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Memantine for AIDS Dementia Complex: Open-Label Report of ACTG 301

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Abstract

Objective—To evaluate the long-term safety and efficacy of memantine use as treatment of HIV-associated cognitive impairment.

Background—The results of a 20-week, randomized, double-blind, placebo-controlled trial of memantine in HIV-infected participants with cognitive impairment (ACTG 301) were previously reported. We report the results of the up-to-60-week open-label phase following the double-blind phase.

Method—Participants received open-label memantine and were escalated to a 40 mg/day dose or their maximum tolerated dose in the double-blind phase. Adverse experiences were used to evaluate safety, and changes in the mean of eight neuropsychological test scores (NPZ-8) were used to evaluate efficacy.

Results—Ninety-nine participants entered the initial 12-week open-label phase and 45 in the additional 48-week extension. Twenty-seven participants reported severe adverse experiences. During the initial 12-week open-label phase, participants randomized to memantine in the double-blind phase had a statistically significant higher improvement in NPZ-8 compared to those randomized to placebo in the double-blind phase. No statistically significant NPZ-8 changes were detected during the 48-week extension.

Conclusion—Long-term use of memantine appears safe and tolerable. Future randomized studies with longer follow-up are necessary to establish efficacy of memantine for the treatment of HIV-associated cognitive impairment.

Keywords

AIDS dementia; cognitive impairment; memantine; HIV

INTRODUCTION

Cognitive impairment remains an important manifestation of HIV-1 infection even in the setting of highly active antiretroviral therapy (HAART).[1–5] Therefore, safe and effective adjuvant therapies are needed to attenuate or prevent neuronal injury and loss. Memantine (1-amino-3,5-dimethyl-adamantane), an uncompetitive low affinity antagonist of the N-methyl-D-aspartate (NMDA) receptor currently approved by the US Food and Drug Administration (FDA) for treating Alzheimer's disease,[6,7] has been shown to be neuroprotective against HIV neurotoxicity in vitro and in animal models.[8–11]

Based on the above rationale, we conducted and reported the results of a 20-week, randomized, double-blind, placebo-controlled trial that showed good tolerability but without significant clinical efficacy of memantine in HIV-infected participants with mild to severe cognitive impairment.[12] Study participants met the following criteria prior to enrollment in the double-blind phase: AIDS Dementia Complex (ADC)[13] stage 1 or greater and neuropsychological impairment. Neuropsychological impairment was defined as at least 2 *SD* below the normative value on one or more neuropsychological tests, or 1 *SD* below the normative on at least two tests. We report the results of the open-label phase of this trial with up to 60 weeks of follow-up. The primary objectives of the open-label phase were to provide further safety and efficacy information of long-term memantine use as adjuvant therapy in patients with HIV-associated cognitive impairment.

METHODS

ACTG 301

AIDS Clinical Trials Group (ACTG) 301 was a randomized, double-blind, placebo-controlled trial of oral memantine taken alone or concurrently with an antiretroviral regimen in participants with ADC stage 1 or greater, followed by an optional open-label treatment phase. The double-blind phase of the trial included a 16-week treatment period (memantine up to 40 mg/day vs. matching placebo) followed by a 4-week washout period. All participants who completed the 20-week double-blind phase were offered the option to participate in an open-label phase. The open-label phase initially included 12 weeks of memantine administration and then was extended by an additional 48 weeks for a total of 60 weeks in Version 4.0 of the protocol. Participants who completed the initial 12-week open-label phase may have entered the 48-week extension continuously or with a time gap if they had completed the initial open-label phase before Version 4.0 of the protocol was approved and the extension period was available. The protocol underwent review and approval by the institutional review boards at all participating sites. Informed consent was obtained from all subjects or their authorized representatives. The data of open-label phase were collected from July 1997 to July 2001. The flow of study participants during the trial is displayed in the CONSORT diagram (Figure 1).

Cognitive function was evaluated by a series of neuropsychological assessments. A summary neuropsychological test score, the NPZ-8, was defined as the average of eight individual neuropsychological test scores standardized for the participant's age and education, including Timed Gait, Grooved Pegboard Dominant Hand and Non-dominant Hand, Trail Making Part A and B, Symbol Digit, Choice Reaction Time, and Sequential Reaction Time.

