Drug Forecast

Memantine: A New Treatment Option for Patients with Moderate-to-Severe Alzheimer’s Disease

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INTRODUCTION

Alzheimer’s disease (AD) affects approximately 15 million people worldwide and more than four million Americans in the U.S. alone.1,2 This disease targets the elderly population, and the incidence increases with age. Women are at a higher risk for AD, whereas men tend to develop vascular dementia. AD progresses slowly and results in impairment of both cognitive and functional capabilities.3 A gradual loss of neurons is linked to changes in catecholaminergic, serotonergic, and cholinergic transmissions.4 The involvement of multiple neuronal pathways acts as a barrier to neuronal pathways and allows calcium (Ca2+) to enter the neurons.5 The binding of glutamate to AMPA receptors triggers NMDA receptors, thus altering membrane permeability and allowing the influx of calcium (Ca2+) into the neurons.

The pathogenesis of AD has been linked to the “glutamate excitotoxicity hypothesis,” which states that an excess of glutaminergic stimulation causes an overactivation of NMDA receptors. This leads to calcium overflow into the neurons, activating catabolic enzymes such as nucleases, proteases, and phospholipases. Increased activity of these enzymes promotes cell death, as a result of hypoxia and ischemia, and eventually causes learning and memory recall signals to be disrupted and unrecognized.

Memantine is a noncompetitive, low-to-moderate-affinity NMDA receptor antagonist6 with an apparent dual mechanism of action. At the receptor level, it displays rapid binding properties and a pronounced voltage dependency that modulates the glutaminergic neurotransmission system. In a state of reduced glutamate release, memantine produces improved neurotransmission and activation of neurons. However, when glutamate release is excessive, memantine inhibits the excitatory action of glutamate by antagonizing NMDA receptors.6–10 The drug thus blocks NMDA receptors from excessive glutaminergic stimulation and prevents an increase in calcium influx; it subsequently results in decreased cell death and alleviates symptoms of AD. The affinity of memantine for cerebellar tissue is thought to be higher than that for frontal lobe brain tissue.11

PHARMACOLOGY

Glutamate is a primary excitatory neurotransmitter in the brain, and glutamate receptor activity is required for memory, motor function, and perception. Levels of glutamate increase during times of learning and memory and bind to alpha amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. The binding of glutamate to AMPA receptors triggers NMDA receptors, thus altering membrane permeability and allowing the influx of calcium (Ca2+) into the neurons.

Although the pathogenesis of AD has been linked to the “glutamate excitotoxicity hypothesis,” it is not the only factor. Other factors, such as amyloid plaques and neurofibrillary tangles, also contribute to the progression of the disease. Amyloid plaques are deposits of amyloid beta (Aβ) protein, which is derived from the amyloid precursor protein (APP). Neurofibrillary tangles are abnormal tau protein filaments that form in the cytoplasm of neurons.

PHARMACOKINETICS

After oral administration, memantine is absorbed rapidly and completely. It has linear pharmacokinetic properties over the therapeutic dose range,12 and the time to peak concentration is three to seven hours.12 A therapeutic response in patients with dementia has been observed within 14 days of therapy.12,13

Memantine is not highly protein-bound; although its protein binding varies greatly (from 10% to 45%),14 it is

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Efficacy

Alzheimer’s Disease

Reisberg et al.15

In a 28-week, randomized, double-blind, parallel-group study, Reisberg and colleagues evaluated the efficacy of memantine in patients with probable moderate-to-severe AD. The investigators confirmed the diagnosis of AD using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), criteria; the Mini-Mental Status State Examination (MMSE) scores of 3 to 14; and the Global Deterioration Scale (GDS), stage 5 or 6.

Overall, 252 patients were randomly assigned to receive either memantine 20 mg/day or an equivalent placebo. The memantine patients received an initial dose of 5 mg once daily, followed by an escalating regimen of 5 mg weekly, to a dose of 10 mg twice daily. The assessments and observations of the patients were made at the baseline evaluation, at 12 weeks, and at 28 weeks.

The Clinician’s Interview-Based Impression of Change Plus Caregiver Input (CIBIC–Plus) score, the Alzheimer’s Disease Cooperation Study–Activities of Daily Living Inventory modified for severe dementia (ADCS–ADLsev) score, and the Severe Impairment Battery (SIB) score were used to evaluate the efficacy of the therapy. The CIBIC–Plus measured overall global change on a scale of 1 (markedly improved) to 7 (markedly worse). The ADCS–ADLsev measured functional capacity on a scale of 0 to 54 (with 54 representing optimal performance). The SIB evaluated the cognitive performance on a scale of zero (0) to 100 (with 0 representing the greatest impairment).

