Published in final edited form as:

Am J Gastroenterol. 2010 July ; 105(7): 1551–1560. doi:10.1038/ajg.2010.3.

Cognitive function does not worsen during long-term low dose peginterferon therapy in patients with chronic hepatitis C

Robert J. Fontana, MD¹, Linas Bieliauskas, PhD^{2,3}, Carla Back-Madruga, PhD⁴, Karen L Lindsay, MD⁵, Heather J. Litman, PhD⁶, Anna S.F. Lok, MD¹, and Ziad Kronfol, MD⁷ on behalf of the HALT-C Trial Group

¹Division of Gastroenterology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI

²Neuropsychology Section, Department of Psychiatry, University of Michigan, Ann Arbor, MI

³Psychology Service, Veterans Affairs Health System, Ann Arbor, MI

⁴Department of Psychiatry and the Behavioral Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA

⁵Division of Gastrointestinal and Liver Diseases, Keck School of Medicine, University of Southern California, Los Angeles, CA

⁶New England Research Institutes, Watertown, MA

⁷Depression Center, University of Michigan, Ann Arbor, MI

Abstract

OBJECTIVES—Neuropsychiatric toxicity is a common dose-limiting side effect of interferon therapy. The primary aim of this study was to determine if patients receiving long-term low dose peginterferon therapy had a higher incidence of cognitive side effects compared to untreated patients enrolled in the HALT-C Trial.

METHODS—129 patients with chronic hepatitis C and advanced fibrosis completed a battery of 10 neuropsychological tests and the Beck Depression Inventory at pretreatment baseline and months 12, 24, 36, and 48 while receiving long-term peginterferon 2a (90 ug/week) or no therapy during the randomized phase of the HALT-C Trial. Cognitive impairment was defined as a global deficit score (GDS) ≥ 1.0 .

RESULTS—The mean age was 51.2 years, 67% were male, and 42% had cirrhosis. After accounting for baseline GDS scores, the mean GDS scores did not significantly change over time ($p = 0.46$) nor with treatment group ($p = 0.49$). Cognitive function was also not influenced by medication adherence in the 66 patients receiving maintenance peginterferon ($p = 0.14$) after controlling for baseline GDS scores and time. Beck Depression scores did not significantly increase over time ($p = 0.60$) nor did they vary by treatment group ($p = 0.74$). Although 32% of patients experienced objective worsening of their liver disease during follow-up, the frequency

Address all correspondence to: Robert J. Fontana, MD, Associate Professor of Medicine, 3912 Taubman Center, Ann Arbor, MI 48109-0362, Tel: 734-936-4780, Fax: 734-936-7392, rfontana@med.umich.edu.

*The HALT-C Trial was registered with clinicaltrials.gov (#NCT00006164).

Financial Disclosures

Financial relationships of the authors with Hoffmann-La Roche, Inc., are as follows:

R.J. Fontana is on the speaker's bureau; K.L. Lindsay is a consultant and receives research support; and A.S.F. Lok is a consultant.

Authors with no financial relationships related to this project are: L. A. Bieliauskas, C. Back-Madruga, H. J. Litman, and Z. Kronfol.

and severity of cognitive impairment did not differ in those with and without disease progression ($p=0.71$).

CONCLUSIONS—Measures of cognitive function were not influenced by low dose peginterferon treatment nor with objective evidence of liver disease progression in patients with advanced chronic hepatitis C prospectively followed for 3.5 years.

Keywords

neuropsychiatric toxicity; cirrhosis; interferon; brain; encephalopathy

Introduction

Cross-sectional studies suggest that patients with chronic hepatitis C virus (HCV) infection have a higher incidence of cognitive impairment compared to uninfected controls (1–3). Nevertheless, the association between liver disease severity and cognitive impairment has been inconsistent raising the possibility that the observed impairment may reflect psychiatric co-morbidities, prior substance abuse, or other factors (4, 5). On the other hand, detection of replicating HCV in the cerebrospinal fluid of patients with chronic hepatitis C also raises the possibility that this virus may have direct or indirect effects (via pro-inflammatory cytokines) on the brain that can alter mood and cognition (6,7). For example, studies using sensitive physiological measures have demonstrated objective abnormalities in brain metabolism among patients with hepatitis C that improve after antiviral therapy and with viral clearance (1, 8–10).

