Review article

Current evidence of the impact of acetylcholinesterase inhibitors on mild cognitive impairment and vascular dementia

Alexandre de Mattos Gomes*

Ricardo Koszuoski**

* Specialist. Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil. Geriatrician, Hospital Universitário Oswaldo Cruz, Universidade de Pernambuco (UPE), Recife, PE, Brazil.

** Geriatrician. Porto Alegre, RS, Brazil.

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INTRODUCTION

The acetylcholinesterase inhibitor therapy offers improvements in the cognitive, behavioral and functional symptoms associated to hypocholinergic states, represented specially by the Alzheimer's disease (AD).[1]

These agents (AChEIs) have been used since the end of the 1970's, when different studies detected in AD a neurochemical basis of depletion of cholinergic neurons in the Meynert basal nucleus and others that are projected to the lower mesial temporal region, specifically the hippocampal region.[2-4]

These drugs are classified as asymptomatic in the treatment of AD.[5]

Many drugs have been tested with the goal of changing the course of this disease, as the so called stabilizing and modifying drugs, however, none of them showed consistent and positive evidence so far.

Many clinical trials using AChEIs for the treatment of AD have been carried out. Tacrine was the first drug to be tested and clinically used. It was approved by the Food and Drug Administration (FDA) in 1993 and by the Brazilian Agency ANVISA (Agência Nacional de Vigilância Sanitária) in 1994. The major inconvenience of this drug is that it must be taken four times a day and has a large potential for hepatic toxicity, which was responsible for the decrease in its use after new generation AChEIs started to be employed. Donepezil was the second AChEI to come up. It was approved by the FDA in 1996 and ANVISA in 2000. It is taken once a day, however its half-life is very long, it may come to 73 hours, which is considered a disadvantage, as well as all long half-life drugs used with elder patients. Rivastigmine is the third drug in the class of cholinesterase inhibitors, it became available in Europe in 1997 and in 1998 it was liberated by ANVISA. The FDA released it only after 2000. This drug has the additional advantage of inhibiting butyrylcholinesterase (BuChE). The BuChE is believed to have increased participation in the enzymatic degradation of acetylcholine in the synaptical cleft as the AD develops. The inhibition of BuChE is also believed to mean a decrease of the amyloid protein toxicity in the senile plates.

Galantamine is the most recent drug of the cholinesterase inhibitors class, approved by the FDA and ANVISA in 2001. It has an additional effect, the allosteric modulatory actions on nicotinic receptors, allowing for the increase of the cholinergic synapses and a possible and questionable neuroprotective effect.[2]

There is not evidence about the clinical superiority of one of AChEI drugs over the others yet, but further studies on this topic will soon bring some new responses to the issue.

A number of clinical trials are now concluded and have already proved the real efficacy of AChEIs for mild and moderate AD treatment, however, there is evidence of the utility of this drug for patients with severe AD, especially in behavioral symptoms. The regulatory organs only allow for the use of this class of drugs for mild and moderate AD. These drugs are in the frontline of a still scarce arsenal to treat AD therapeutically. This treatment is effective in many patients, but not all of them respond to it. Those who have an asymptomatic improvement show a typical curve of response, which demonstrates an improvement in the first 3 months of treatment followed by a decrease, which is less accentuated than the vertiginous decrease found in the placebo group. Although many controlled and randomized clinical trials have been supporting the use of these drugs, up to September 2003 none quantitative analysis of the efficacy of this class of drugs for AD treatment had been carried out. Eventually, the publication of a meta-analysis studies brought into light data regarding AChEIs.[5] After this study, one could observe that the therapeutic impact of such drugs in the treatment of AD is modest, though statistically significant: The number needed to treat (NNT) to bring benefits to a patient was equal 7 (CI 95% 9-16); for stabilization or enhancement it was 12 (CI 95% 9-16); and for significantly remarkable enhancement it was 42 patients treated per one response (CI 95% 26-114).