At 28 weeks, the analysis of change in scores from baseline showed a statistically significant improvement in favor of memantine therapy compared with placebo. The memantine group experienced better outcomes (i.e., less deterioration), according to the mean change in CIBIC–Plus ($P = .06$ with the last observation carried forward [LOCF] and $P = .03$ for the observed cases), the ADCS–ADLsev ($P = .02$ with the LOCF and $P = .003$ for the observed cases), and the SIB ($P < .001$ with the LOCF and $P = .002$ for the observed cases). However, no significant differences were observed for the MMSE, Global Deterioration Scale stage, or Neuropsychiatric Inventory assessments between the actively treated and the placebo-treated patients.

Ferris et al.16

In an extension phase of the 28-week study, 175 patients who completed the previous double-blind study were given an open-label treatment with memantine for another 24 weeks. The CIBIC–Plus, ADCS–ADL, and SIB scales were used to measure the efficacy variables.

The patients who had previously been given placebo and who were switched to memantine therapy improved in terms of the projected rate of continued decline. Memantine was also well tolerated, and there were no important differences in adverse drug effects (ADEs) between patients who switched from placebo to memantine and those who continued memantine therapy. The overall findings supported the long-term use of memantine in patients with moderate-to-severe AD.

Farlow et al.17

In another randomized, 24-week, double-blind, placebo-controlled trial, researchers recruited 403 patients with moderate-to-severe AD who had also been taking the cholinesterase inhibitor donepezil for at least six months and who achieved stabilization by taking the same dose for at least three months.

The patients were randomly assigned to receive 10 mg of memantine twice daily or an identical placebo. The memantine group initially received 5 mg daily; this amount was increased weekly by 5 mg to achieve the dose of 20 mg/day (10 mg twice daily). The primary efficacy assessments were analyzed by the SIB, the ADCS–ADL, and the CIBIC–Plus.

At week 24, statistically significant improvement ($P < 0.001$) in cognitive function, as measured by the SIB, was observed in patients taking the combination of donepezil and memantine. The mean difference in the change in SIB scores for the combination group taking memantine and donepezil, compared with the patients receiving placebo and donepezil, was 3.3 units.

At week 24, the patients receiving combination therapy experienced significantly improved daily functioning according to the ADCS–ADL evaluation ($P = .028$) compared with the patients receiving placebo.

At the end of the study, the mean difference in ADCS–ADL scores was 1.6 units. The CIBIC–Plus global assessment also showed statistically significant results ($P = .027$) in favor of the combined memantine/donepezil therapy. This trial demonstrated the superior efficacy of memantine, combined with donepezil, in treating moderate-to-severe AD over that of donepezil alone.

Vascular Dementia

Wilcock et al.18

The efficacy, tolerability, and safety of memantine was evaluated in a 28-week, double-blind study in patients with mild-to-moderate vascular dementia. A total of 579 patients completed a two-week washout period with placebo, followed by the randomization schedule of either 20 mg of memantine or placebo. Therapy was begun with an initial dose of 5 mg daily, which was escalated by 5 mg weekly to a final dose of 20 mg daily.

The investigators evaluated the primary efficacy variables using the Alzheimer’s Disease Assessment Scale–Cognitive Subscale (ADAS–Cog) and the Clinical Global Impression of Change (CGI–C). The ADAS–Cog, a quantitative instrument that assesses the severity of cognitive impairment over time, consists of 11 tests, including word recall, naming objects and counting fingers, and word recognition. The CGI–C shows the change of clinical status from baseline values. Secondary efficacy variables included the Nurses’ Observation Scale for Geriatric Patients (NOSGER), the Gottfries–Brane–Steen Scale (GBS) score, and the MMSE score.

Patients in the memantine group showed significant improvement in ADAS–Cog total scores compared with the placebo group. The mean difference between the groups was 1.75 ($P = .0005$). At the end of the 28 weeks, there was no significant difference in CGI–C values between the groups ($P = .1103$). The NOSGER assessment, which included a
rating of memory, indicated higher memory scores (by 0.72 points) in patients taking memantine \( (P = 0.02) \). All other secondary efficacy scores showed no significant difference between the two treatment groups.

In general, treatment with memantine resulted in significant improvement in the cognitive performance in patients with vascular dementia.

Gortelmeyer and Erbler\(^{10} \)

In another placebo-controlled, randomized study, the authors studied the efficacy and tolerability of memantine in patients with mild-to-moderate dementia syndrome. After a one-week washout period, 88 patients received either memantine or placebo. Patients received 10 mg/day for the first three days, after which time the dose was increased to 20 mg/day for the remainder of the study period.

The investigators assessed the patients as follows:

- at the psychopathological level:
  - the [Sandoz] Clinical Assessment Geriatric Scale (SCAG), which measures cognitive, affective, and social functioning
  - the Clinical Global Impression (CGI), which assesses the risks and benefits of drug treatment in patients who are mentally ill
- at the behavioral level: the GBS, which evaluates the patients’ functional capacity
- at the performance level: the Activities of Daily Living (ADL) scale, which represents the patients’ capacity to carry out simple daily tasks

After 14 days of therapy, the SCAG score, which indicates global assessment of change in the patient’s condition, showed a statistically significant difference between the two groups in favor of memantine; the mean baseline for six weeks’ difference was -18.1 points with memantine and -6.4 points with placebo \( (P \leq 0.05) \).