Many HCV patients complain of difficulty concentrating and completing tasks during interferon treatment (11–13). Impaired cognitive function can not only lead to reduced work productivity and health-related quality of life but may also contribute to mood disturbances that develop in 40 to 60% of patients receiving interferon and ribavirin (14–15). However, previous studies of cognition during antiviral therapy have enrolled a limited number of patients, used various treatment regimens, and have not identified a consistent pattern of interferon-induced alterations in cognition. Recently, we assessed cognitive function using a battery of validated neuropsychological tests in 201 HCV patients with advanced fibrosis who were treated with full-dose peginterferon and ribavirin in the lead-in phase of the Hepatitis C Antiviral Long-term treatment against Cirrhosis (HALT-C) Trial (13). Contrary to expectations, the incidence and severity of cognitive impairment did not increase with full dose peginterferon and ribavirin therapy compared to pretreatment baseline. However, the question remains regarding the safety and tolerability of low-dose peginterferon given for several years compared to no treatment in HCV patients with advanced fibrosis. The aim of the current study is to report upon longitudinal changes in cognitive function and mood status in virological non-responders enrolled in the randomized phase of the HALT-C Trial (16). In the current study, 129 patients with chronic hepatitis C who were non-responders to prior antiviral therapy were randomized to receive either low-dose peginterferon 2a versus no additional treatment for 3.5 years. We hypothesized that subjects receiving maintenance peginterferon would have a higher incidence of mood and cognitive disturbances compared to the untreated controls. In addition, we hypothesized that subjects experiencing liver disease progression during follow-up would have a higher incidence of cognitive impairment compared to patients with stable liver disease (17).

Methods

Study design & patient population

Patients failing to achieve a sustained virological response with peginterferon and ribavirin treatment, advanced hepatic fibrosis on biopsy (i.e. Ishak stage ≥ 3 fibrosis) and no history of hepatic decompensation or hepatocellular carcinoma (HCC) were eligible for enrollment into the randomized phase of the HALT-C Trial (16, 18, 19). Subjects were randomized to receive peginterferon $\alpha 2a$ at a dose of 90 ug/week (Pegasys; Roche Laboratories, Nutley, NJ) or no treatment for 3.5 years. Patients were seen every 3 months and underwent a history, physical examination, and laboratory testing to monitor the effects of treatment and assess for clinical endpoints and adverse events. The primary outcome of the study was progression of liver disease within 1,400 days of randomization including clinical outcomes defined as death, hepatic decompensation (i.e. variceal hemorrhage, ascites, hepatic encephalopathy etc), HCC, or a Child-Turcotte Pugh (CTP) score of ≥ 7 on two consecutive study visits. In addition, for subjects with precirrhotic fibrosis at entry, a ≥ 2 point increase in Ishak fibrosis score on a liver biopsy done at month 18 or month 36 following randomization was considered clinically significant histological progression.

Participants in the HALT-C Trial enrolled at the University of Michigan and University of Southern California were asked to participate in this prospective study of cognitive function and mood status. All details of the study were approved by the local Institutional Review Boards and all patients provided separate written informed consent for this ancillary study of the HALT-C Trial.

Cognitive function

A battery of 10 standardized neuropsychological tests were administered in a predetermined order at pretreatment baseline (i.e prior to the lead-in phase) and months 12, 24, 36, and 48 of the randomized phase as previously described (4, 13). The baseline cognitive assessment was generally done on the same day as the initiation of antiviral medication with nearly all subjects having completed the battery within 1 month before starting medication. Briefly, verbal memory was assessed using the Selective Reminding test; non-verbal memory using the Continuous Visual Memory test; speed and efficiency of information processing using the Serial Digit Learning, Digit Span, and Digit Symbol tests from the Wechsler Adult Intelligence Scale; Visuomotor tracking using the Simple Reaction Time, Choice Reaction Time, Trail's A and B; executive function using The Wisconsin Card Sorting test; and verbal processing using the Controlled Oral Word Association test. Alternate forms were available for the Selective Reminding test, Serial Digit Learning, and the Controlled Oral Word Association test. The Shipley Institute of Living scale was administered at baseline and a full scale Intelligence Quotient (IQ) estimate from the Wechsler Adult Intelligence Scale-Revised was calculated using population controls with a mean of 100 and standard deviation of 15 (20). Standard scores (SS) (also known as T-scores) were calculated for each neuropsychological test using normative data and controlling for patient age, education, and gender where appropriate. Cognitive impairment was defined by a global deficit score (GDS) which was calculated as the mean of the standard scores of the component tests and strongly correlated with clinician assessment (21). Similar methodology has been used in studies of cognition in patients with HIV infection and been shown to be superior to standard deviation cutoff approaches in terms of sensitivity and specificity in identifying impaired patients (22, 23). A global deficit score of > 1.0 which represents a mean standard score of more than 1 standard deviation below the population mean across the individual tests was chosen as our criteria for cognitive impairment which was previously shown to correlate with clinician assessment in the HALT-C Trial population (21).

Assessment of mood status

The Composite International Diagnostic Interview (CIDI) is a computerized self-administered instrument for the assessment of mental health disorders according to the Diagnostic and Statistical Manual of Mental Disorders –IV (DSM-IV) criteria (24). In this study, the lifetime (LT) version of the CIDI that included depression, anxiety, alcohol, and substance abuse modules was self-administered at baseline (Week 0).

The Beck Depression Inventory version 2 (BDI-II) is a 21-item, self-administered questionnaire designed to screen for depressive symptoms over the past 2 weeks (25). The BDI-II was administered at pretreatment baseline (week 0 prior to the lead-in phase) and at months 12, 24, 36, and 48 of the randomized phase. A score < 10 was considered as no depression, 11–14 as minimal, 15–19 as mild, 20–28 as moderate, and > 28 as severe depression. Lifetime alcohol consumption was estimated using a modification of the Skinner survey (26).

