum in approximately 50% of patients.[1,2] Peginterferon and ribavirin may also be successful in selected nonresponders or relapsers to standard interferon with or without ribavirin.[3] Combination therapy, however, is associated with considerable side effects that can be dose limiting and lead to dose reductions in 40% and early discontinuation in up to 20% of treated patients.[1,2,4] Side effects of combination therapy include fatigue, muscle aches, hemolytic anemia, bone marrow suppression, exacerbation of autoimmune disorders, and a spectrum of neuropsychiatric complications.[4,5] Mood disorders such as depression, anxiety, and irritability are particularly common and reported in up to 50% of treated patients but can improve with peginterferon dose reductions and adjuvant medications.[6] Many patients also complain of "cloudy thinking" and describe difficulties in word finding, memory, and concentration, suggesting possible impairment of cognitive function, but prospective studies using objective measures of cognitive function have not been reported.[7,8] Subtle abnormalities in cognitive function have also been described in patients with chronic hepatitis C not receiving antiviral therapy.[8-10] The cause of these abnormalities is not known; however, possibilities include a direct effect of HCV, which may replicate in neurons as well as the effects of systemic cytokines, concomitant psychiatric disease, and subclinical hepatic encephalopathy.[11]

The Hepatitis C Antiviral Long-term Treatment Against Cirrhosis Trial (HALT-C) is a prospective multicenter study designed to investigate the potential benefit of maintenance therapy with peginterferon in reducing the rate of clinical outcomes in prior nonresponders with advanced fibrosis.[3,12] Initially, all patients were treated with peginterferon alfa-2a and ribavirin for 24 weeks in the "lead-in phase." Subjects who remained viremic at week 20 were eligible for entry into the randomized phase of the HALT-C trial, while subjects with undetectable HCV RNA by PCR continued in the "responder arm" of the study and were given a complete 48-week course of combination antiviral treatment. The cognitive study conducted at 2 of the HALT-C sites was designed to prospectively assess neuropsychiatric parameters before, during, and after treatment in the lead-in and responder arms of the study and in the randomized phase. Using a battery of 10 standardized neuropsychological tests, we hypothesized that patients receiving peginterferon and ribavirin would demonstrate evidence of reversible cognitive impairment.[13,14] We also hypothesized that patients with low cognitive scores at baseline and those experiencing depression on treatment would have the greatest incidence and severity of cognitive impairment. In this work, the results of neuropsychological testing in 177 patients who received peginterferon and ribavirin for 24 weeks during the lead-in phase and in 57 subjects who received 48 weeks of antiviral treatment in the responder arm of the HALT-C trial are reported.

Patients and Methods

Patient Population

Inclusion criteria for the HALT-C trial include the presence of detectable HCV RNA in serum, a liver biopsy within 12 months of enrollment demonstrating bridging hepatic fibrosis or cirrhosis, and lack of a sustained response to a prior course of standard interferon with or without ribavirin.[3,12] Patients with any other liver disorders or hepatic decompensation (Child-Turcotte-Pugh score >6, history of variceal hemorrhage, ascites, or hepatic encephalopathy) were excluded. Additional exclusion criteria included intolerance to interferon, anti-HIV reactivity, active alcohol or injection drug abuse, suicide attempt or hospitalization for depression within the past 5 years, and a history of a severe or uncontrolled psychiatric condition within the past 6 months. Participants in the HALT-C trial enrolled at the University of Michigan and University of Southern California were asked to also participate in this prospective study of cognitive testing at baseline, week 24, week 48, and week 72 of treatment. All details of this study were approved by the local Institutional Review Board and all patients gave written informed consent.

Baseline Assessment

Years of education, occupation, and baseline medication use were recorded. Lifetime psychiatric history was obtained using the computerized Composite International Diagnostic Interview (CIDI-LT).[15] A semiquantitative estimate of lifetime alcohol consumption was obtained using an adaptation of the Skinner survey.[16]

