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Efficacy and Tolerability of MIC601 in Patients with Mild to Moderate Alzheimer Disease Who Were Unable to Tolerate or Failed to Benefit from Treatment with Rivastigmine

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aim: To evaluate the efficacy and tolerability of MLC601 in patients with mild to moderate Alzheimer disease (AD).
Study Design: This is an open-label pilot study.
Place and Duration of Study: It was conducted at three university referral centres in Iran from September 2009 until November 2011.
Methodology: One-hundred and twenty four outpatients with mild to moderate AD who had previously failed to tolerate or benefit from treatment with Rivastigmine for 6 months at a dose of 2 to 12 mg per day were switched to a MLC601 regimen of one capsule three times per day for up to 18 months. Outcome measures included adverse events (AEs), withdrawal rate, and changes in the Mini-Mental State Examination (MMSE) and the cognitive subscale of the AD Assessment Scale (ADAS-cog) relative to baseline measurements.

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Results: Two patients were lost to follow up, and 122 patients completed the 18-month trial. The mean age of the participants was 65.3±6.4 years (range 54-82), and 77 (63.1%) of the participants were female. Improved cognitive function was observed in the first 6 months of the regimen (ADAS-cog=-3.1±10.1; MMSE=1.2±3.0), and the stabilisation of cognitive decline was observed over the remaining 12 months (ADAS-cog=-1.6±7.6; MMSE=0.8±4.2). AEs were predominantly gastrointestinal and occurred in 7.3% of patients.
Conclusions: MLC601 showed good tolerability and promising effects on cognitive function in AD patients during 18 months of treatment.

Keywords: Alzheimer disease; cholinesterase inhibitors; MLC601; NeuroAiD; neuroprotection; neuroregeneration.

1. INTRODUCTION

Alzheimer disease (AD) is a fatal progressive illness and the most common form of dementia, affecting as many as 25 million people worldwide [1]. There is currently no treatment to prevent the progression of these diseases [2]. Current therapeutic approaches for the treatment of AD merely offer limited and often transient symptomatic benefits to patients and do not mitigate the insidious loss of neuronal cells that underlies these conditions [2,3]. Cholinesterase inhibitors (ChEIs), inhibitors of acetylcholine breakdown, and glutamate receptor effectors are the current therapies available for AD. However, these drugs are commonly associated with adverse events (AEs), including diarrhea, tiredness, dizziness, confusion, headache, vomiting, nausea, fatigue, insomnia, heart attack, and stroke [4].

New therapeutic strategies for AD as a severe, progressive neurodegenerative brain disorder are designed to act on multiple neural and biochemical targets involved in the underlying neurodegenerative and pathological processes; candidate drugs are neuroprotective (i.e., prevent or slow neuronal death) or neurorestorative (i.e., stimulate the replacement of dying or dead neuronal cells with viable cells) [5-7]. Traditional Chinese Medicine (TCM) appears to include several promising combination therapies. They usually contain several types of medicinal herbs, and their use is based on more than 2500 years of clinical experience. MLC601 is a TCM that is used extensively in China to improve recovery after stroke [8,9]. MLC601 has been shown to have both neuroprotective and neuroregenerative properties *in vitro* and *in vivo* [10]. Because of these interesting properties, we designed a trial to evaluate the efficacy and tolerability of MLC601 in patients with AD.

2. MATERIALS AND METHODS

An 18-month open-label pilot study was conducted at three university referral centres in Iran. All patients were at least 50 years old, met the criteria for AD according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and failed treatment with the Rivastigmine for any reason. The study protocol was registered in http://ClinicalTrials.gov/ (Identifier: NCT01696123). A baseline medical history was taken and physical examination was performed for all participants, and any comorbidities and concomitant therapies were noted. Patients with mild to moderate severity of the disease based on Mini-Mental State Examination (MMSE) score (mean of MMSE 18.0; range 10-24)