Data analyses

Descriptive statistics of baseline demographic and clinical features are reported as number and percent or mean and standard deviation (SD). T-tests were used to assess whether mean standard scores, GDS, and BDI-II scores varied between treatment and control groups at baseline and at each subsequent study visit. Changes in mean GDS and BDI-II scores over time adjusting for baseline scores were assessed using repeated measures analysis of variance (ANOVA). This method allows us to use all available data for each patient over time. Cox proportional hazards survival analysis was used to predict liver disease progression. All analyses were performed at the Data coordinating center (New England Research Institutes, Watertown, MA) with SAS statistical software (9.2, SAS Institute, Cary, NC). P-values less than 0.05 were considered statistically significant.

Results

Patient population

A total of 129 HCV patients enrolled at the two clinical sites underwent cognitive testing during the randomized phase of HALT-C. The baseline characteristics of these 129 patients were not significantly different from the 91 subjects at the two sites who did not participate. In addition, there was no significant difference in baseline parameters in subjects enrolled from the two sites except for the proportion of Caucasian patients (78% UMich vs 61% USC). The mean patient age was 51.2 years, 67% were male, 70% were Caucasian, and 42% had cirrhosis. The educational level of the overall cohort was high with a mean of 13.6 years of education, 24% having completed a college degree, and a mean (SD) Shipley IQ of 99.2 (13.1). Baseline demographic, clinical, and liver disease characteristics were similar in the patients randomized to peginterferon treatment compared to the untreated controls (Table 1).

The mean (SD) pretreatment baseline Global Deficit Score (GDS) was 0.68 (0.61) and 28% met criteria for pretreatment baseline cognitive impairment with a GDS ≥ 1.0 (Table 2). Mild abnormalities in baseline verbal recall and working memory were noted including learning of word lists and repetition of an extended series of digits as previously reported (13). There was a low prevalence of slowed/delayed fine motor skills as reflected by the simple and choice reaction time scores. The mean (SD) pretreatment baseline BDI-II score was 6.4 (6.6) and 25.6% of the cohort met criteria for mild depression.

Cognitive function during the randomized phase

Repeat cognitive testing was completed in 117 randomized patients at month 12, 106 at month 24, 94 at month 36, and 82 patients at month 48. Careful inspection of the individual

test standard scores indicates significantly improved performance on the Continuous Visual Memory Test, Digit symbol test, and Trail's A test at subsequent time points compared to baseline in the peginterferon treated patients and the untreated controls (Table 2) as well as when the patients were pooled together (data not shown). Using repeated measures ANOVA and controlling for baseline scores and treatment group, some of the GDS components including the Selective reminding test, ($p=0.03$), digit span ($p=0.009$), and Trail's A ($p=0.05$) significantly improved over time. These improvements likely represented the effects of repeated administration ("practice effects") since the improvements were evident at the 12 month study visit and changed little thereafter (27). However, the other individual test standard scores did not consistently change at subsequent time points compared to baseline in either the peginterferon nor the untreated control patients (Table 2). After accounting for baseline GDS scores, the overall mean GDS scores did not significantly change over time ($p=0.46$) and the percent of subjects with a GDS > 1.0 also did not significantly change over time compared to pretreatment baseline. In summary, overall cognitive function did not significantly decline during the 3.5 years of follow-up.

Analysis of the impact of treatment group on individual test scores and the summary GDS scores demonstrated no significant effect of maintenance peginterferon treatment on cognitive test scores during the randomized phase (Table 3). Using repeated measures ANOVA, mean GDS scores did not vary by treatment group ($p=0.49$) or over time ($p=0.46$) after accounting for baseline GDS scores ($P < 0.001$). In order to determine if subjects with pretreatment cognitive impairment (i.e. GDS ≥ 1) were at increased risk for more frequent or severe impairment over time compared to the patients without baseline impairment, these two groups were analyzed separately. Among the 36 patients with baseline cognitive impairment, the mean GDS scores at subsequent visits improved compared to baseline whereas the GDS scores of the 93 subjects without baseline impairment remained unchanged (Figure 1). However, after controlling for baseline levels, the trend in GDS scores in the impaired versus unimpaired patient groups were not significantly different over time (repeated measures ANOVA, interaction $p=0.36$). In addition, further models demonstrated no significant interaction between time, baseline impairment status and treatment group ($p=0.77$) indicating that peginterferon was not associated with changes in cognition over time.

Beck Scores during the randomized phase

The BDI-II scores were expected to be significantly worse (i.e. higher) in the patients receiving maintenance peginterferon compared to the untreated patients during the randomized phase. Although the mean BDI-II scores at the study visits tended to be higher in the treated patients, they were not significantly different compared to those of the untreated patients at baseline (6.7 vs 6.0), month 12 (7.7 vs 6.5), month 24 (7.0 vs 6.4), month 36 (7.6 vs 6.7), and month 48 (6.0 vs 6.1). In a repeated measures ANOVA of the BDI-II scores over time, there were no significant differences by treatment group ($p=0.74$) or over time ($p=0.60$) when controlling for baseline BDI-II scores. Furthermore, analysis of specific questions addressing difficulties in concentration and indecisiveness from the BDI-II did not demonstrate significant worsening in the treated patients compared to the untreated controls as previously reported in patients during the lead-in phase of the HALT-C Trial (13) (Data not shown).