HALT-C Study Design

All subjects were treated with peginterferon alfa-2a at a dose of 180 μg per week (Pegasys; Roche Laboratories, Nutley, NJ) and ribavirin in doses of 1.0 to 1.2 g per day (Copegus, Roche Laboratories). Serum HCV RNA testing was done using the quantitative COBAS Amplicor HCV Monitor test v.2.0 (Roche Molecular Diagnostics, Branchburg, NJ), which has a lower limit of detection of 600 IU/mL. All samples with undetectable HCV RNA on the quantitative assay were retested with the qualitative COBAS Amplicor HCV test v.2.0 (Roche Molecular Di-

agnostics, Branchburg, NJ), which has a lower limit of detection of 100 IU/mL. Patients who failed to clear serum HCV RNA by week 20 were randomized at week 24 to receive low dose peginterferon (90 μg per week) or no therapy for the next 3.5 years. Patients who tested HCV RNA-negative at week 20 were considered virological responders and continued with combination antiviral therapy for 48 weeks in the responder arm of the study. Repeat HCV RNA testing was obtained at weeks 48 and 72. Subjects with undetectable HCV RNA at week 72 were considered to have achieved a sustained virological response.

Cognitive Function

A battery of 10 standardized neuropsychological tests with alternate forms when available were administered in a predetermined order at weeks 0, 24, 48, and 72.[9,17] The battery included tests designed to assess differing domains of cognitive function as follows: verbal memory using the selective reminding test; nonverbal memory using the continuous visual memory test; speed and efficiency of information processing using the serial digit learning, digit span test, and digit symbol test from the Wechsler Adult Intelligence Scale; visuomotor tracking using the simple reaction time, choice reaction time, and Trail's A and B; executive function using the Wisconsin card sorting test (WCST); and verbal processing using the Controlled Oral Word Association test (COWAT). The test-retest reproducibility varied from 0.62 for simple reaction time to 0.78 and 0.85 for digits forward and backward, respectively, and 0.80 and 0.92 for Trail's A and B, respectively.[18] The Shipley Institute of Living scale was administered at baseline and a full-scale intelligence quotient estimate from the Wechsler Adult Intelligence Scale-Revised was calculated using population controls with a mean of 100 and SD of 15.[19] Standard scores (SSs) were calculated for each neuropsychological test using normative data.

Cognitive impairment was defined by a global deficit score (GDS), which was calculated as the mean of the SSs of the component tests and strongly correlated with clinician assessment.[17] A GDS of >1.0, which represents a mean SS of >1 SD below the population mean on each individual test was chosen as our criteria for cognitive impairment. A GDS of 2.0 represents a mean SS of 2 SD below the mean of each individual test and a GDS of 3.0 represents a mean SS that is 3 SD below the mean of each test.

Mood Status

The Beck Depression Inventory-II (BDI-II) was used to assess mood at weeks 0, 4, 12, 24, 36, 48, and 72.[20] The BDI-II scores were coded as follows: no depression, ≤ 10; minimal depression, 11 to 14; mild depression, 15 to 19; moderate depression, 20 to 28; and severe depression, ≥ 29. The brief symptom inventory was used to assess emotional distress at the same times.[21] Subjects were classified as having clinically significant emotional distress if the global severity index (GSI) T-score was ≥ 63 (i.e., ninetieth percentile).

Data Analyses

Descriptive statistics of baseline demographic, clinical, and liver disease parameters are reported as mean $\pm$ SD or median and range. Changes in mean GDSs over time were assessed using repeated measures ANOVA (SAS Proc Mixed version 9.1). Similarly, change in the proportion with cognitive impairment over time was assessed using a repeated measures logistic regression analysis (SAS Proc Glimmix version 9.1). Change over time from week 0 to week 24 was assessed in the 177 patients with complete week 24 data. Change over the 4 time points of weeks 0, 24, 48, and 72 was assessed in the 57 patients in the responder arm with data available through week 72.

Results

Study Population

A total of 201 subjects were enrolled in the cognitive study at the 2 participating sites and were treated with peginterferon and ribavirin. At week 24, 177 subjects completed the cognitive testing while the remaining 24 subjects had either withdrawn from the HALT-C trial ($n = 14$), withdrawn from the cognitive study ($n = 5$), or had incomplete testing ($n = 5$) (Fig. 1). The demographic features and baseline cognitive scores of the 24 patients who did not complete the week 24 testing were not significantly different from those who remained in the study (data not shown). Among the 177 subjects completing 24 weeks of treatment in the lead-in phase, 68 were week 20 virological responders with undetectable HCV RNA and continued in the responder arm of the trial and 62 and 57 of them completed cognitive testing at weeks 48 and 72, respectively. The remaining 109 week 20 virological nonresponders had treatment discontinued at week 24 and were eligible for entry into the randomized phase of the HALT-C trial.

