Randomized Double-blind Placebo-Controlled Trial of Peptide T for HIV-Associated Cognitive Impairment

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Background: Cognitive impairment is a common consequence of human immunodeficiency virus (HIV) infection, and dementia is one of the diseases that defines the acquired immunodeficiency syndrome. Peptide T (d-ala-peptide-T-amide) has been reported to block the binding of gp120 to brain tissue and to protect neurons from the toxic effects of gp120 in vitro. In pilot studies, administration of peptide T to HIV-positive patients with cognitive impairment was associated with improvement in cognition and constitutional symptoms.

Objective: To determine whether the intranasal administration of peptide T would improve cognitive function of HIV-positive patients with cognitive impairment.

Patients and Methods: This was a 3-site, double-blind, placebo-controlled trial of peptide T given intranasally at a dosage of 2 mg 3 times a day for 6 months. Participants were HIV-seropositive persons with evidence of cognitive deficits on a screening test battery. Concomitant antiretroviral therapy was allowed. Randomization to the 2 study arms was balanced according to several stratification variables, such as CD4+ cell count, severity of cognitive impairment, and antiretroviral therapy at study entry. A comprehensive neuropsychological (NP) battery, which yielded 23 scores, was administered at baseline and the study end point. The primary outcome measure was a global NP score derived from the 23 standardized scores. The efficacy end point was the change in NP score at 6 months compared with baseline. Secondary efficacy measures were 7 cognitive domain scores and deficit scores of global and domain performance. The patients who completed the baseline and final NP evaluations (after at least 4 months in the randomized treatment arm) were included in the efficacy analyses. Additional analyses were conducted on subgroups of patients according to the CD4+ count and baseline NP deficit. The incidence of NP improvement in the 2 treatment arms was also compared.

Results: There was no statistically significant difference between the peptide T and placebo groups on the global NP change score, the individual domains, or the deficit scores. Because of an imbalance in the baseline CD4+ cell count between treatment arms, analyses were also adjusted for this variable. These CD4+-adjusted analyses suggested a greater improvement in the peptide T group. Subgroup analyses indicated a treatment effect for patients whose CD4+ cell count was above 0.200×10⁹/L (200 cells/µL) at baseline. Moreover, peptide T treatment was associated with overall cognitive improvement in patients with baseline global deficit scores of at least 0.5, while overall deterioration was more common among the placebo group (P = .02; Mantel-Haenszel χ² test).

Conclusions: Peptide T was not significantly different from placebo on the study primary end points. However, additional analyses indicated that peptide T may be associated with improved performance in the subgroup of patients with more evident cognitive impairment (ie, NP global deficit score ≥0.5) or with relatively preserved immunological status (ie, CD4+ cell count >0.200×10⁹/L).

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Infection with the human immunodeficiency virus type 1 (HIV) is associated with primary disease of the central nervous system that can manifest with a spectrum of neurocognitive disturbances. Severe cognitive impairment—HIV-associated cognitive/motor complex, or dementia—affects about 15% of persons with frank acquired immunodeficiency syndrome (AIDS), with an annual incidence of about 5%. A less severe disorder, recognized clinically as HIV-associated minor cognitive/motor disorder, seems to be more prevalent than HIV-associated cognitive/motor complex, or dementia. Other, more subtle neurocognitive disturbances, which do not substantially interfere with everyday functioning, can be detected on detailed neuropsychological testing. These deficits are prevalent in AIDS and in less advanced HIV infection.
METHODS AND PATIENTS

STUDY DESIGN

This was a multisite, double-blind, placebo-controlled study. Patients with HIV-associated cognitive impairment were randomized to receive peptide T intranasally at a dose of 2 mg (1 mg of spray per nostril) 3 times a day or a similarly administered placebo for 6 months. At the end of 6 months of blinded treatment, all participants were offered open-label peptide T.

A stratification with minimization procedure by site was used to increase the likelihood of balanced distributions of the following possible modifiers of response: (1) current use or no use of an antiretroviral agent, (2) moderate or severe cognitive dysfunction, (3) age (18-39 years or 40-60 years), (4) length of antiretroviral use (≤6 months or >6 months), (5) time of previous antiretroviral use (never, ≤3 months ago, or >3 months ago), (6) education (<12 years, 12-15 years, ≥16 years), (7) history of previous substance abuse (including alcohol), (8) sex, and (9) CD4+ lymphocyte count (<0.200×10^9/L [≤200 cells/µL] or 0.200-0.500×10^9/L [200-500 cells/µL] or >0.500×10^9/L or less for UM and UCSD sites only) or 0.200-0.500×10^9/L [200-500 cells/µL] or >0.500×10^9/L or less at the University of Southern California, Los Angeles, only).