However, there are different conditions that affect cognition, not only AD, so it is important that further morbid features of the human cognition be acknowledged and understood. The mild cognitive impairment (MCI) is one of those conditions and must be differentiated from the

impairment of memory resulting from age, this can occur even in healthy aging processes, once it is much more close to physiological problems than to pathologic ones, different from the MCI.[6,7]

In memory impairment associated to age, the individual must fulfill three criteria: be older than 50 years-old, present complaints of lack of memory and at least one standard deviation below the mean of the young adult in the neuropsychological assessment. In some population studies, more than 50% of elder people meet criteria for the impairment of memory associated to age. This is an important aspect because when we talk about MCI we talk about a condition close to pathologic problems. For an individual to be characterized as having MCI, he or she must fulfill the following criteria: report of memory problems, preferably confirmed by another person; normal overall thinking and reasoning skills, and at least 1.5 standard deviation below the mean of individuals the same age and educational level in the standard assessment tests.This way, the diagnosis of MCI and its differences from the memory impairment resulting from aging requires neuropsychological assessment instruments, which make such diagnosis a more complex practice, involving professionals that major the assessment tests validated for such purposes.

The MCI, especially in amnesia sub-type, has an evolution of 10 to 15% for AD a year.[6]

Besides AD, a series of other types of dementia have been responsible for the cognitive impairment. One of the most common types of dementia not associated to Alzheimer is the vascular dementia, which can have a pathophysiologic substrate of a cerebral-vascular disease, but with a certain frequency it also presents mixed component with the pathophysiology of AD.

Taking into consideration the context mentioned above, a major issue of interest is to know if the AChEIs would have a wider action spectrum and if they would really have a therapeutic impact on the MCI, whose amnestic type is a prodrome of AD in a significant number of patients.[6-11] Another issue to be addressed is the real impact of this drug in the treatment of a wider spectrum of hypocholinergic demential syndromes, as vascular dementia, which have been showing neurochemical evidence of hypocholinergic substrate.[12,13]

Another justification for this work is approaching drugs as the AChEIs, which are really effective in the AD treatment. It must be noticed that as early as this disease is managed, the better the outcomes are. Considering that the amnestic MCI is a type of AD prodrome,[14,15] literature reviews that bring real evidence on the action of these drugs in avoiding or decreasing the development of Alzheimer are of paramount importance, not forgetting they are costly drugs and are not free of side affects. A survey on data available about the real impact of AChEIs on the treatment of vascular dementia is also necessary, provided that the vascular dementia is hypocholinergic as well. We need, therefore, bring into light the clinical outcomes of randomized clinical trials.

The goal of the present article is to search the medical literature database for evidence that prove or not the AChEIs importance in the treatment of MCI and vascular dementia.

Concerning MCI, we intend to discover if AChEIs improve the cognitive symptoms and also if they delay or interrupt the AD progression.

As for vascular dementia, the main objective is to search concrete evidence of the impact of AChEIs on cognitive symptoms, both functional and behavioral in the daily life of patients with this disease.

METHODOLOGY

The digital database MEDLINE, Lilacs and Evidence-Based Medicine Reviews (EBMR) were searched from 2000 to 2005. Studies with AChEIs intervention in the treatment of MCI and vascular dementia, but with emphasis on the randomized and placebo-controlled trials, were included and searched with the following key-words: mild cognitive impairment, vascular dementia, cholinesterase inhibitor.

Case reports, observational studies (non-interventionist) and letters to the editors were included.