The baseline features of the 177 HALT-C patients that completed cognitive testing at weeks 0 and 24 were similar to the baseline features of the 57 subjects who completed 48 weeks of antiviral therapy and cognitive testing at week 72 (Table 1). A majority of the patients were Caucasian men infected with HCV genotype 1. The mean Shipley intelligence quotient scores of the HALT-C patients were normally distributed and similar to that of

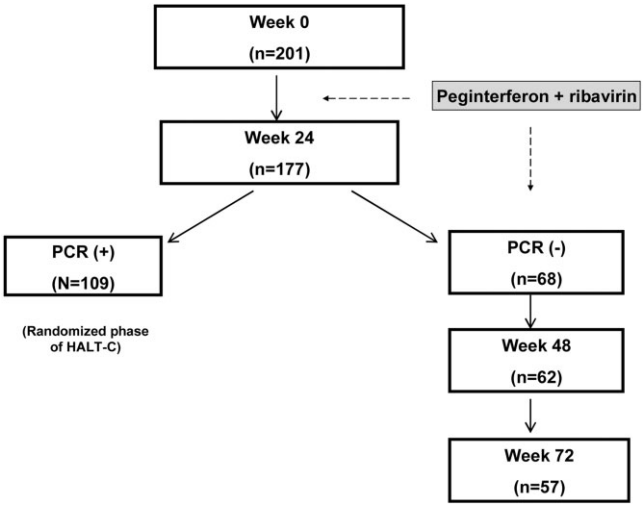

Fig. 1. Patient population. At week 24, 177 of the 201 chronic hepatitis C patients enrolled in the HALT-C cognitive study underwent repeat neuropsychological testing. The 68 patients who suppressed HCV RNA to undetectable levels at week 20 continued on peginterferon and ribavirin for a total of 48 weeks. At week 72, 57 responder arm subjects underwent a final neuropsychological evaluation.

the general United States population (i.e., mean U.S. score = 100 ± 15), suggesting that the general intellectual abilities of this patient cohort was not reduced as a group.[22] Nonetheless, a substantial proportion had evidence of cognitive impairment at baseline as defined by a GDS exceeding 1.0. Specifically, 32% of the 177 HALT-C subjects in the lead-in cohort and 25% of the week 20 virological responders had cognitive impairment with alterations in verbal recall and working memory at week 0, while other domains of cognitive function, including visuomotor tracking and executive function, remained largely intact (Table 2). Although the majority of patients had normal BDI-II scores (i.e., <11), 30% of the lead-in patients and 26% of the responder arm patients were receiving either an anxiolytic or antidepressant medication at baseline. However, there was no significant relationship between the use of these medications and cognitive impairment at baseline ($P = 0.79$).

Changes in Cognitive Function Through Treatment Week 24

Contrary to expectations, the overall frequency of cognitive impairment remained unchanged in the 177 patients receiving antiviral therapy during the lead-in phase of the HALT-C trial (32% at week 24 versus 34% at week 0, $P = 0.64$) (Fig. 2). More specifically, 22 of the 120 patients (18%) without cognitive impairment at week 0 met criteria for impairment at week 24 with a GDS >1.0. However, 19 of the 57 patients (33%) with cognitive impairment at week 0 were no longer impaired at week 24. Thus, there was no net increase in the frequency of cognitive impairment at week 24 compared to week 0. In addition, there was no significant change in the mean GDS at weeks 0 and 24 (0.76 versus 0.75, $P = 0.84$). Furthermore, there was no correlation between the week 20 virological response and cognitive impairment at week 24 (Fig. 2). There was also no significant relationship between the total dose of peginterferon and ribavirin received and the incidence of cognitive impairment during the first 24 weeks of treatment (data not shown). Reported reasons for peginterferon dose reductions in 106 patients included myelotoxicity (65%), fatigue (22%), mood disorders (14%), and other reasons (20%), while indications for ribavirin dose reductions in 108 patients included anemia (67%), fatigue (19%), cough (18%), and other reasons (21%). Finally, there was no significant relationship between changes in the BDI-II score and the incidence of cognitive impairment ($P = 0.18$).