Neuropsychological, psychiatric, medical, and neurologic evaluations were administered at baseline, periodically during the study, and at its completion.

STUDY SITES

The study was conducted at the 3 following sites: the University of Southern California, Los Angeles (USC), the University of Miami, Miami, Fla (UM), and the University of California, San Diego (UCSD).

PATIENTS

HIV-positive patients with specified cognitive deficits at a screening neuropsychological (NP) battery (see the “Assessments” section) were enrolled according to inclusion and exclusion criteria. The inclusion criteria were as follows: (1) either sex, aged 18 to 60 years, with documented HIV-seropositivity (enzyme-linked immunosorbent assay confirmed with Western blot analysis or polymerase chain reaction); (2) cognitive dysfunction as defined by the NP screening battery and judged as likely due to HIV; (3) agreement to use barrier methods of contraception (for men) or a reliable method of contraception (for women); (4) negative results on a pregnancy test within 1 month of study entry; (5) CD4+ lymphocyte count of 0.500×10^9/L or less (for UM and UCSD sites only); (6) expected survival of at least 6 months; (7) screening laboratory results meeting the following values: total granulocyte count, 0.750×10^9/L or more; hemoglobin, more than 80 g/L; platelet count, 75×10^9 or more; prothrombin time, more than 70% of the control; creatinine, 130 µmol/L or less (1.5 mg/dL); aspartate aminotransferase, less than 5 times normal; bilirubin, 51 µmol/L (3.0 mg/dL); and (8) a normal baseline electrocardiogram or urinalysis or abnormalities for which the patient’s condition would still be judged medically stable. The exclusion criteria were as follows: (1) the presence of active AIDS-defining opportunistic infections or malignant neoplasm that required treatment at study entry or Kaposi sarcoma or another malignant neoplasm likely to require chemotherapy during the first 6 months of the study; (2) a requirement of more than 2 transfusions per month to achieve a hemoglobin level of more than 80 g/L; (3) alcohol or substance dependence or abuse during the last 3 months, judged by the investigators as likely to interfere with the study; (4) underlying serious medical problems that could complicate the interpretation of the treatment results, including unstable diabetes mellitus, clinical ischemic disease, uncontrolled hypertension, and hepatic or renal failure; (5) current or recent (within the past 6 months) DSM III-R Axis I psychiatric disorder (from the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised) or history of psychotic disorder or bipolar mania; (6) a history of mental retardation or learning disability; (7) treatment with psychoactive agents within 4 weeks, or within 8 weeks for long-acting agents (eg, fluoxetine); (8) previous use of peptide T; and (9) inability to participate in NP testing or to comply with the instructions for medication administration.

Prospective study participants were recruited through advertisements, community outreach, and physician referral. On the basis of a telephone interview, potential candidates were scheduled for screening, including a detailed explanation of the study, written informed consent, and neuropsychological, psychiatric, and medical screening evaluations.

STUDY MEDICATION

Peptide T, 2 mg, was administered intranasally 3 times a day for 6 months. The choices for dose and route were based on previous data from limited pharmacokinetics and phase I studies. An indication of a possible penetration into the central nervous system was provided by identification of peptide T in the CSF of 2 patients who were given an intravenous infusion of peptide T, with a CSF-plasma ratio of 0.2. Peptide T was purchased from Carbiltech, Hillerød, Denmark, and was formulated in a 10-mg/mL solution at the pharmacy at the National Institutes of Health (Bethesda, Md) or at the University of Iowa School of Pharmacy (Iowa City). Analytical testing was conducted to ensure the purity of peptide T and the sterility of the solution. Identical vials of placebo and peptide T were prepared with tamper-resistant closures. Vials were uniquely labeled at the study sites with the patient’s name and study identification number and were weighed before and after use to assess compliance.