Statistical Analyses

The primary analyses focus on the 12-week initial open-label phase, where participants are classified into one of two groups according to their randomized treatment assignment in the double-blind phase:

- Mem/O: randomized to memantine arm in the double-blind phase
- Placebo/O: randomized to placebo arm in the double-blind phase

Baseline is defined as Week 0, the beginning of the double-blind phase. Descriptive statistics are used to describe the study sample at the beginning of the initial open-label phase, Week 20. Among-groups comparisons are performed using the Kruskal-Wallis test for continuous and ordinal variables and exact tests for categorical variables. To evaluate the safety of memantine, participants' follow-up completion, dosage status, and adverse events are summarized, because HIV RNA viral load and CD4+ count data were not collected in the open-label follow-up. To assess efficacy, changes in NPZ-8 from Week 20 are evaluated and compared between groups Mem/O and Placebo/O at Weeks 26 and 32. GEE models with an autoregressive correlation structure are used to estimate the time trend of the changes in NPZ-8 from Week 20 throughout the initial open-label follow-up. The initial model included NPZ-8 at Week 20, follow-up time in weeks since the beginning of the initial open-label phase, group (Mem/O vs. Placebo/O), and the interaction between group and follow-up time. Then backward covariate selection strategy is applied until all covariates left in the model with P value lower than .15.

In protocol Version 4.0, the open-label follow-up was extended to 60 weeks. Participants in the 48-week open-label extension are further classified into three groups defined by their randomized treatment assignment in the double-blind phase and their open-label extension status:

- Mem/No Gap: originally randomized to memantine in the double-blind phase and continuing open-label memantine without a time gap from Week 12 of the initial open-label phase
- Placebo/No Gap: as above but originally randomized to placebo in the double-blind phase
- Gap: time gap between the end of 12 weeks initial open-label memantine and the beginning of 48-week extension

To assess efficacy, changes in NPZ-8 from the beginning of the open-label extension in groups Mem/No Gap, Placebo/No Gap, and Gap are evaluated at 16, 32, and 48 weeks after the beginning of the open-label extension. GEE models with autoregressive correlation structure and adjusted to the NPZ-8 at the beginning of the open-label extension are used to estimate the time trend of the changes in NPZ-8 from the beginning of the open-label extension in groups Mem/No Gap, Placebo/No Gap, and Gap. No comparisons among groups are performed.

All significant tests are two-sided and performed at the .05 level without adjustment for multiple testing. All analyses are based on available data without imputation.

SUMMARY OF DOUBLE-BLIND PHASE RESULTS

In the 20-week double-blind phase, memantine was safe and well tolerated but was not efficacious in HIV-infected participants with mild to severe cognitive impairment.[12] One hundred forty participants enrolled in the double-blind phase. The percentages of participants reaching the 40 mg/day dose in the memantine and placebo groups were 61% and 88%, respectively. The reported adverse experiences between the two groups were not dissimilar. A weak trend of neuropsychological improvement was observed in both groups, favoring memantine therapy. However, statistically significant differences in the improvement between the two groups were not observed, possibly due to larger than expected variability.

OPEN-LABEL PHASE RESULTS

Demographics and Characteristics at the Entry of the Initial Open-Label Phase

Of 140 participants randomized into the 20-week double-blind phase of ACTG301 (70 in the memantine arm and 70 in the placebo arm), 106 successfully completed the double-blind phase; 99 (51 from the memantine arm and 48 from the placebo arm) entered into the initial 12-week open-label phase. Demographics and baseline and Week 20 characteristics were not dissimilar between the two groups (Table 1). Participants were primarily male, non-Hispanic white, and with a median age of 43. No statistically significant differences between groups Mem/O and Placebo/O were detected in the demographics or characteristics at baseline and Week 20.

At Week 20, participants who did not enter into the open-label phase had significantly lower baseline CD4 count [median (Q1, Q3) = 207 (80, 279) cells/μL] than participants entering the open-label phase [median (Q1, Q3) = 316 (189, 473) cells/μL], with $P < .001$. There were no statistically significant differences in other demographics and baseline characteristics between these two cohorts.