Changes in Cognitive Function Through Week 72 in the Responder Arm

Among the 57 patients who received 48 weeks of antiviral therapy, there was no significant increase in the incidence of cognitive impairment over time ($P = 0.48$, ANOVA) (Fig. 3). In addition, the mean GDSs also remained unchanged over time (data not shown). Although subjects who experienced a virological relapse or breakthrough at week 72 tended to have a higher incidence of cognitive impairment at week 24, the incidence of impairment through week 72 was not significantly different from subjects with a sustained virological response (Fig. 3). Analysis of the individual neuropsychological test results demonstrated that the SSs actually improved on the continuous visual memory test (CVMT), Digit Span, Digit Symbol, Trail's B, and the WCST at various times compared to baseline (Table 2). In particular, the SSs of the CVMT and Trail's B tests significantly increased at weeks 24, 48, and 72 compared to baseline. In comparison, the improvements in the SSs of the Digit Symbol, Digit Span, and the WCST were less dramatic and consistent. Adherent subjects who received at least 80% of the intended doses of peginterferon and ribavirin through week 48 were not more likely to develop evidence of cognitive impairment compared to nonadherent subjects (data not shown).

Changes in Mood Status and Emotional Distress Through Week 72 in the Responder Arm

The mean BDI-II scores of the 57 patients who received 48 weeks of therapy significantly increased at weeks 24 and 48 compared to baseline and then subsequently improved off-treatment at week 72 ($P = 0.0002$ by re-

Table 1. Clinical Characteristics of the Study Population

	Lead-in phase (n = 177)	Responder phase (n = 57)
Age (yr)	50.2 ± 7.8	49.4 ± 7.4
Male (%)	69	68
Ishak fibrosis 5/6 (%)	37	25
HCV RNA (log_{10} IU/ml)	6.5 ± 0.5	6.5 ± 0.6
HCV genotype 1 (%)	87	81
Ethnicity		
White (%)	71	84
Black (%)	14	4
Other (%)	3	4
Hispanic (%)	12	9
Educational level (1-16 yr)	10.5 ± 2.2	10.3 ± 2.2
At least high school (%)	89	89
At least college (%)	24	18
Occupational level (1-6)	4.0 ± 1.6	4.0 ± 1.4
1 = Unskilled labor, farm labor (%)	2	0
2 = Semiskilled, operative, service (%)	27	23
3 = Not in work force > 10 yr (%)	11	13
4 = Skilled labor/craftsman/foreman (%)	13	21
5 = Manager/clerical/ sales work (%)	26	25
6 = Professional/technical (%)	21	18
Intelligence quotient	99.5 ± 12.7	101.6 ± 12.1
Diabetes mellitus (%)	25	28
Prior IFN + ribavirin (%)	69	53
Week 0 on antidepressant/anxiolytic (%)	30	26
Week 0 global deficit score	0.76 ± 0.6	0.70 ± 0.7
Global deficit score >1 (%)	32	25
Week 0 BDI-II score	6.2 ± 6.2	5.9 ± 6.0
% <11	79	81
% 11–14	8	9
% 15–19	7	5
% 20–28	5	5
% >29	1	0
Week 0 GSI score	51.2 ± 11.5	51.4 ± 10.8
GSI score ≥63 (%)	15	11
Taking >80% pegIFN and ribavirin (week 0 to 20) (%)	46	51
Taking >80% pegIFN (week 0 to 20) (%)	70	81
Taking >80% ribavirin (week 0 to 20) (%)	63	61
Taking >80% pegIFN and ribavirin (week 0 to 48) (%)	NA	42
Taking >80% pegIFN (week 0 to 48) (%)	NA	70
Taking >80% ribavirin (week 0 to 48) (%)	NA	60

NOTE: Results reported as mean ± SD or %.
Abbreviation: IFN, interferon; pegIFN, peginterferon (pegylated interferon)

peated measures ANOVA) (Fig. 4). Similarly, the mean GSI score, which reflects emotional distress, significantly increased during treatment in the 57 responder patients and subsequently improved off-treatment at week 72 ($P < 0.0001$ by repeated measures ANOVA) (data not shown). The proportion of patients with clinically significant emotional distress defined as a GSI score >63 also significantly increased over time from 11% at week 0 to 14% and 25% at weeks 24 and 48, respectively, and then returned to 12% at week 72 ($P = 0.043$) (data not shown). Analysis of specific questions addressing difficulty concentrating and indecisiveness from the BDI-II also demonstrated significant worsening during antiviral therapy, which improved off-treatment (Fig. 5).