CONCOMITANT MEDICATIONS

Patients were required to have used no antiretroviral drugs within 4 weeks or to have had stable antiretroviral use for at least 12 weeks before study entry. Permitted antiretroviral use was based on the standard recommended doses at the time the patients were enrolled. The recommended doses were as follows: AZT (zidovudine), more than 400 mg/d by mouth (po) at USC and more than 300 mg/d po at UCSD and UM; didanosine (ddI), 250 or 375 mg (for body weight >60 kg) or 167 or 250 mg (for body weight ≤60 kg) po twice a day (bid) at USC, 200 mg (for body weight >50 kg) or 125 mg (for body weight ≤50 kg) po bid at UCSD and UM; zalcitabine (ddC), 0.01 or 0.03 mg/kg per day po at USC, >0.375 mg po 3 times per day at UCSD and UM; AZT and ddC, stable concurrent use of AZT and
ddl or ddC at the aforementioned doses. The use of stavudine (d4T) 40 mg po bid or combination therapy of AZT and ddl was permitted at the UM and UCSD sites. Thus, there were site differences in the antiretroviral drugs permitted because of staggered recruitment periods and approval by the US Food and Drug Administration and marketing of d4T, zalcitabine (ddC), and combination therapy.

Prophylaxis against major HIV-related infections or treatment of minor HIV-related infections was permitted, including inhaled aerosolized pentamidine, dapsone, or sulfamethoxazole and trimethoprim for the prophylaxis of Pneumocystis carinii pneumonia; topical antifungal agents; nystatin or ketoconazole; and acyclovir. Treatment for the relief of peripheral neuropathy with amitriptyline hydrochloride or trazodone hydrochloride at a maximum dose of 50 mg/d, which was expected to remain unchanged during the first 6 months of study, was allowed.

ASSESSMENTS

Screening Evaluations

The NP screening battery was used to provide a relatively brief standardized procedure for determining study eligibility. It was designed to sample impaired performance in cognitive domains that are frequently affected by HIV infection, such as the speed of information processing, learning and retention, motor performance, language, and abstract thinking (Table 1). Cognitive dysfunction was defined as scores less than the corresponding population-based norm by at least 1.5 SD on 2 tests or at least 2.5 SDs on 1 test. The degree of cognitive impairment was classified as severe (S) if scores on at least 2 tests of the NP screening battery were 1.5 SDs or more below the norm and 1 of those was at least 2.5 SDs below the corresponding norm; otherwise the deficit was classified as mild to moderate (M). Individuals fulfilling the criteria for cognitive dysfunction underwent further psychiatric and medical screening for eligibility. The psychiatric screening included the Structured Clinical Interview for DSM III-R, nonpatient version2 with the HIV-related adjustment disorder module; the Hamilton Depression Rating Scale4; the Montgomery-Asberg Depression Rating Scale (MADRS)4; the Folstein Mini-Mental Status Exam (MMSE)4; the Karnofsky scale4; and the San Diego HIV Neurobehavioral Research Center (HNRC) Initial Drug and Alcohol History Interview.

Baseline Examinations

After determination of study eligibility and before the initiation of treatment with peptide T or placebo, the comprehensive NP battery, which included 22 tests (Table 1) and yielded a total of 23 scores, was completed. The tests assessed the patients’ performance in 7 cognitive domains (ie, verbal fluency, abstract thinking, speed of information processing, working memory, learning and retention, and motor performance). This battery constituted the primary efficacy assessment and was readministered at the end of the study, with the exception of the 2 measures of premorbid intelligence (American version of the Nelson Adult Reading Test and Wechsler Adult Intelligence Scale-Revised [WAIS-R] Vocabulary).

Other psychiatric assessments included the Brief Psychiatric Rating Scale (BPRS)4; the Beck Depression Inventory (BDI)48, the Profile of Mood States (POMS)49, the State-Trait Anxiety Inventory (STAI)50, and the Quality of Well-being scale (QWB).51

The medical and neurologic history and examinations included a lumbar puncture and testing of the CSF for cells, glucose, protein, and toxoplasma and cryptococcus antibodies. A VDRL test was also performed on the CSF. Blood samples were obtained for a complete blood cell count and CD4+ and CD8+ lymphocyte counts, a fluorescent titer antibody test, hepatitis B testing, electrolyte levels, and measures of renal and hepatic function. Urine was obtained for standard clinical analysis and drug screening. Plasma and lymphocytes were obtained and stored. Skin tests (Merieux Multitest) for delayed cutaneous hypersensitivity were obtained.