Safety

Open-label follow-up completion and dosage—Eighty-two (83%) of 99 participants completed the 12-week initial open-label memantine treatment; 66 (80%) of these 82 reached 40 mg dosage at Week 32. There was no statistically significant difference in the 12-week treatment completion rate (Mem/O 82% vs. Placebo/O 83%) or the percentage of participants reaching 4 0 mg dosage at Week 32 (Mem/O 76% vs. Placebo/O 85%) between the groups,

with *P* values 1.000 and .407, respectively. The percentage of completion rate is very similar to the 88% in the placebo arm during the double-blind phase.

Among 45 participants entering the 48-week open-label extension period, 17 participants had a time gap with median length of 210 [(Q1, Q3) = (132, 321)] days between the completion of the initial open-label phase and the beginning of the extension period, 34 (76%) participants completed the extension treatment, and 27 (79%) of these 34 reached 40 mg dosage at the end of the extension period. The extension treatment completion rates in the three groups were 82% (14 out of 17) in the Mem/No Gap group, 55% (6 out of 11) in the Placebo/No Gap group, and 82% (14 out of 17) in the Gap group. The percentage of participants reaching 40 mg dosage at end of the extension period among those who completed the open-label extension treatment in groups Mem/No Gap, Placebo/No Gap, and Gap were 79%, 100%, and 71%, respectively.

Adverse events—One participant from the Mem/O group died of progressive HIV dementia during the initial open-label phase, one from the Mem/No Gap group died of septicemia, and one from the Gap group died of suspected cardiac failure during the open-label extension, all of which were judged to be not related to memantine.

Table 2 summarizes sign/symptoms and lab toxicities that were graded as severe or higher, judged as not “unrelated to the study treatment”, and reported during the initial 12-week open-label follow-up. Eighteen participants experienced severe or higher signs/symptoms, including 10 participants in the Mem/O group and 8 in the Placebo/O group. In addition, three participants in the Mem/O group and two in the Placebo/O group reported severe or higher lab toxicities.

During the open-label extension, eight participants experienced severe or higher sign/symptoms, including three participants in the Mem/No Gap group (pain [n=1]; pain and numbness [n=1]; fever, pain, diaphoresis, numbness, tingling, nausea, and fatigue [n=1]); three in the Placebo/No Gap group (fatigue and mental cloudiness [n=1], seizure [n=1], depression [n=1]); and two in the Gap group (somnolence and lethargy [n=1], tremor [n=1]). In addition, one participant in the Mem/No Gap reported severe lab toxicity (increased amylase).

Efficacy

In the initial open-label follow-up, NPZ-8 changes from Week 20 over time were used to assess the efficacy of memantine. Participants in the Mem/O group had a marginally significant increase in NPZ-8 at Week 32 compared to Week 20 (Table 3), with a median increase of 0.14 [(Q1, Q3) = (−0.10, 0.36); $P = .072$]. The median NPZ-8 change in the Placebo/O group was −0.13 [(Q1, Q3) = (−0.37, 0.13); $P = .261$]. The median NPZ-8 change at Week 32 in the Mem/O group was significantly higher than in the Placebo/O group ($P = .020$). Participants in the Mem/O group had significantly higher NPZ-8 improvement than those in the Placebo/O group throughout the initial open-label follow-up: the 95% CI of the NPZ-8 improvement in the Mem/O group minus the NPZ-8 improvement in the Placebo/O group (0.059, 0.461) ($P = .011$).

Table 4 displays the median (Q1, Q3) of NPZ-8 changes from the beginning of the open-label extension for groups Mem/No Gap, Placebo/No Gap, and Gap over the 48-week open-label extension. Participants in the Mem/No Gap group had a marginally significant decrease in NPZ-8 with a median change of −0.11 [(Q1, Q3) = (−0.57, 0.02), $P = .057$] after 16 weeks follow-up in the open-label extension. For the Gap group, a marginally significant increase in NPZ-8 with a median change of 0.20 [(Q1, Q3) = (0.05, 0.56); $P = .052$] was noted. No statistically significant changes in NPZ-8 from the beginning of the open-label extension were detected in the Placebo/No Gap group. A 0.014 (95% CI 0.005, 0.022; $P = .001$) per week increase in the NPZ-8 changes from the beginning of the open-label extension was detected for the Placebo/No Gap group throughout the initial open-label follow-up, and no statistically

significant time trend of the NPZ-8 changes was found for the Mem/No Gap group or the Gap group.