who were not sufficiently stabilized, as defined by an MMSE score that was worse than baseline, on maximum tolerated dose of Rivastigmine up to 12 mg/day during 6 months of treatment with ChEI have been considered as non-responder [11]. Patients with controlled concomitant diseases, such as hypertension and diabetes, were allowed to enter the study. Patients were excluded when cognitive impairment was attributed to causes other than AD including vascular dementia, dementia with Lewy bodies, Parkinson's disease with dementia, frontotemporal dementia and reversible dementias. Individuals with uncontrolled diabetes mellitus, hypertension, unstable cardiac disease, severe obstructive pulmonary disease, renal or hepatic failure and/or other life threatening conditions were also excluded. Patients were instructed not to use any anticholinergic drug, health food supplement containing ACh precursors, putative memory enhancers or insulin. All psychotropic drugs were also prohibited, with the exception of chloral hydrate, short-acting benzodiazepines and haloperidol, for not more than three days in succession and not within 72 hours before any efficacy assessment.

The MMSE [12,13] and Alzheimer disease assessment scale-cognitive sub scale [14] (ADAS-cog) were used to measure treatment efficacy. ADAS-cog scores range from 0 (no impairment) to 70 (very severe impairment).

MLC601 (NeuroAid, Moleac Pte. Ltd, Singapore) (0.4 g per capsule) was prescribed as one capsule three times daily without an escalation dose. MLC601 combines 9 herbal components (0.57 g Radix *astragali*, 0.114 g Radix *Salvia miltiorrhizae*, 0.114 g Radix *Paeoniae rubra*, 0.114 g *Rhizoma chuanxiong*, 0.114 g Radix *Angelicae sinensis*, 0.114 g *Prunus persica*, 0.114 g *Carthamus tinctorius*, 0.114 g Radix *polygalae*, and 0.114 g *Rhizoma acori tatarinowii*) and 5 animal components (0.0285 g *Cornu saigae tataricae*, 0.095 g *Buthus martensii*, 0.0665 g *Hirudo*, 0.0665 g *Eupolyphaga seu steleophaga*, and 0.0285 g *Calculus bovisartifactus*).

Safety and tolerability evaluations included physical examinations, electrocardiography, vital sign monitoring and laboratory testing (complete cell blood count, serum AST, ALT, BUN, Creatinine, Na, K, Ca, P, PT, PTT, INR) weekly for the first 8 weeks and every 4 weeks thereafter. AEs were defined as any sign, symptom, syndrome or disease that occurred for the first time or worsened after baseline, whether they were considered treatment related. The MMSE and ADAS-cog were recorded at each efficacy follow-up visit (every 24±2 weeks). All AEs and changes in therapy were noted. The study was conducted in accordance with ethical standards of the institutional committee on human experimentation and with the Helsinki Declaration of 1975, revised in 1983. The initial study protocol was reviewed by the institutional review board in our centre, and all patients or their caregivers provided informed consent to participation.

The data were expressed as the mean ± standard deviation (SD) and were analysed using the Chi-square test and repeated measured analysis in SPSS version 11.0 software (SPSS Inc., Chicago, IL). P values <0.05 were considered statistically significant.

3. RESULTS

MLC601 was prescribed to 124 volunteer patients with AD who had previously been treated for 6 months with Rivastigmine and failed to benefit from treatment. Rivastigmine treatment was discontinued due to lack of efficacy (worsening of MMSE than baseline on maximum tolerated dose of Rivastigmine) in 66 (53.2%) patients, poor tolerability (unable to tolerate the minimum dose of Rivastigmine (1.5 mg bid) due to AEs) in 29 (23.3%) patients, and both