Monthly Examinations

After patients began taking the study medications, the following assessments were obtained at monthly intervals to monitor safety: medical and neurologic examinations; adverse events recording; blood cell count; serum chemistry for electrolytes and hepatic and renal function; and urinalysis and urine drug screening. An abbreviated NP battery of 8 of the cognitive tests (Table 1) and the BPRS, MADRS, HNRC Intervial Interview on Substance Use, STAI, BDI, and POMS psychiatric rating scales were administered.

End-of-Study Examinations

At the completion of the scheduled 6-month study, or earlier in case of study discontinuation (but in any case after at least 4 months of treatment), the following assessments were completed: (1) The comprehensive NP battery was readministered as it had been at baseline, except the WAIS-R Vocabulary test was not repeated. (2) Medical and neurologic examinations; blood, urine, and spinal fluid tests; and psychiatric rating scales, as conducted at baseline, were repeated.

OUTCOME MEASURES

Primary Efficacy End Point

The primary index of change in cognitive function, derived from the baseline and 6-month NP battery results, was the global z score change and was computed as follows. The mean and SD of the total randomized sample were derived for each of the 23 NP scores at baseline and used to compute z scores for each patient’s scores at baseline and month 6. For each patient, the difference between z scores at month 6 and baseline for each score was computed. Then, the average of the 23 z score changes constituted the global z score change. If more than half of the 23 NP change scores were missing, then the global z score change was counted as missing. Otherwise, the global z score change was computed as the mean of all nonmissing NP change scores.

Neuropsychological Domains

The neuropsychological outcome variables were classified a priori into 7 cognitive domains. Only 1 representative...
score from each test was analyzed (Table 1). Within each domain, average z score changes were computed in the same manner as for the global z score change.

**Deficit Scores**

To better account for the specific cognitive deficits of the patients, a deficit score was computed for each NP test, using z and t scores from available population norms (see the references for each cognitive test), as follows:

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The mean deficit score of all tests constituted the global deficit score. Within each cognitive domain, deficit scores were averaged to obtain the domain deficit score.

**MONITORING FOR TOXIC EFFECTS**

Monthly medical, laboratory, psychiatric, and NP assessments were conducted as described in the preceding sections. Adverse medical events were recorded according to the AIDS Clinical Trials Group 1989 scoring system (National Institute of Allergy and Infectious Diseases, Division on AIDS, unpublished data, September 1989). The emergence of any grade 3 toxicity (ie, a severe event resulting in marked limitation in activity and the need for medical intervention) suspended further study medication until the toxicity had resolved or decreased. Following a grade 4 toxicity (ie, a life-threatening event), the study medication was discontinued. The following additional end points for toxicity were used as the guidelines for terminating protocol therapy for a patient: (1) anemia, decrease in hematocrit below 18% without concomitant acute bleeding, below 24% with bleeding, or 30% below the baseline measurement; (2) granulocytopenia, absolute granulocyte count below 0.500×10⁹/L; (3) thrombocytopenia, platelet count below 100×10⁹/L; (4) eosinophilia, total eosinophil count exceeding 3×10³/L in association with a maculopapular rash that seemed to progress over 3 days; (5) azotemia, serum creatinine level 200% higher than the baseline measurement; (6) proteinuria, a urine reaction for protein of 4+ and a subsequent 24-hour protein collection of more than 3 g; (7) rash; (8) bullae; (9) fever, temperature greater than 39°C for more than 7 days; (10) abnormal hepatic function, an increase of aspartate aminotransferase beyond 3 times the baseline measurement, frank jaundice (or bilirubin >86 µmol/L [5.0 mg/dL]), or a rise in the alkaline phosphatase level to twice that of the baseline measurement or above 500 IU; (11) neurologic dysfunction, development of peripheral neuropathy with motor loss or paresthesias; (12) psychiatric dysfunction, development of psychosis, delirium, or another neuropsychiatric disorder (eg, severe depression) requiring treatment; or (13) a decline in NP test performance during 1 month of 1.5 SDs on at least 2 different tests or of 3 SDs on 1 test for which the result was unimpaired at baseline, which was sustained on the subsequent monthly evaluation.

**SALVAGE PROTOCOL**

If a patient reached 1 of the above end points for toxic effects during the double-blind phase of the trial, the study medication was discontinued but not unblinded. Such patients who were receiving an antiretroviral drug were offered the opportunity to be placed in the other arm of the study for the remainder of the 6-month blinded phase. Such patients not receiving an antiretroviral drug were offered antiretroviral therapy and the opportunity to be placed in the other arm of the study. At 6 months, the medical and psychiatric conditions of the patients were reevaluated for toxic effects, and the patients were assessed for eligibility to receive open-label peptide T.