Discussion

Previous studies have demonstrated frequent and problematic neuropsychiatric toxicity in oncology patients receiving high daily doses of standard interferon, including depression and anxiety.[23-25] In some oncology patients, cognitive impairment during interferon therapy was severe and disabling and persisted even after treatment was discontinued.[26] The pattern of described cognitive abnormalities is suggestive of a frontal or subcortical effect of interferon that may be due to changes in central adrenergic or serotonergic neurotransmission or cerebral blood flow.[27] Clinical trials of peginterferon and ribavirin for chronic hepatitis C also reported high rates of

Table 2. Standard Scores of Individual Neuropsychological Tests in 57 Patients Completing 48 Weeks of Antiviral Therapy

Test	Week 0	Week 24	Week 48	Week 72
Selective reminding test SS	31.42 (15.1)	30.35 (16.7)	32.85 (15.8)	32.33 (17.9)
CVMT SS	42.92 (14.5)	48.23 (16.3)*	53.50 (15.5)*	54.47 (14.6)*
Digit span SS	43.92 (7.5)	44.72 (7.9)*	46.55 (11.0)*	44.92 (7.4)
Digit symbol SS	47.58 (8.8)	47.68 (9.6)	49.65 (10.4)	53.07 (10.5)*
Serial digit learning SS	38.73 (17.9)	37.58 (18.4)	36.17 (19.0)	41.25 (18.0)
Trail's A SS	48.14 (12.8)	49.72 (11.8)	51.61 (13.52)	53.37 (12.7)
Trail's B SS	46.96 (16.4)	49.24 (13.9)*	51.47 (14.1)*	54.28 (14.5)*
Finger tapping test SS	56.86 (14.4)	55.39 (14.8)	58.34 (12.2)	56.83 (11.3)
WCST SS	47.93 (13.6)	47.92 (14.7)	49.80 (13.1)*	51.75 (9.9)*
COWAT SS	54.70 (10.1)	52.78 (9.6)†	54.81 (11.4)	58.35 (10.5)*
Simple reaction time (msec)	352.6 (78.6)	384.1 (102.4)*	396.8 (88.5)*	367.1 (90.6)
Choice reaction time (msec)	494.5 (130.4)	499.9 (105.5)	504.8 (103.1)	492.7 (106.1)
Simple reaction time >425 msec (%)	20	25	33*	21
Choice reaction time >550 msec (%)	29	25	30	25

NOTE: All SSs reported as mean (SD).

Abbreviations: COWAT, Controlled Oral Word Association test; SS, standard score.

*SS significantly better (higher) compared to week 0 at $P < 0.05$.

†SS significantly poorer (lower) compared to week 0.

mood disorders and self-reported symptoms of difficulty thinking and concentrating, fatigue, and depression.[2,5,28] Therefore, we postulated that chronic hepatitis C patients receiving antiviral therapy in the HALT-C study would demonstrate an increasing frequency of cognitive impairment using a comprehensive battery of 10 neuropsychological tests.[8] However, the frequency of cognitive impairment did not increase at week 24 compared to baseline in the 177 patients completing the lead-in phase (Fig. 2). In addition, the frequency of impairment did not increase through week 48 compared to baseline in the 57 responder arm patients, despite statistically and clinically significant increases in depression and emotional distress scores (Figs. 3 and 4). Finally, there was no significant relationship between viral suppression and the frequency or severity of cognitive impairment during the lead-in and responder arms of the trial (Figs. 2 and 3).

The lack of new or worsening cognitive impairment during antiviral treatment in the HALT-C study may reflect differences in study design and methodology or the dose of interferon used compared to previous studies of oncology and chronic hepatitis C patients.[26-28] The current study was adequately powered since each subject was compared to his or her pretreatment baseline status and the total sample size exceeded that utilized in other studies of chronic hepatitis C patients.[2,5,28] A battery of 10 standardized neuropsychological tests was selected to detect subtle changes in multiple domains of cognitive function over time.[7-9] In addition to comparing individual test