reasons in 29 (23.3%) patients. Two patients were lost to follow up, while 122 patients with mild to moderate AD completed the study. The mean patient age was 65.3±6.4 years (range 54-82). The study group included 77 (63.1%) females and 45 (36.8%) males. Mean and 95% Confidence Intervals for the ADAS-cog and MMSE scores at baseline, months 6, 12 and 18 are shown in Fig. 1. The repeated measured analysis showed a significant improvement in cognitive function as measures by ADAS-cog and MMSE in the first 6 months (ADAS-cog=-3.1±10.1; MMSE=1.2±3.0), but the changes over the remaining 12 months were non-significant (ADAS-cog=-1.6±7.6; MMSE=0.8±4.2) (Table 1). AEs reported by patients were predominantly gastrointestinal, most commonly transient nausea and vomiting (9 patients, 7.3%) while on MLC601. No patients withdrew from the study due to AEs. No abnormalities or clinically significant changes in haematology, hepatic or renal laboratory parameters were reported. The most common adverse effects reported by the patients under treatment with Rivastigmine (previous) and MLC601 (study) are shown in Table 2.

Table 1. Mean ± SD of Mini-Mental State Examination (MMSE) and Alzheimer disease assessment Scale-cognitive subscale (ADAS-cog) at 6-month intervals from baseline to 18 months in AD patients treated with MLC601

	Baseline	6th month	12th month	18th month	p-value
MMSE	18.0±4.8	19.2±5.2	19.0±5.5	18.9±5.4	0.067
ADAS-cog	23.2±8.1*	20.0±8.3*	20.8±8.5	21.5±8.4	0.048*

**There is a significant difference between the baseline and 6-month measurements of ADAS-cog according to repeated measured analysis of all visits.*

Table 2. Adverse effects in patients during previous treatment with Rivastigmine and during treatment with MLC601

	Rivastigmine	MLC601	p-value
Nausea	48 (40%)	9 (7.3%)	<0.0001
Vomiting	18 (15%)	5 (4.0%)	0.008
Agitation	9 (7.8%)	0	-
Weight loss	8 (6.6%)	0	-
Anorexia	8 6.6%)	1 (0.8%)	0.035
Diarrhea	6 (5%)	0	-
Headache	6 (5%)	0	-
Falling	5 (4.7%)	0	-
Hypertension	4 (4.1%)	2 (1.6%)	0.68*
Depression	4 (4.1%)	0	-
Urinary tract infection	2 (1.6%)	0	-
Aggression	2 (1.6%)	0	-