**DATA COMPUTERIZATION, MANAGEMENT, AND EDITING**

Data collected at USC were entered into an electronic file at USC and forwarded to Cosmos Corp, Bethesda, Md, which was under contract with the National Institute of Mental Illness. Neurocognitive impairment may be associated with an increased risk of mortality. Identifying effective treatment for HIV-associated brain disease has therefore become an important priority.

The observation that zidovudine (AZT) in controlled trials is associated with reversal of some HIV-associated cognitive symptoms and signs suggests that mechanisms in addition to neuronal death are responsible for the cognitive impairment. These mechanisms include direct viral invasion of brain tissue, an immune response secondary to HIV, or the sequelae of an opportunistic infection. Importantly, there is evidence to suggest that gp120, an HIV envelope protein, may be a specific neurotoxin, even at very low concentrations.

Pert and coworkers derived a short peptide sequence from the structure of gp120, with a presumptive similarity to the endogenous neurotransmitter, vasoactive intestinal peptide. This octapeptide, d-ala-peptide-T-amide (peptide T), is part of the core HIV envelope sequence required for attachment to the CD4+ receptor. Peptide T was shown to interact with CD4+ receptors and to block the binding of radiolabeled gp120 to CD4+ receptors in brain tissue. Peptide T was observed to have in vitro antiretroviral activity in some assessments, but not by all methods used. Vasoactive intestinal peptide and peptide T have each shown trophic growth factor activity in hippocampal neural cell culture, and peptide T has been reported to inhibit the production of tumor necrosis factor α in vitro and in vivo. While there was no evidence of antiviral activity by peptide T in phase 1 human trials, cognitive improvement was noted in some HIV-infected patients receiving peptide T primarily patients with measurable cognitive dysfunction at the outset. In addition, peptide T seemed to neutralize the gp120-like neurotoxic activity detected in the cerebrospinal fluid (CSF) of HIV-infected patients.
These findings provided a rationale for a randomized, double-blind, placebo-controlled clinical trial of peptide T for HIV-associated cognitive dysfunction. The primary objective of this study was to compare the effect on cognitive function of peptide T (6 mg/d) with placebo when both were administered in 3 daily doses by intranasal spray for 6 months. We hypothesized that peptide T would improve HIV-associated cognitive dysfunction in these patients.

**RESULTS**

Of 457 persons screened for cognitive impairment, 205 men and 109 women were randomized (106 to peptide T and 109 to placebo). Demographic descriptors are given in Table 2. Participants at USC (n=99) were enrolled between March 1, 1991, and June 30, 1992, and participants at UM (n=60) and UCSD (n=56) were enrolled between April 1, 1993, and March 30, 1994. Of 215 randomized patients, 72 did not contribute to the efficacy analysis, 43 because of discontinuation of the study treatment before completing month 4 and 29 because of other reasons. Early discontinuation was caused by death (9 patients); rapid cognitive deterioration resulting in entry into the salvage protocol (7 patients); and physical deterioration that prevented meeting the protocol requirements of follow-up visits and testing, active drug abuse, participant moving to other location, or other personal reasons (27 patients). Other patients could not be included in the final analysis because of earlier peptide T use (5 patients); negative HIV confirmation tests (1 patient); unmet inclusion criteria for cognitive impairment (6 patients); and the lack of an end-of-study NP evaluation (17 patients). Of the last 17 patients, 2 died between months 4 and 6; 7 withdrew between months 4 and 6 without completing outcome measures; 3 with-
drew just after month 6 but did not complete the end-point NP evaluation; and 5 provided incomplete or invalid end-point NP data. Thus, 143 patients who provided complete NP outcome data constituted the sample for the primary efficacy analyses (peptide T group, 66 patients; placebo group, 77 patients).