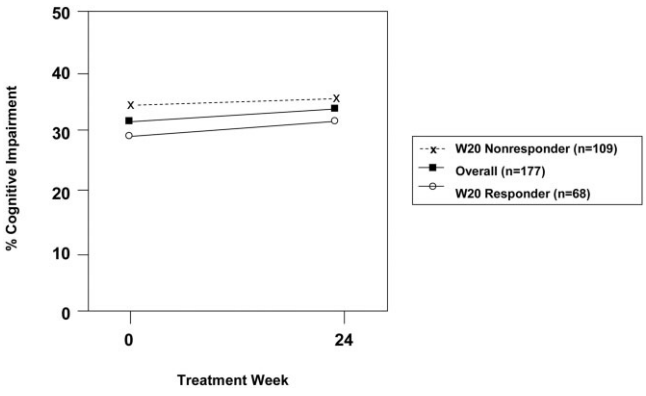

Fig. 2. Cognitive impairment during the lead-in phase of HALT-C. The frequency of cognitive impairment in the 177 patients treated in the lead-in phase of HALT-C did not significantly change between week 0 and week 24 (32% versus 34%, $P = 0.64$). In addition, the frequency of impairment did not correlate with suppression of HCV RNA to undetectable levels in the 68 virological responders compared to the 109 patients who remained HCV RNA-positive ($P = 0.58$).

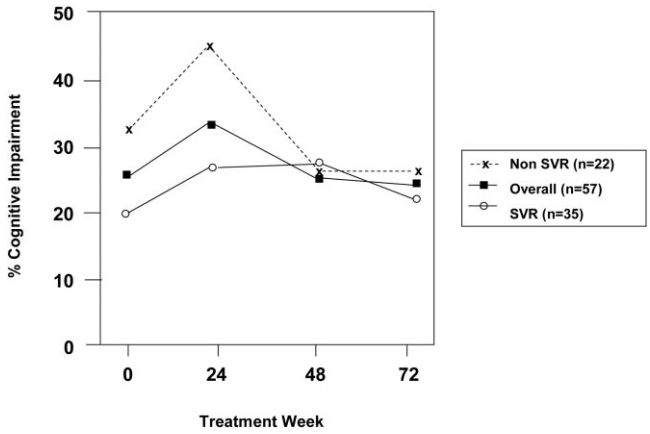

Fig. 3. Cognitive impairment in the responder arm of HALT-C. The frequency of cognitive impairment in the 57 HALT-C patients treated for 48 weeks did not significantly change over time ($P = 0.48$). Although the 22 subjects without a sustained virological response (SVR) tended to have a higher incidence of impairment at week 24 compared to the 35 with an SVR, this trend was not statistically significant ($P = 0.28$).

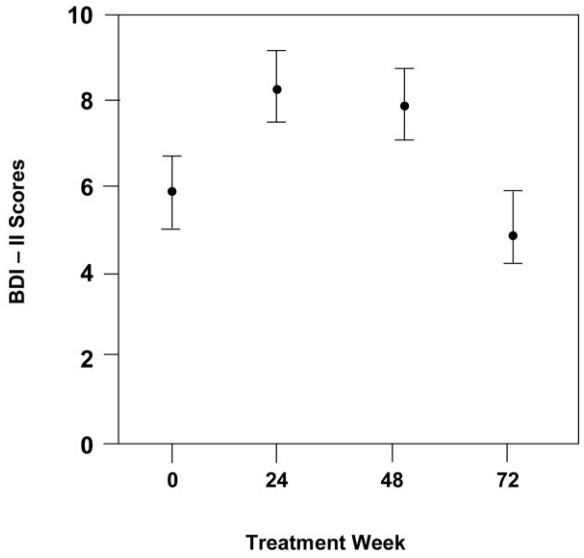

Fig. 4. Beck depression scores. The mean Beck scores of the 57 patients receiving 48 weeks of peginterferon and ribavirin significantly increased during antiviral therapy and then returned to their pretreatment values at week 72 ($P = 0.0002$).

scores over time, a GDS previously shown to correlate with clinician assessment was used to define cognitive impairment.[17] It is possible that the early studies of oncology patients were methodologically flawed or not representative of the neurotoxic profile of standard doses of peginterferon used to treat chronic hepatitis C patients. For example, in a randomized controlled study of standard interferon given for 36 months to 75 melanoma patients, there was no evidence of worsening cognitive function despite increased anxiety over time in the interferon treated group compared to the untreated group.[29] Small pilot studies in HIV as well as chronic hepatitis C patients receiving standard interferon at low to moderate doses (i.e., 3 to 6 million units 3 times a week) also failed to show any significant changes in cognitive function despite development of neurophysiological abnormalities in some.[30-32] Therefore, the literature on the effects of interferon therapy on cognitive function is mixed at best, and our initial hypotheses based upon the published reports of high dose interferon therapy in oncology patients may have been incorrect. In addition, the selection of patients with demonstrated tolerance to prior interferon therapy in the HALT-C study may have precluded us from observing an adverse effect of treatment on cognitive function. Nonetheless, 7% of the lead-in patients prematurely discontinued treatment due to severe side effects and 30% and 37% of the lead-in patients required a peginterferon or ribavirin dose reduction, respectively, due to side effects that were most commonly due to myelotoxicity or fatigue (Table 1).