Peginterferon dose and cognitive function

Only 60% of the peginterferon-treated patients in the HALT-C Trial were able to take the prescribed dose of 90 ug per week for more than 80% of the time due to side effects and other reasons (16). Because the neuropsychiatric toxicity of interferon is dose-dependent, the impact of medication adherence on the frequency and severity of cognitive impairment in

the patients randomized to peginterferon was analyzed. Per Table 4, only 30 of the 66 (45%) peginterferon treated patients took at least 80% of the prescribed dose of peginterferon through month 42 of the study. Using repeated measures ANOVA, the mean GDS scores did not vary by peginterferon adherence ($p=0.14$) or over time ($p=0.63$) after controlling for baseline GDS scores in the peginterferon treated patients.

Cognitive function and liver disease progression

During the 3.5 years of prospective follow-up, 36 patients experienced either a two point increase in Ishak fibrosis score ($n=18$) or developed a clinical outcome ($n=18$). The cumulative incidence of liver disease progression was 15% at year 1.5 and 32% at year 3.5 which is similar to what was reported in the overall HALT-C Trial (16). The clinical outcomes included 1 death, 5 patients with HCC, 5 patients with an increase in their CTP scores, 3 patients with variceal hemorrhage, 3 patients with new onset ascites, and 1 patient with spontaneous bacterial peritonitis. Nine of the 18 patients who experienced a clinical outcome during the trial did not complete subsequent cognitive study visits due to discontinuation from the study.

Because prior cross-sectional studies have demonstrated more frequent cognitive abnormalities in patients with decompensated versus compensated cirrhosis, the relationship between clinical decompensation over time and cognition was analyzed. When the mean GDS scores of patients with and without disease progression were compared, there was no significant relationship between disease progression ($p=0.71$) nor study visit ($p=0.68$) nor treatment group ($p=0.52$) with GDS scores after controlling for baseline GDS scores (Table 5). Furthermore, using Cox proportional hazards survival analysis, pretreatment cognitive function was not a predictor of disease progression ($p=0.52$). In addition, the presence of depression at baseline was not a predictor of disease progression ($p=0.51$).

Discussion

Peginterferon has antiviral, anti-inflammatory, and anti-fibrotic effects which led to the hypothesis that prolonged peginterferon treatment would lead to a significant reduction in the rate of liver disease progression in prior non-responders with advanced fibrosis. However, no benefit from low-dose maintenance peginterferon was identified in the 1050 randomized patients prospectively followed for a mean of 3.5 years in the HALT-C Trial (16). Two other studies using prolonged courses of standard interferon or peginterferon 2b also failed to demonstrate a clinical benefit with maintenance therapy in prior non-responders with advanced histology (28, 29). When designing the randomized phase of the HALT-C Trial a major concern was the tolerability of peginterferon administered over several years. Interferon is associated with a number of dose-dependent neuropsychiatric side effects, including mood disorders, emotional distress, and symptoms of impaired memory that can be serious and progressive in some (14). As a result, the cognitive study was implemented at two sites to prospectively assess the frequency and severity of mood and cognitive effects of treatment using a validated battery of objective neuropsychological tests.

Our current study results demonstrate no significant impact of prolonged peginterferon therapy on cognitive function in the 129 randomized patients that were prospectively studied (Table 3). Although 28% of the patients had evidence of mild baseline impairment prior to therapy, the frequency and severity of cognitive impairment did not increase in subjects with and without baseline impairment and also was not influenced by treatment (Figure 1). In fact, the GDS scores of the patients with baseline impairment actually improved over time (Figure 1). Though the number of patients in the impaired group is small, the improvement in performance most likely reflects regression to the mean but it is possible that practice

effects were greater in those who had poorer initial performance. In addition, a significant improvement in the standard scores of several individual tests was noted in both the peginterferon and untreated control patients (Table 2). These improvements in test scores were most likely due to practice effects since the subjects were repeatedly tested with the same battery over time. The CVMT, Digit symbol, and Trail's A tests have been shown to have similar practice effects in prior studies (30–33). Although the use of alternate forms and 12 month intervals between test administrations should have minimized practice effects, the relatively high level of education in this study population may, in part, explain a trend towards improved test performance. To be certain that medication adherence did not substantially influence our results, a careful analysis of the dose of peginterferon received and cognitive impairment was undertaken in the treated patients. However, there was no discernible relationship between the cumulative exposure to peginterferon and cognitive function (Table 4).