**statistically significant p value using chi-square test.*

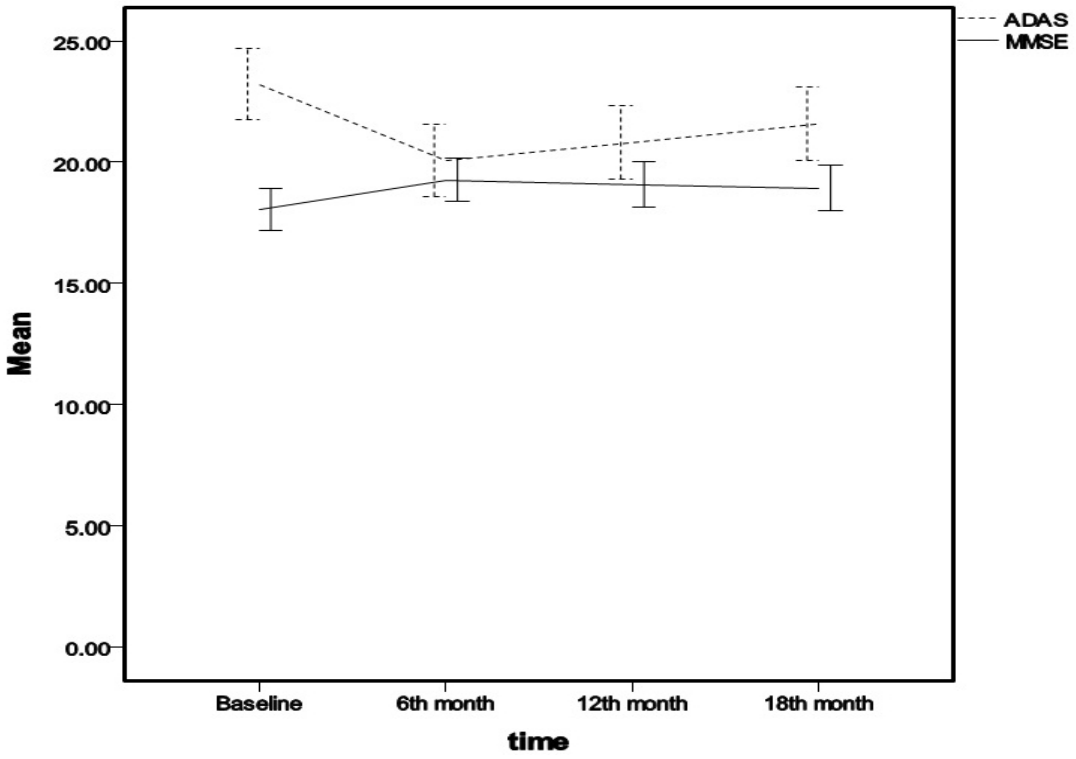

Fig. 1. Mean and 95% confidence intervals (Y axis) of Mini-Mental State Examination (MMSE) and Alzheimer Disease Assessment Scale-cognitive subscale (ADAS-cog) at 6-month intervals from baseline to 18 months (X axis) in AD patients treated with MLC601

4. DISCUSSION

Our results demonstrate that the MLC601 regimen was well tolerated. There was no withdrawal due to AEs on treatment with MLC601. This tolerability represents a key improvement compared to current AD treatments, i.e., ChEIs, in which a modest but significant therapeutic effect is often compromised by the occurrence of adverse events and discontinuation of treatment, as shown in a meta-analysis of Rivastigmine, Donepezil and Galantamine [15].

The results of 10 randomized, double blind, placebo controlled trials demonstrate that treatment for 6 months, with donepezil, galantamine or rivastigmine at the recommended dose for people with mild, moderate or severe dementia due to AD produced improvements in cognitive function, on average -2.7 points (95%CI -3.0 to -2.3), in the midrange of the 70 point ADAS-Cog Scale [16]. We found similar improvement with MLC601 in cognitive function as measures by ADAS-cog in the first 6 months (ADAS-cog=-3.1±10.1), and over the remaining 12 months (ADAS-cog=-1.6±7.6). MLC601 showed promising effects on cognitive function in AD patients during 18 months of follow up. In our trial, we observed improvement in cognitive function in the first 6 months of MLC601 use and a subsequent stabilisation of cognitive decline over the subsequent 12 months.

Neurodegenerative diseases have a multifactorial pathoaetiology [17]. Therefore, it is not surprising that conventional drug discovery approaches that embrace a 'one gene, one drug, one disease' philosophy may not be ideal for the development of therapies for multifactorial diseases [18,19]. AD is initiated by a cascade of neurotoxic events, including oxidative stress, brain iron dysregulation, glutamate excitotoxicity, nitric oxide, inflammatory process, neurotoxic processing misfolding, and aggregation of a amyloid beta peptide. AD subjects presently benefit from the treatment of symptoms with cholinesterase inhibitors and Memantine, but none of the currently available drugs has been shown to block the degenerative aspects of the disease [20]. Thus, new therapeutic strategies for AD are needed. These new strategies involve drug candidates that are designed to act on multiple neural and biochemical targets in the pathological process and that ideally possess both neuroprotective and neurorestorative properties [6].

In a rodent model of focal ischemia, MLC601 and MLC901 exhibited neuroprotective and neurogenesis properties both *in vivo* and *in vitro*. MLC601 prevents neuronal death *in vivo*, and *in vitro*, it induces neurogenesis in rodent neuroblasts and human neuronal precursor cells, promotes cell proliferation and neurite outgrowth, stimulates the development of a dense axonal and dendritic network, protects against exaggerated oxidative processes, and stimulates Brain Derived Neurotrophic Factor (BDNF) production [10,21].