Furthermore, ADC staging was used to evaluate participants' functional changes during the open-label follow-up. It was found that participants' ADC staging was very stable during the up-to-60-week open-label follow-up. At each open-label visit, approximately 15% among those with available ADC stage measurement had advanced ADC (stage 2 or higher).

CONCLUSION

Data from the open-label study of memantine for the treatment of HIV-associated dementia suggest that long-term use of memantine is safe and tolerated by HIV-infected individuals with cognitive impairment. Data from the first 12 weeks of open label also suggest that the group previously randomized to memantine in the double-blind phase performed cognitively better than the group previously randomized to placebo. This poses the question of whether a longer study would have been necessary to observe a measurable clinical benefit of memantine.[12] This hypothesis was reinforced by the improvement seen in brain metabolites in those treated with memantine.[12]

The efficacy data from the extended 48-weeks open-label follow-up suggest that cognitive performance tends to improve over time in the Placebo/No Gap group and appears stable in groups Mem/No Gap and Gap.

Several limitations are inherent to the transition from a double-blind study to an open-label extension that affect the generalizability of the study results. Specifically there is a selection bias in study participation and lack of a comparative placebo arm.

We assessed the generalizability of demographics and baseline characteristics between participants who did and did not enter the open-label phase. We were unable to identify any significant differences except for a higher baseline CD4 count in those who entered the open-label phase. However, this alone does not prevent selective entry of participants into the open-label phase.

Taking into consideration the aforementioned limitations, this open-label study provides reassurance regarding the safety and tolerability of long-term exposure to memantine in HIV-infected individuals; however, questions remain on the efficacy of memantine for the treatment of HIV-associated cognitive impairment. Combining the results of the double-blind and the open-label study suggests that a randomized trial $\geq$ 28 weeks of appropriate sample size could address the efficacy of memantine for the treatment of HIV-associated cognitive impairment. As the HIV population ages, it is likely that older HIV patients will experience other dementias, including Alzheimer's dementia, in addition to HIV-associated cognitive impairment. Memantine may be of particular interest in an aging HIV population with cognitive impairment.

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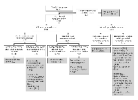

Figure 1.
CONSORT diagram.

Table 1

Demographics and clinical characteristics at baseline and Week 20

	Total (N = 99)	Mem/O (n = 51)	Placebo/O (n = 48)	*P*
Sex, n (%)				.517[a]
Male	89 (90%)	47 (92%)	42 (88%)	
Female	10 (10%)	4 (8%)	6 (13%)	
Race/ethnic, n (%)				.266[b]
White non-Hispanic	74 (75%)	39 (76%)	35 (73%)	
Black non-Hispanic	10 (10%)	5 (10%)	5 (10%)	
Hispanic	12 (12%)	4 (8%)	8 (17%)	
Other	3 (3%)	3 (6%)	0 (0%)	
Injecting drug user, n (%)				.175[a]
Never	83 (84%)	40 (78%)	43 (90%)	
Previously	16 (16%)	11 (22%)	5 (10%)	
Education level, n (%)				.666[c]
≤12 years	30 (30%)	14 (27%)	16 (33%)	
12–16 years	44 (44%)	24 (47%)	20 (42%)	
<16 years	25 (25%)	13 (25%)	12 (25%)	
Baseline age, years				.774[c]
n	99	51	48	
Median (Q1, Q3)	43 (37, 49)	42 (38, 48)	44 (37, 49)	
Baseline CD4 count, cells/μL				.917[c]
n	97	49	48	
Median (Q1, Q3)	316 (189, 473)	320 (211, 483)	316 (177, 469)	
Week 20 Karnofsky score				.307[c]
n	97	50	47	
Median (Q1, Q3)	80 (70, 90)	80 (70, 90)	80 (70, 90)	
Week 20 NPZ-8				.104[c]
n	80	42	38	
Median (Q1, Q3)	−0.76 (−1.49, −0.05)	−0.62 (−1.34, 0.10)	−0.89 (−1.53, −0.37)	

[a] Fisher's exact test.