BASELINE COMPARISONS

No differences were found between the randomized and completer groups on demographic variables, CD4+ count group distribution, or use of antiretroviral drugs (Table 2). Compared with the randomized group (N=215), patients entering the efficacy analysis (n=143) had significantly better (P<.05) scores on 15 of the 23 NP baseline variables (P<.05, data not shown) and on the following psychiatric measures than those who were randomized but not included in the efficacy sample: MADRS; BPRS; BDI; POMS depression, vigor, fatigue, and total mood disturbance scales; and QWB scale (P<.05; Table 3). Within the efficacy sample (n=143), no statistically significant differences were found between the peptide T and placebo groups on baseline variables with the exception of a lower CD4+ cell count in the peptide T group (0.195±0.201×10⁹/L) compared with the placebo group (0.255±0.022×10⁹/L; P=.05), an imbalance that was in part already evident, although not statistically significant, in the entire sample as randomized (peptide T, 0.208±0.018×10⁹/L vs placebo, 0.231±0.019×10⁹/L). No significant differences were found between the peptide T and placebo groups in the prevalence of concomitant medication use during the 6 months of the study.

Efficacy End Points

No significant difference was found between the peptide T and placebo groups on the NP global z score change at end of treatment compared with baseline (0.24±0.05 for the peptide T group vs 0.16±0.03 for the placebo group, P=.18). Also, no difference was found between the 2 treatment groups on the score changes of the 7 cognitive domains (Table 4). Likewise, analyses of the deficit scores
showed no treatment effects on the global or the domain scores (data not shown).

After adjustment for the baseline CD4+ cell count, the peptide T group showed a trend toward a greater improvement on the global z score change (0.26±0.04 for the peptide T group vs 0.15±0.04 for the placebo group, P=.072); none of the 7 domain change scores reached statistical significance (Table 5). Similar analyses of the individual 23 NP scores identified 1 single change score (Wechsler Memory Scale visual reproduction) to have improved more in the peptide T group, but no differences were found on the other 22 scores. Analysis of the deficit scores, both global and by domain, after adjustment for baseline CD4+ cell count, showed no treatment difference on the global deficit score; however, 2 of the 7 domains (ie, abstract thinking and speed of information processing) showed improvement (P<.05) in the peptide T group.

**SUBGROUP ANALYSES**

**By CD4+ Cell Count Group**

Because of the trend toward better performance in the peptide T group after adjusting for the baseline CD4+ cell count, the relationship between the CD4+ cell count and efficacy end points was further explored by analyzing the study efficacy end points by CD4+ cell count groups. Patients were divided into 2 subgroups according to their baseline CD4+ cell count: 0.200×10^9/L or less and more than 0.200×10^9/L. In the subgroup with a CD4+ cell count of more than 0.200×10^9/L (n=43), the peptide T group performed better than the placebo group on the NP global score change (0.36±0.08 for the peptide T group vs 0.20±0.03 for the placebo group, P=.05) and on 2 cognitive domains (speed of information processing, P=.01, and working memory, P=.03). In the subgroup with a CD4+ cell count less than 0.200×10^9/L, no differences were found between the peptide T and placebo effects.

**By Level of Baseline Cognitive Impairment**

Of the 143 patients who completed the efficacy phase of the study, 54 (37.8%) had a baseline global deficit score of at least 0.5. Among these more clearly impaired patients, a significant difference was found that favored peptide T on the global z change score in analyses that were adjusted for the baseline CD4+ cell count and study site (0.41±0.12 for the peptide T group vs 0.17±0.08 for the placebo group, P=.03). Among these patients, the peptide T group scored significantly better than the placebo group on 2 of the 7 cognitive domain measures (speed of information processing, 0.48±0.17 vs 0.16±0.11, P=.04; working memory, 0.54±0.16 vs 0.07±0.12, P=.008), with a trend in the same direction (P=.08) for abstraction. No significant treatment group differences were found among the patients with baseline deficits score below 0.5.

**By Treatment Outcome**

Completers were grouped according to categorical NP outcome (ie, worse, same, better), as previously described. The conditions of twice as many peptide T–treated patients improved (Table 6), whereas the conditions of about twice...
as many placebo-treated patients deteriorated ($P=.02$). When only patients with baseline global NP deficit scores of at least 0.5 were included, there was an even greater treatment difference in the improvement rates (32.0% for the peptide T group and 3.5% for the placebo group, $P=.02$), whereas there were no outcome differences among patients with global deficit scores less than 0.5 (Table 6).