An alternative explanation for the lack of cognitive impairment observed in the current study is the potential for practice effects when neuropsychological tests are administered repeatedly over time.[33,34] At least several of the tests used in our battery (i.e., Trail's test, Finger Tapping test, Digit Span forward, Reaction time) have been reported to lack significant practice effects.[35] To minimize potential practice effects in the current study, tests with alternate forms were selected whenever possible (e.g., 4 forms of the Selective reminding test) and the tests were administered in a predetermined order.[36] The testing was also spaced as far apart in time as possible (e.g., every 6 months), yet still allowing us to study the effects of a 48-week course of antiviral therapy. Upon careful inspection of the SSs of the 10 tests administered, the mean SS

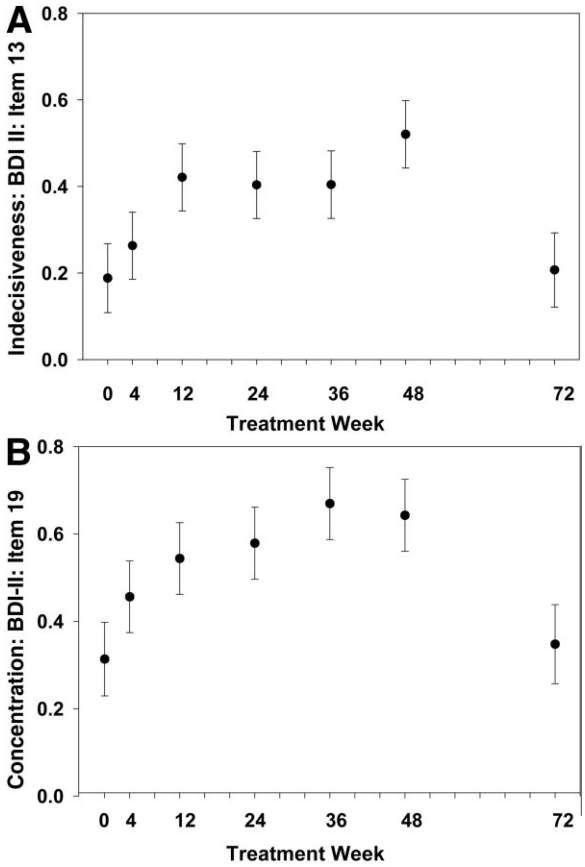

Fig. 5. Self-reported symptoms of cognitive dysfunction during combination antiviral treatment (from the BDI-II). (A) Indecisiveness. Subjects reported a significant increase in difficulty making decisions while receiving antiviral therapy compared to baseline (Scale 0 to 3: 0 = make decisions well; 3 = trouble making decisions) (week 12, week 24, week 36, and week 48 versus week 0, $P < 0.05$, McNemar's test). (B) Difficulty concentrating. Subjects reported a significant increase in difficulty concentrating during antiviral therapy compared to baseline which improved after treatment cessation (Scale 0 to 3: 0 = concentrate well; 3 = can't concentrate on anything) (week 12, week 24, week 36, and week 48 versus week 0, $P < 0.05$, McNemar's test). (Data plotted as mean + SD).

of the Trail's B and the CVMT demonstrated statistically significant improvements over time (Table 2). Prior studies have shown that figural memory tests, which measure a similar cognitive domain as the CVMT, demonstrate a significant practice effect on short-term readministration, while practice effects have generally not been reported for Trail's B.[36,37] Nevertheless, practice effects based upon procedural learning, (i.e., improved performance due to increasing familiarity with the test rules), cannot be excluded, particularly in this cohort of generally well-educated patients with high levels of occupational functioning.[38,39] Future longitudinal studies of cognitive function in chronic hepatitis C patients should incorporate tests with multiple alternate forms as well as a control group of patients not receiving antiviral therapy to minimize any potential procedural learning or practice effects.