Our prior study demonstrated no evidence of cognitive impairment with 48 weeks of full dose peginterferon and ribavirin therapy (13). However, many patients complained of “difficulty concentrating” and “indecisiveness” and some developed symptoms of depression which resolved following treatment cessation (13, 15). The results of the current study are in keeping with our prior findings and demonstrate that low-dose peginterferon given over 3.5 years also does not cause any objective evidence of worsening cognition which is reassuring for patients and practitioners. The rare patient with HCV related cryoglobulinemia or renal disease that requires prolonged peginterferon therapy should not be concerned about potential worsening of cognitive function. However, HCV patients treated with peginterferon in the randomized phase of HALT-C did experience clinically significant decrements in their quality of life and increased symptoms of fatigue and weakness compared to the untreated controls (34). However, contrary to expectations, BDI-II scores did not significantly worsen over time in the peginterferon treated patients compared to the untreated patients. Therefore, maintenance peginterferon was generally well tolerated with minimal neuropsychiatric side effects during a mean follow-up of 3.5 years. This unexpected finding may, in part, be related to the frequent dose reductions or early discontinuation of peginterferon in the treated patients. In addition, the inclusion of prior non-responders in HALT-C who were capable of tolerating full dose peginterferon and ribavirin may have selected a subgroup of patients who were very tolerant of interferon.

Another aim of our study was to determine the relationship between liver disease progression and changes in cognition over 3.5 years of follow-up. A number of prior cross-sectional studies have demonstrated more frequent and severe cognitive abnormalities in cirrhotic patients with clinical decompensation and advanced portal hypertension compared to patients with compensated cirrhosis (17,35, 36). In addition, reductions in perception and conduction of nervous system impulses have been shown. Finally, subjects with minimal hepatic encephalopathy have been shown to have a poorer survival during follow-up presumably due to more severe portal hypertension (35). However, most of these studies have included a small number of patients who were compared in a cross-sectional manner rather than longitudinally over time. In addition, the criteria for a diagnosis of “minimal” or subclinical hepatic encephalopathy have not been well-characterized and validated. The HALT-C Trial provided a unique opportunity to study serial changes in cognition in a large cohort of well-characterized subjects with a single underlying cause of liver disease.

Contrary to expectations, the GDS scores of subjects with objective evidence of worsening liver disease did not significantly differ over time from the GDS scores of patients with stable liver disease (Table 5). In addition, baseline cognition was not associated with liver disease progression and serial assessment of cognition was also not associated with disease progression. These novel findings raise questions regarding prior studies that have

associated more advanced liver disease with impaired cognition. The lack of association in our cohort may relate to our ability to control for baseline cognition with a longitudinal study design and the inclusion of a generally well-educated group of ambulatory outpatients. In addition, it is possible that the GDS scores of patients with disease progression may have worsened but that patient drop-out or discontinuation from the study could have biased our results. In support of this, month 48 cognitive testing was not available in 47% of the patients with disease progression compared to 31% of the patients without liver disease progression. We also only measured cognitive function annually during the randomized phase and a test battery could not be administered at the time of actual disease progression. Finally, it is possible that the association between liver disease progression and cognitive decline is better represented by a tipping point rather than a linear function. In other words, cognitive decline may be precipitous at a certain stage of liver failure rather than continuously declining as the disease progresses.

Of note, our study was conducted exclusively in outpatients who were otherwise relatively healthy except for their liver disease. In comparison, many of the studies describing “minimal hepatic encephalopathy” were done in hospitalized or recently hospitalized patients who may have had other acute infectious or inflammatory co-factors leading to poorer test performance (36, 37). Nevertheless, the baseline pattern of cognitive deficits identified in the current study population with difficulties in verbal encoding and recall as well as complex working memory and slowed reaction to visual stimuli (Table 2) is similar to more recent conceptualizations of minimal hepatic encephalopathy (37).

Strengths of our study include the large number of patients with hepatitis C who were prospectively studied in a standardized manner during a randomized controlled trial. In addition, a battery of validated neuropsychological tests were used that have previously been shown to be sensitive to the effects of neurotoxic medications (e.g. interferons) and progression of chronic systemic diseases (e.g. HIV infection) on cognition (38, 39). The absence of an increasing frequency or severity of cognitive impairment in the patients receiving prolonged low-dose peginterferon is consistent with our prior results in the patients treated with 24 to 48 weeks of full dose peginterferon and ribavirin (13). It is possible that the low dose of peginterferon used in the randomized phase of HALT-C may have been insufficient to cause significant cognitive impairment. In addition, fewer than 50% of the treated patients were able to maintain 80% adherence. The use of aggregate scores to assess cognitive function (i.e. Global Deficit Scores) may have also masked some variation in the individual tests comprising the battery. However, significant changes in individual tests or domains of cognitive function over time were not readily apparent in the peginterferon treated nor untreated control patients (Table 2). An analysis of the raw scores also failed to show a difference in the two treatment groups (Data not shown). A final issue to consider is the GDS cut-off score used to define cognitive impairment of ≥ 1 used in our study. Recently, Carey et al demonstrated that a GDS cut-off of ≥ 0.5 improves the overall diagnostic accuracy in asymptomatic HIV patients compared to a cut-off of ≥ 1 (23). However, we previously demonstrated that a GDS of ≥ 1 correlated the best with gold standard “clinician ratings” of impairment in HCV patients (21). Carey et al also noted that the positive likelihood ratio for correctly identifying a patient as impaired was higher when using a GDS of ≥ 1.0 rather than 0.5 (23). Analysis of our data using a GDS of > 0.5 to define impairment demonstrated generally similar results to the GDS criteria of > 1 regarding the frequency and severity of impairment in treated versus untreated patients over time (data not shown).