The prevention of neurodegenerative diseases is a primary goal of medical research. However, to make prevention feasible, two objectives must be achieved: (i) individuals at high risk for the disease must be identified before the symptoms become evident, and (ii) compounds that are safe and effectively reduce or slow disease progression must be developed. Unfortunately, to date, no such safe preventive agents have been successfully developed. Therefore, there is an urgent need for agents that are pharmacologically safe, cost-effective, and immediately available with minimal AEs [4].

The majority of RCTs and systematic reviews conducted to date have reported that all ChEIs have similar effects on cognition [22-24]. However, across trials, differences have been reported in the incidence of AEs; generally, Donepezil has the fewest AEs, and Rivastigmine has the most AEs [19,25-27]. The Investigation into the Delay to Diagnosis of AD with Exelon (InDDEx) study is a large, multicentre, double-blind, placebo-controlled parallel-group trial of 3–12 mg/day Rivastigmine as a therapy for mild cognitive impairment [28]. The primary outcomes of the InDDEx were time to clinical diagnosis of AD (NINCDS-ADRDA criteria) and change in cognitive function as measured by change on overall summary score on neurocognitive test battery (a series of individual tests measuring working memory, immediate and delayed recall, cued recall, attention/concentration, language, executive functioning, and praxis). The preliminary results of the per-protocol analysis show that the study objectives were not satisfied. The dropout rate was high; only 51% of Rivastigmine-treated patients and 63% of placebo-treated patients completed the trial. The preliminary reported conversion rate during the 3-4 years of the trial was 19.4%, lower than expected; 17.3% of patients in the Rivastigmine group and 21.4% in the placebo group progressed to probable or possible AD [29]. While one study reported a numerically lower non-significant withdrawal rate due to AEs in Donepezil (14.6%) than Rivastigmine (22.8%) [30], a second study found a statistically significantly higher proportion of withdrawals due to nausea for Rivastigmine compared with Donepezil [25].

The tolerability of a treatment is particularly important for a condition such as AD, where patients being treated are typically elderly and often have significant medical comorbidities and polypharmacy. Consequently, any treatment-related AEs can be clinically significant and

may result in treatment discontinuation. In our study, approximately 45% of selected patients experienced AEs with their previous 6-month treatment with Rivastigmine, while no patients discontinued their 18-month treatment with MLC601 due to AEs.

Treatment of neurodegenerative disorders such as AD may be limited by the ability to deliver drugs efficiently to the central nervous system due to restrictions imposed by the blood brain barrier (BBB).

Over the past few decades, there has been considerable interest in developing biodegradable nanoparticles as effective drug delivery systems, using various polymers that pass through certain biological barriers like BBB, have the capacity to encapsulate high levels of therapeutic agent, and effectively deliver the drug to a desired site to increase the therapeutic benefit while minimizing side effects [31-34]. This technique could be considered for delivering new drugs in future studies.

Our study suggests that MLC601 has beneficial effects in patients with AD. However, it has some limitations. We had no control group, and neither patients nor physicians were blind to treatment and assessments. As such, we could not exclude a placebo effect. In addition, the phase of the disease of patients included was actually heterogeneous. Because other aetiologies of dementia were ruled out by brain imaging at the time of diagnosis, we did not perform any imaging during the study period; i.e., there was no evaluation of anatomical and functional changes in the brain.

5. CONCLUSIONS

In addition to some efficacy on cognitive functions during 18 months of therapy in patients with mild to moderate AD, MLC601 has shown a favourable tolerability profile, as exemplified by the absence of withdrawals due to AEs and an overall lower incidence of AEs than that observed during previous treatment with Rivastigmine in the same patient cohort. Nevertheless, further controlled studies are necessary to evaluate the long-term efficacy of MLC601 compared to placebos and other standard AD treatment regimens.

CONSENT

All authors declare that written informed consent was obtained from all patients or their caregivers before to be enrolled for the study.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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