The total GBS score, which measures behavioral changes, also showed a decrease in dementia-associated symptoms. The differences between the two groups were significant after 14 days of therapy \( (P \leq 0.001) \). The mean GBS score was 37.5 for the memantine group (baseline mean score, 47) and 46.3 for the placebo group (baseline mean score, 47.2).

The analysis of the ADL assessment revealed superior results with memantine therapy for both the time required for performing the activity and the quality of the performance \( (P \leq 0.003) \). After six weeks of treatment, 26.8% of placebo patients versus 58.5% of memantine patients showed improvement in their initial condition.

Overall, this study showed a statistically significant alleviation of dementia-induced disturbances in both the behavioral and psychopathological measures and improvement in the quality of performing daily activities.

Orgogozo et al.\(^{19} \)

In another study of patients with mild-to-moderate vascular dementia, the investigators randomly selected 321 patients to receive either memantine or placebo, followed by a week-long washout period. The patients initially received a dose of 5 mg of memantine daily that was titrated up weekly by 5 mg until it reached 20 mg/day by week four. The assessments were performed at baseline and at weeks two, four, 12, 20, and 28.

The ADAS–Cog was used to determine the primary efficacy endpoint for evaluating cognitive function. Scores ranged from 0 (best) to 70 (worst).

The CIBIC–Plus was used to rate global change, and a score of 1 to 7 was given for this assessment \((1 = \text{very much improved}, 7 = \text{very much worse})\). Secondary efficacy variables included the MMSE and the GBS scale.

The NOSGER was used to observe functional assessments.

At the end of the study period, the CIBIC–Plus scores in the intent-to-treat population with the LOCF were higher in the memantine group (60%) than in the placebo group (52%), although the difference between the two groups was not statistically significant \( (P = 0.227) \). The mean ADAS–Cog scores improved from the baseline value in the memantine group but deteriorated in the placebo group. In the intent-to-treat population assessment, the scores of the memantine patients improved by a mean of 0.4, whereas those of the placebo group decreased by a mean of 0.4.

The MMSE scores, which were analyzed for each protocol, declined in the placebo group but significantly improved in the memantine group \( (P = 0.003) \).

Both the GBS and NOSGER scales showed significant differences from baseline in favor of memantine \((P = 0.04 \text{ and } P = 0.07, \text{ respectively})\).

SAFETY PROFILE

The Reisberg Study. Eighty-four percent of patients receiving memantine and 87% receiving placebo experienced ADEs, although most effects were mild to moderate in severity.\(^{15} \) However, the authors concluded that the events were either not related to, or were unlikely to be related to, memantine. Furthermore, ADEs were more common in the placebo group; 17% of the placebo group patients discontinued the study prematurely, compared with 13% in the memantine group. Agitation was the most common cause of premature withdrawal from the study in 32% of the placebo patients versus 18% of the memantine group. Other reported ADEs included urinary incontinence, urinary tract infections, insomnia, and diarrhea.

The Wilcock Study. Memantine was well tolerated in patients with mild-to-moderate vascular dementia.\(^{18} \) The most frequently seen ADEs in the memantine patients were dizziness (11% of patients taking memantine and in 8% taking placebo) and constipation (10% taking memantine and in 4% taking placebo). There was a slight increase in the number of reports of gastrointestinal and respiratory disorders in the memantine group but more reported psychiatric disorders in the placebo group. Overall, most ADEs during the study were rated as mild (52%) or moderate (39%) in severity.

The Orgogozo Study. Memantine was also well tolerated in this trial. Reported ADEs were comparable in both the memantine (76%) and the placebo (74%) groups.\(^{19} \) The most common ADEs included agitation, confusion, and dizziness. The serious ADEs reported were also comparable between the two groups (23% in the memantine group, 26% in the placebo group), the most severe being cerebrovascular events. None of the reported ADEs occurred at a significantly greater rate in the memantine arm. There were no drug-related deaths in either group.
CONCLUSION

Memantine belongs to a new class of agents and is the first drug approved for the treatment of patients with moderate-to-severe AD. The drug’s mechanism of action differs from that of other currently available AD therapies. Patients have tolerated the drug well and have experienced reduced symptomatic clinical deterioration when taking memantine therapy compared with placebo. The improvements have included cognitive, functional, and overall global progress. Most ADEs that occurred were mild to moderate in severity.

Memantine is a promising medication for some patients. Although additional long-term and comparative studies are needed to assess its efficacy and safety, its benefits outweigh the risk of the disease progression.

REFERENCES