The lack of an association between cognitive function and liver disease progression over time is a potentially important finding (Table 5). If confirmed in other longitudinal studies, further clarification of the definition of minimal hepatic encephalopathy and other cognitive

disorders associated with chronic liver disease may be warranted (38). For example, a more quantitative and objective analysis of psychomotor slowing and altered executive function may be required for future prospective studies of cognition in patients with chronic liver disease as well as a better-delineated representation of change over time including potential threshold models. Lastly, the lack of discernible cognitive impairment in our patients during a mean follow-up of 3.5 years suggests that maintenance peginterferon can be safely administered for prolonged periods of time if clinically warranted in selected patients.

Acknowledgments

This study was supported by the National Institute of Diabetes & Digestive & Kidney Diseases (contract numbers are listed below). Additional support was provided by the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute, the National Center for Minority Health and Health Disparities and by General Clinical Research Center and Clinical and Translational Science Center grants from the National Center for Research Resources, National Institutes of Health (grant numbers are listed below). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health. Additional funding to conduct this study was supplied by Hoffmann-La Roche, Inc., through a Cooperative Research and Development Agreement (CRADA) with the National Institutes of Health.

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, RN, Susan L. Milstein, RN, and the USC Neuropsychology Technicians

University of Michigan Medical Center, Ann Arbor, MI: (Contract N01-DK-9-2323, Grant M01RR-00042, Grant 1 UL1 RR024986, Michigan Center for Clinical and Health Research) Joel K. Greenson, MD, Pamela A. Richtmyer, LPN, CCRC, R. Tess Bonham, BS, Leslie Giudotti, Emily Anderson.

National Institute of Diabetes and Digestive and Kidney Diseases, Division of Digestive Diseases and Nutrition, Bethesda, MD: James E. Everhart, MD, Leonard B. Seeff, MD, Patricia R. Robuck, PhD, Jay H. Hoofnagle, MD, Elizabeth C. Wright, PhD

New England Research Institutes, Watertown, MA: (Contract N01-DK-9-2328) Kristin K. Snow, MSc, ScD, Anne M. Stoddard, ScD, Teresa M. Curto, MSW, MPH

Data and Safety Monitoring Board Members: (Chair) Gary L. Davis, MD, Guadalupe Garcia-Tsao, MD, Michael Kutner, PhD, Stanley M. Lemon, MD, Robert P. Perrillo, MD

Abbreviations

ANOVA	Analysis of variance
BDI-II	Beck Depression Inventory
CTP	Child-Turcotte-Pugh
GDS	Global Deficit Score
HALT-C	Hepatitis C Antiviral Long-term Treatment against Cirrhosis
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
SD	Standard deviation
SS	Standard score

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Study highlights

What is current knowledge?

- Neuropsychiatric toxicity is a common and dose limiting side effect of interferon therapy for chronic hepatitis C.
- Objective abnormalities in brain physiology have been noted during interferon therapy that improve following viral clearance but the treatment regimens and instruments used to assess cognition in previous studies have been variable.
- The safety and tolerability of prolonged low-dose peginterferon therapy in patients with chronic hepatitis C is largely unknown.

What is new here?

- Administration of low-dose peginterferon to a large group of hepatitis C patients prospectively followed over 3.5 years was not associated with an increased incidence or severity of cognitive impairment.
- The frequency and severity of cognitive impairment also did not increase in those with objective evidence of liver disease progression/decompensation during follow-up in contrast to prior cross-sectional studies.
- Improved criteria for a diagnosis of “minimal hepatic encephalopathy” and its relationship to disease severity are needed.

Figure 1.

Mean Global Deficit Scores over time in patients with and without baseline cognitive impairment by treatment group. Among the 36 patients with baseline cognitive impairment, the mean GDS scores at subsequent visits improved compared to baseline whereas the GDS scores of the 93 subjects without baseline impairment remained unchanged over time. However, after controlling for baseline levels, the trend in GDS scores over time did not significantly vary by baseline cognitive impairment status (repeated measures ANOVA, interaction $p=0.36$) nor by treatment group ($p=0.77$)