**SAFETY**

Analyses of the safety variables were performed on the entire randomized sample (N=215). No differences in the prevalence of the following adverse events were found between the 2 treatment groups: hepatic, gastrointestinal, hematologic, or renal function; urinalysis; neurologic abnormalities; mood disturbances; or globally defined allergic reactions. The difference between the 2 treatment groups was statistically significant ($P<.05$) for the following adverse events: (1) greater severity of instances of mood disturbance (eg, depression or irritability) in the peptide T group (grade 3 events, 7 for the peptide T group vs 1 for the placebo group); (2) greater severity of rash in the peptide T group (grade 4 events, 1 in the peptide T group vs none in the placebo group; grade 3 events, 3 in the peptide T group vs none in the placebo group; grade 2 events, 8 in the peptide T group vs 5 in the placebo group; and
grade 1 events, 22 in the peptide T group vs 37 in the placebo group). Grade 1 events were defined as events causing only mild or transient discomfort and no limitation in activity, and requiring no medical intervention or therapy. Grade 2 events were defined as events causing mild to moderate limitations in activity, but requiring no or minimal medical intervention or therapy.

In addition, there was borderline significant difference ($P<.10$) in the prevalence of nasal congestion (12 in the peptide T group vs 5 in the placebo group), proteinuria (18 in the peptide T group vs 9 in the placebo group), and eosinophilia (4 in the peptide T group vs none in the placebo group). The eosinophilia and rashes occurred in the same 4 people, 3 of whom had a history of allergies. A higher prevalence of peripheral neuropathy was found in the placebo group (22 cases vs 8 in the peptide T group), but this was explained by a higher prevalence at baseline in the placebo group (19 cases randomized to placebo vs 7 cases randomized to peptide T). For patients without peripheral neuropathy at study entry, no difference was observed between the 2 groups. The psychiatric scales did not show any clinically significant group differences, except for the cognitive-affective subscale of the BDI (that subscale does not include the somatic symptoms, such as weight loss and anergy), for which the baseline score was higher for the peptide T group (5.23±0.53) than for the placebo group (3.7±0.4, $P<.05$). The MMSE score did not change in the peptide T group (28.3±0.2 at baseline and 28.9±0.16 at month 6) or in the placebo group (28.2±0.2 at baseline and 29.0±0.14 at month 6).

**DEATH AND EARLY WITHDRAWAL**

Survival analysis showed no significant differences between the 2 treatment arms during the first 6 months in the number of deaths (8 in the peptide T group vs 3 in the placebo group, $P=.22$; Cox proportional hazards model), entry into the salvage protocol (8 vs 6, respectively, $P=.45$; Fisher exact test), or voluntary withdrawals (31 vs 25, respectively, $P=.22$; Fisher exact test). All of these analyses were adjusted for the patient’s actual baseline CD4+ cell counts.

**COMMENT**

This study is the first large-scale controlled trial in HIV-associated cognitive impairment and the first to adopt a comprehensive battery of cognitive tests to assess a possible drug effect in this condition. The analysis of the primary efficacy end point (ie, NP global score change) failed to show a difference between peptide T and placebo. This result is consistent with the analyses of the 7 cognitive domain scores and of the deficit scores. However, despite the attempt to balance randomization by CD4+ cell–count group at baseline, the peptide T group had a lower baseline CD4+ cell count than did the placebo group. After adjusting for the baseline CD4+ cell count, a trend ($P=.07$) suggesting a therapeutic effect of peptide T was detected on the global NP score change; this effect, however, was not significant for any of the 7 cognitive domain scores or the global deficit score. On the deficit scores of 2 domains (ie, abstract thinking and speed of information processing), the peptide T group performed better than did the placebo group ($P<.05$).

Subgroup analyses revealed that patients with a baseline CD4+ cell count higher than 0.200×10^6/L or with a baseline NP global deficit score of 0.5 or more fared better on peptide T than on placebo ($P<.05$).

Peptide T was well tolerated and no clinically significant toxic effects emerged. The higher severity of episodes of mood changes (eg, depression and irritability) in the peptide T group can be explained by more severe mood disturbance at study entry, as indicated by a higher baseline BDI cognitive-affective subscore for the peptide T group. In addition, for each of these episodes of mood changes, specific environmental stressors seemed to be a more likely cause than the study medication.