[b] Exact test from $R \times C$ tables.

[c] Kruskal-Wallis test.

Table 2

Summary of signs/symptoms and lab toxicities graded as severe or higher and not judged as "unrelated to study treatment" in the initial open-label phase*

		Mem/O (n = 51)	Placebo/O (n = 48)	Total (N = 99)
Sign/Symptom		10	8	18
General body	Ache/pain/discomfort	1[a]	3	4
	Asthenia/fatigue/malaise	0	1[d]	1
Gastrointestinal	Diarrhea/loose stools	3	0	3
	Gastrointestinal dysfunction	0	1[e]	1
Renal	Renal/urinary system dysfunction	0	1[e]	1
Reproductive	Contraction/cramp	1[b]	0	1
Neurological	Agitation/hyperactive	0	1[f]	1
	Confusion/difficulty concentrating/ cognition	2	1[d]	3
	Consciousness level changes/lethargy	0	1[g]	1
	Depression	1[c]	1[g]	2
	Dreams/insomnia/sleeping problems	1	1	2
	Inappropriate/changed behavior	1[c]	0	1
	Mental status changes	0	2[e,f]	2
	Numbness/paresthesia/tingling	1	0	1
	Rigid/tight/stiff	1[b]	0	1
	Weakness	1[a]	0	1
Lab toxicity		3	2	5
Hematology	Atypical lymphocytes	1	0	1
	Neutropenia	1	0	1
Liver/hepatic	Serum glutamic-oxaloacetic transaminase (SGOT)	0	1[h]	1
	Serum glutamic-pyruvic transaminase (SGPT)	1	2[h]	3

*Eight participants reported multiple events during the initial open-label phase. The events reported by the same participant are labeled with same superscript. For example, one participants in the Mem/O group reported one ache/pain/discomfort and one depression.

Table 3

NPZ-8 changes from Week 20 in the 12 weeks initial open-label phase (available data)

	Total	Mem/O	Placebo/O	*P*[a]
NPZ-8 Changes at Week 26				.144[a]
n	67	33	34	
Median (Q1-Q3)	0.00 (−0.23, 0.30)	0.13 (−0.20, 0.47)	−0.04 (−0.35, 0.17)	
P [b]	.843[b]	.213[b]	.359[b]	
NPZ-8 Changes at Week 32				.020[a]
N	62	32	30	
Median (Q1-Q3)	0.05 (−0.31, 0.31)	0.14 (−0.10, 0.36)	−0.13 (−0.37, 0.13)	
P [b]	.711[b]	.072[b]	.261[b]	

[a]Using Kruskal-Wallis test to compare the NPZ-8 changes between the Mem/O and Placebo/O groups.

[b]Using signed rank test to evaluate whether the NPZ-8 changes are different from 0 or not.

Table 4

NPZ-8 changes from the entry to the open-label extension in the 48 weeks open-label extension follow-up (available data)

	Mem/No Gap	Placebo/No Gap	Gap
NPZ-8 changes at Week +16			
n	13	8	16
Median (Q1-Q3)	−0.11 (−0.57, 0.02)	−0.18 (−0.32, 0.11)	0.06 (−0.16, 0.25)
P [a]	.057[a]	.461[a]	.669[a]
NPZ-8 changes at Week +32			
n	9	4	12
Median (Q1-Q3)	−0.19 (−0.33, 0.27)	−0.17 (−0.51, 0.49)	0.20 (0.05, 0.56)
P [a]	.359[a]	1.000[a]	.052[a]
NPZ-8 changes at Week +48			
n	7	5	14
Median (Q1-Q3)	−0.15 (−0.23, 0.18)	0.22 (0.03, 0.65)	0.23 (−0.32, 0.51)
P [a]	.469[a]	.313[a]	.463[a]

[a]Using signed rank test to evaluate whether the NPZ-8 changes are different from 0 or not.