Table 1

Baseline characteristics of the overall study population and by treatment group

	Overall N=129*	Peginterferon 90 ug/week N=66**	Untreated Patients N=63***
Demographics			
Age (years)	51.2 (7.9)	50.2 (7.1)	52.3 (8.6)
% Male	87 (67.4%)	48 (72.7%)	39 (61.9%)
Ethnicity			
% White	90 (70.0%)	44 (66.7%)	46 (73.0%)
% Black	23 (17.8%)	15 (22.7%)	8 (12.7%)
% Hispanic	13 (10.1%)	5 (7.6%)	8 (12.7%)
Educational level (years)	13.6 (2.5)	14.0 (2.5)	13.2 (2.4)
Occupational codes	3.9 (2.0)	4.0 (1.6)	3.8 (2.3)
% Married	87 (67.4%)	48 (72.7%)	39 (61.9%)
% Diabetes	27 (20.9%)	16 (24.2%)	11 (17.5%)
Lifetime alcohol consumption (drinks)	17,347 (25,178)	15,390 (25,475)	19,365 (24,909)
Baseline Cognition			
Global Deficit Score	0.68 (0.61)	0.65 (0.62)	0.70 (0.61)
% Global Deficit Score 1	36 (27.9%)	17 (25.8%)	19 (30.2%)
Shipley Intelligent Quotient	99.2 (13.1)	99.7 (13.2)	98.8 (13.1)
Baseline Depression			
BDI-II score	6.4 (6.6)	6.7 (6.8)	6.0 (6.4)
% Depression [^]	33 (25.6%)	16 (24.2%)	17 (27.0%)
% Antidepressants	35 (27.1%)	20 (30.3%)	15 (23.8%)
Liver disease parameters			
Ishak Fibrosis score			
2-4	75 (58.2%)	37 (56.1%)	38 (60.3%)
5-6	54 (41.8%)	29 (43.9%)	25 (39.7%)
Serum AST (IU/ml)	96.4 (70.8)	102.2 (79.5)	90.4 (60.5)
Serum AST/ALT ratio	0.77 (0.24)	0.80 (0.27)	0.75 (0.19)
Platelets (10 ³ /ml)	162.4 (61.2)	155.5 (57.3)	169.6 (64.6)
INR	1.05 (0.10)	1.06 (0.11)	1.03 (0.07)
Total bilirubin (mg/dl)	0.72 (0.33)	0.70 (0.30)	0.73 (0.35)
Log HCV RNA (IU/mL)	6.52 (0.46)	6.52 (0.50)	6.51 (0.42)
Prior response to pegIFN & ribavirin			
% Breakthrough/relapse	22 (17.1%)	11 (16.7%)	11 (17.5%)
% Lead-in non-responder	107 (82.9%)	55 (83.3%)	52 (82.5%)
% Liver disease progression during randomized phase	36 (29.8%)	18 (28.6%)	18 (31.0%)
Compliance with peginterferon			

	Overall N=129[*]	Peginterferon 90 ug/week N=66^{**}	Untreated Patients N=63^{***}
< 80%	36 (54.6%)	36 (54.6%)	--
>= 80%	30 (45.4%)	30 (45.4%)	--

Data presented as mean (std dev) or n (%).

^{*} The sample size for educational level and occupational codes was n=128, baseline Beck score was n=125 and for development of liver disease progression was n=121.

^{**} The sample size for baseline Beck score was n=64 and for development of liver disease progression was n=63.

^{***} The sample size for educational level and occupational codes was n=62, for baseline Beck score was n=61, for development of liver disease progression was n=58

[^] Depression is defined as either a BDI >= 11 or fulfilling the DSM-IV criteria for major depression during the previous 12 months on the CIDI.

Table 2

Mean Global Deficit Scores and individual neuropsychological test results over time by treatment group.

Individual Test Standard scores	Baseline		12 Months		24 Months		36 Months		48 Months	
	Control (n=63 ^b)	Peg (n=66 ^f)	Control (n=56 ^f)	Peg (n=61 ^g)	Control (n=49 ^m)	Peg (n=57 ^h)	Control (n=47 ⁿ)	Peg (n=47 ⁱ)	Control (n=41 ^o)	Peg (n=41 ^p)
Selective reminding test	34.7	36.3	37.4	38.5	39.5	38.6	42.17 *	42.0 *	39.7	40.4
CVMT	42.89	45.29	51.91 *	52.97 *	53.51 *	53.89 *	50.11 *	53.74 *	55.33 *	54.34 *
Digit span	44.69	43.57	44.31	44.50	46.86	45.53	45.83	45.80	47.45	46.35
Digit symbol	47.54	46.88	51.59 *	50.84 *	51.45 *	51.39 *	53.28 *	52.98 *	54.00 *	51.37 *
Serial digit learning	37.27	41.95	36.41	35.10 *	39.60	39.44	35.81	42.23	39.49	38.83
Trail's A	45.98	47.88	49.73	50.62	52.96 *	51.81	54.89 *	53.85 *	54.66 *	53.51 *
Trail's B	47.43	44.83	49.70	49.72	49.29	47.35	51.26	50.66	52.07	53.41 *
Finger tapping test	56.72	53.79	56.89	54.66	59.26	55.74	59.40	58.74	61.47	60.31 *
WCST	48.65	47.15	49.02	48.03	49.52	48.25	50.56	47.32	50.24	47.35
COWAT	53.97	54.41	56.07	54.97	54.82	53.28	56.66	54.85	57.05	57.50
Mean GDS	0.70	0.65	0.59	0.62	0.54	0.57	0.53	0.51	0.48	0.52
N (%) GDS 1	19	17	10	16	9	13	10	8	5	10
Simple reaction time (msec)	365.9	342.4	365.3	379.0 *	370.6	376.7 *	349.7	368.0	373.2	351.7
Choice reaction time (msec)	494.6	491.6	487.1	491.8	478.4	493.3	454.4 *	461.0	492.4	469.2
Simple reaction time > 425 msec, N (%)	7	4	11	11	13	12	7	5	5	8
Choice reaction time > 550 msec, N (%)	12	11	11	11	13	13	7	5	6	9

NOTE: The individual test scores are standardized values while the GDS is not. All standard scores reported as mean or n(%).