Prior studies have demonstrated a high prevalence of mood disorders among chronic hepatitis C patients prior to treatment, as was seen in our study population (Table 1).[5-7] In addition, clinically and statistically significant decrements in health-related quality of life have consistently been reported with interferon and ribavirin therapy.[5,40] Hilsabeck et al.[32] recently demonstrated that chronic hepatitis C patients frequently complain of subjective symptoms of impaired cognition during antiviral therapy that are not related to objective performance on neuropsychological tests, but are associated with symptoms of depression, anxiety, and fatigue. Similarly, multiple studies of epilepsy and multiple sclerosis patients demonstrate a consistently stronger relationship between subjective cognitive complaints with measures of depression and anxiety than with performance on objective neuropsychological tests.[41-44] Therefore, it is possible that the battery of neuropsychological tests used in this study and others do not adequately measure the everyday problems in short-term memory that patients notice the most. Our data clearly demonstrates an increased frequency of depression and emotional distress during treatment, and symptoms of difficulty concentrating and making decisions (Figs. 4 and 5). Therefore, self-reported symptoms of cognitive impairment and difficulty thinking during antiviral treatment may reflect psychiatric side-effects and mood disorders resulting from treatment rather than impairment of cognitive function as measured by the test battery. Alternatively, the assessment of cognitive function using a battery of objective tests may not adequately capture the cognitive demands and challenges of everyday life that chronic hepatitis C patients experience during antiviral therapy.[44] To further explore these issues, studies using standardized assessment of subjective cognitive symptoms during antiviral treatment compared to mood status and objective performance on a battery of neuropsychological tests are needed.

The lack of impaired cognition during peginterferon and ribavirin treatment is reassuring to the many chronic hepatitis C patients in need of future therapy. In fact, fear of medication side-effects may preclude many patients and physicians from considering antiviral treatment altogether. Other investigators have suggested that the presence of replicating HCV in the body and particularly in the brain may contribute to the high incidence of mood disorders, impaired cognition, and reduced quality of life reported in chronic hepatitis C patients compared to uninfected controls.[10,45,46] The lack of a correlation between HCV RNA suppression with objective measures of cognitive function in the current study may, in part, be due to the small number of patients enrolled or to the lack of a true biological effect of HCV replication on cognitive function. In patients with myeloproliferative disorders who are prothrombotic and have cognitive impairment, improved cognitive function has been reported following interferon treatment, presumably due to improved cerebral blood flow and oxygenation.[47] Similarly, use of interferon beta to treat multiple sclerosis patients has been associated with improved cognition, presumably due to reduced cerebral inflammation.[48] In patients with chronic hepatitis C, the effect of interferon therapy on brain function may be complex, in that any improvement due to suppression of HCV replication may be offset by the concomitant development of serotonin depletion with resultant mood disorders, leading to no discernible net change in cognition.[49,50] Additional prospective studies assessing central neurotransmission, blood flow, and physiology, along with cognitive function during antiviral therapy, appear warranted to further explore these hypotheses.

In summary, no significant change in cognitive function was observed in the 177 prior nonresponders retreated with peginterferon and ribavirin for 24 weeks in the HALT-C study. In addition, the 57 week 20 virological responders who completed a 48-week course of antiviral treatment also failed to demonstrate any significant increase in the frequency or severity of cognitive impairment. Therefore, the common complaint of difficulty thinking and concentrating during antiviral therapy may relate more to the systemic side-effects of treatment (i.e., fatigue, mood disorders) rather than direct effects of peginterferon on cognitive function as measured on a battery of objective neuropsychological tests.

Acknowledgment: In addition to the authors of this manuscript, the following individuals were instrumental in the planning, conduct and/or care of patients enrolled in this study at each of the participating institutions, as

follows: University of Southern California, Los Angeles, CA (Contract N01-DK-9-2325, Grant M01RR-00043): Carol B. Jones, R.N., Susan L. Milstein, R.N., and the USC Neuropsychology Technicians; University of Michigan Medical Center, Ann Arbor, MI (Contract N01-DK-9-2323, Grant M01RR-00042): Pamela Richtmyer, B.S., L.P.N., C.C.R.C., Erin Ford, B.S., Leslie Giudotti, Emily Anderson; New England Research Institutes, Watertown, MA (Contract N01-DK-9-2328): Teresa M. Curto, M.S.W., Margaret C. Bell, R.N., M.S., M.P.H.; National Institute of Diabetes and Digestive and Kidney Diseases, Division of Digestive Diseases and Nutrition, Bethesda, MD: Leonard B. Seeff, M.D., Patricia R. Robuck, Ph.D., Jay H. Hoofnagle, M.D., James E. Everhart, M.D.

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