This study has several limitations that should be underscored. First, the dosage, route of administration, and frequency of drug administration were selected based on rather limited phase 1 and pharmacokinetics data. In particular, only preliminary bioavailability and pharmacokinetics studies have been conducted. Second, the protocol-specified statistical approach was an analysis of the a priori defined “efficacy sample,” rather than an “intent-to-treat” analysis. The efficacy analysis has the disadvantage of potentially being susceptible to limitations of generalizability of the results from the trial completers to the population for whom treatment is intended. In this respect, it is reassuring that there were no significant demographic or cognitive differences between the randomized group (N=215) and the efficacy sample (n=143; Table 2). Third, about one third of the patients enrolled in the study could not contribute to the final efficacy analyses for a variety of reasons. This level of attrition, however,

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<th>Patients*</th>
<th>Treatment</th>
<th>Outcome†</th>
<th>P‡</th>
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<td>All (n=143)</td>
<td>Placebo (n=77)</td>
<td>Worse</td>
<td>16 (21)</td>
</tr>
<tr>
<td></td>
<td>Peptide T (n=66)</td>
<td></td>
<td>6 (9)</td>
</tr>
<tr>
<td>With deficit score ≥0.5 (n=54)</td>
<td>Placebo (n=29)</td>
<td></td>
<td>6 (21)</td>
</tr>
<tr>
<td></td>
<td>Peptide T (n=25)</td>
<td></td>
<td>3 (12)</td>
</tr>
<tr>
<td>With deficit score &lt;0.5 (n=89)</td>
<td>Placebo (n=48)</td>
<td></td>
<td>8 (17)</td>
</tr>
<tr>
<td></td>
<td>Peptide T (n=41)</td>
<td></td>
<td>5 (12)</td>
</tr>
</tbody>
</table>

*The impairment status was defined by external norms, using the global deficit score at baseline (cutoff, 0.50).
†Outcome is defined by the global deficit score at 6 months, corrected for baseline score (see text for details). Data are given as number (percentage).
‡The $P$ values for the $2×3$ contingency tables were based on the Mantel-Haenszel $χ^2$ test.
is not uncommon in clinical trials with HIV-positive patients with cognitive impairment, especially if the length of the placebo-controlled study (6 months) is considered. The dropout rate in the present study is, in fact, comparable to the dropout rate registered in other clinical trials in this patient population. Fourth, there was a heterogeneous level of baseline cognitive performance of the study patients. A substantial number of them (62% of the efficacy sample), although they met the inclusion criteria for cognitive impairment, did not display global impairment on the mean score of the comprehensive NP battery. In a study using a similar NP battery with 500 patients, the placebo group scored better than did the placebo group on the global NP score. This finding underscores the critical importance of the definition of impairment and of the instruments used to measure possible pharmacological effects. The study entry criterion for impairment was a performance of at least 1.5 SDs below the norm on 2 or more tests or at least 2.5 SDs below the norm on 1 test or more on a screening battery of 8 cognitive tests. However, among the study efficacy population (n=143) only 54 patients had a global deficit score of 0.5 or more on the 23-score NP baseline battery. Because the baseline battery was administered after the screening battery and also included the 8-test screening battery, practice effects might have contributed to this finding. On the other hand, the probability of exceeding the cutoff criteria increases with the number of tests administered, and recent statistical work indicates that with an 8-test battery, the probability of exceeding the cutoff of 1.5 SDs on at least 2 tests is slightly above .05.

It is noteworthy that the average cognitive performance of the entire sample showed no deterioration during the 6-month trial, regardless of the treatment arm. This result can be explained, in part, by the practice effects resulting from repeated exposure to neurocognitive testing in the study and, in part, by the inclusion of patients with mild and stable deficits. In fact, patients with frank dementia or who were unable to participate in testing were excluded, as were patients with AIDS-defining opportunistic infections or malignant neoplasms requiring chemotherapy.

The potentially positive effects of peptide T observed in the subgroup analyses, defined by relevant baseline characteristics on a laboratory marker of disease progression and by the presence of clinically meaningful neuropsychological impairment, require support from further studies focused on these subgroups. Moreover, because multiple analyses and comparisons were conducted, caution is required in interpreting these findings.

The primary analyses in the study failed to indicate that peptide T was effective in enhancing cognitive performance in this sample of HIV-positive patients. However, subgroup analyses suggested the possible efficacy of peptide T for patients with less disease progression (ie, CD4+ cell count >0.200×10^9/L) and with more pervasive cognitive impairment (global deficit score, ≥0.5). The methods and results of this study are likely to be helpful in designing future clinical trials in HIV-associated cognitive impairment.

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The study conformed to the National Institutes of Health guidelines on research on human patients and had oversight by the institutional review boards of the University of Southern California; the University of Miami; the University of California, San Diego; and the National Institute of Mental Health.

The views and opinions expressed in this article are those of the authors and should not be construed to be the official view of the National Institute of Mental Health.

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