Abbreviations: CVMT (Continuous Visual Memory Test), WCST (Wisconsin Card Sorting Test), COWAT (Controlled Oral word Association test), GDS (Global Deficit Score).

* SS significantly better (higher except in the case of reaction time where lower is lower) compared to baseline with $P < 0.05$.

^f SS significantly poorer (lower) compared to baseline based on t test at $P < 0.05$.

According to repeated measures ANOVA models controlling for baseline standard scores and treatment group, some of the GDS components including selective reminding ($p = 0.03$), digit span ($p = 0.009$) and Trail's A ($p = 0.046$) significantly improved over time. Choice reaction time also significantly improved over time ($p = 0.03$).

^g Sample size is n=65 in the case of digit span and n=52 for simple and choice reaction time.

^h Sample size is n=59 for WCST.

- h* Sample size is n=56 for simple reaction time, n=55 for choice reaction time, and n=52 for WCST.
- i* Sample size is n=46 for selective reminding, simple reaction time and overall GDS score and n=44 for choice reaction time.
- j* Sample size is n=40 for finger tapping and COWAT and n=34 for WCST.
- k* Sample size is n=50 for simple and choice reaction time.
- l* Sample size is n=55 in the case of finger tapping and n=54 for WCST.
- m* Sample size is n=48 for selective reminding, serial digit, overall GDS score and simple and choice reaction time, and n=46 for WCST.
- n* Sample size is n=46 for selective reminding, digit symbol, Trail's A, Trail's B, overall GDS score and choice reaction time, n=45 for finger tapping and WCST.
- o* Sample size is n=40 for selective reminding, visual memory, and overall GDS score; n=39 for finger tapping, n=37 for simple and choice reaction time and for WCST.

Table 3

Mean Global Deficit Scores during the randomized phase of HALT-C in peginterferon treated and untreated control patients

Study visit	Peginterferon 90 ug/week		Untreated controls	
	N	Mean GDS (SD)	N	Mean GDS (SD)
Baseline	66	0.65 (0.62)	63	0.70 (0.61)
12 month	61	0.62 (0.57)	56	0.59 (0.57)
24 month	57	0.57 (0.55)	48	0.54 (0.53)
36 month	46	0.51 (0.55)	46	0.53 (0.54)
48 month	41	0.52 (0.62)	40	0.48 (0.58)

According to repeated measures ANOVA modeling to predict mean GDS scores over time, there was no significant change in the GDS scores by treatment group ($p = 0.49$) and no significant change in the GDS scores over time ($p = 0.46$) after accounting for baseline GDS levels ($p < 0.001$).

Table 4

Mean Global Deficit Scores over time in peginterferon treated patients by medication adherence *

Study visit	80% of intended peginterferon dose		>80 % of intended peginterferon dose	
	N	Mean GDS (SD)	N	Mean GDS (SD)
Baseline	36	0.64 (0.54)	30	0.67 (0.72)
12 month	33	0.59 (0.48)	28	0.66 (0.67)
24 month	30	0.53 (0.55)	27	0.62 (0.56)
36 month	23	0.44 (0.43)	23	0.58 (0.64)
48 month	19	0.49 (0.67)	22	0.54 (0.59)

* Peginterferon adherence is defined as having received at least 80% of the intended dose up to the three year timepoint (42 months) or not. Mean GDS (SD) is presented at the five study visits. According to repeated measures ANOVA modeling to predict mean GDS scores over time, after controlling for baseline GDS levels ($p < 0.001$), scores did not vary by peginterferon adherence ($p = 0.14$) or across time ($p = 0.63$).

Table 5

Mean Global Deficit Scores over time by liver disease progression *

Study Visit	No Liver Disease progression		Yes Liver Disease progression	
	N	Mean GDS (SD)	N	Mean GDS (SD)
Baseline	85	0.63 (0.59)	36	0.69 (0.61)
12 month	78	0.54 (0.55)	34	0.67 (0.49)
24 month	73	0.52 (0.50)	28	0.61 (0.58)
36 month	66	0.48 (0.51)	21	0.55 (0.59)
48 month	59	0.50 (0.62)	19	0.44 (0.50)

* Liver Disease progression was defined as the development of a clinical outcome during the randomized phase or a two point increase in Ishak fibrosis score compared to the baseline liver biopsy.

Based on results from fitting a repeated measures ANOVA model to predict GDS scores over time, scores do not differ significantly by liver disease progression status ($p = 0.71$) or over time ($p = 0.68$) after controlling for baseline GDS scores ($p < 0.001$).