RESULTS

Concerning the studies on evidence of AChEIs efficacy in the treatment of MCI we found a short clinical trial with donepezil. It was the first study to be concluded using AChEIs in the treatment of MCI. The follow-up period was of 6 months with 269 patients, presenting only a very slight enhancement in the cognitive functions of patients with MCI; on the other hand, the reduction of conversion from MCI to AD could not be observed. When the Alzheimer's Disease Assessment Scale Cognition Component (ADAS-cog) was applied, patients had a three-point improvement as compared to the one-point improvement of patients that used placebo ($p = 0.034$). In the patient's self-evaluation, 14% of those receiving donepezil reported memory improvement, while 10 % of those who were given placebo said their memory had worsened. There was no significant difference in the scores of the Clinicians Global Impression from the modified MCI Test.[16]

In June 2003, a review study entitled "The impact of drugs against dementia on cognition in aging and mild cognitive impairment" was published. It surveyed MEDLINE for drugs and cognition. Drugs analyzed were: donepezil, galantamine, gingko biloba extract (EGB-761), memantine and rivastigmine. This study showed that up to that moment there was no study on the effect of such drugs on the cognition of individuals with MCI. One study from this review showed the effect of donepezil in the increase of the amount and density of the REM (rapid eye movement) sleep in individuals studied, which according to neuroscientists could be related to a cognitive improvement, although this is only a substitute outcome and, even though, very fragile to provide scientific evidence. Another study, published in April 2004, assessed the maintenance of the cognitive function in patients with mild Alzheimer treated with rivastigmine for 12 months as compared to those with mild Alzheimer and MCI not treated.[17] Eleven patients with mild Alzheimer were treated with rivastigmine for 12 months, while 21 were not treated; 22 patients with MCI were not treated in this follow-up. The measure of cholinesterase activity in the plasma and the assessment of global cognition, episode memory, visual spatial ability and attention were taken at 0, 3, 6 and 12 months. At the end of 12 months, the cognitive function was kept or slightly improved

in patients treated, and those with mild Alzheimer not treated did not have their cognitive function worsened, while those with MCI not treated presented, at the end of 12 months, statistically significant worsening in 16,4% of patients studied.

The scientific community was anxious to see the results of the Memory Impairment Study (MIS), which was a randomized study presented at the 9th International Conference on Alzheimer's Disease and Related Disorders in 2004,[18] published in 2005 in an indexed journal.[19] A total of 769 individuals were assessed in a follow-up period of 3 years, in which researchers compared the use of placebo, E vitamin (1,000 UI twice a day) and donepezil (10 mg/day). The outcome studied was the conversion of MCI into AD. The results revealed that, in the 36-month follow-up, the risk of AD development was the same in the three groups at the end; however, in the first 12 months, the group receiving donepezil had a significantly reduced progression to Alzheimer than the placebo and vitamin E groups.

Findings about the use of donepezil in the vascular dementia show a combined analysis of two randomized trials that studied the use of donepezil to treat vascular dementia in a 24-week follow-up. Both studies counted on a total of 1,219 patients with probable or possible vascular dementia according to the criteria of the National Institute for Neurologic Disease and Stroke (NINDS) and the *Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (AIREN). From the total number of patients, 406 were randomized to receive donepezil at 5 mg/day and 421 at 10 mg/day. The other patients remained as the control group. There was a significant enhancement of the cognitive functions in both groups managed with donepezil. Analyzing the ADAS-cog we could realize that the group managed with placebo presented a 0.10 change in the scale, while the group treated with 5 mg donepezil had an alteration of 1.89 as compared to the baseline scores, and the group managed with 10 mg/day had an alteration of 2.38 ($p < 0.001$).[20,21]

As for the use of galantamine in the treatment of vascular dementia, there was a clinical trial published in 2004 involving 788 patients with vascular dementia randomized to receive 8 mg of galantamine twice a day, 12 mg of galantamine twice a day or placebo, in a 26-week follow-up.[22]

Patients receiving galantamine seemed to have more positive results. The analysis of the ADAS-cog showed a mean decrease of 1.8 as compared to the basal score of those that received galantamine, and 0.3 for placebo (p = 0.001). Besides ADAS-cog, significant difference favoring other scales analyzed were found, such as the Alzheimer Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL), which assesses the activities of daily life and showed changes that favored galantamine (p = 0.783). In the EXIT-25, a scale that assesses execution functions, the groups receiving galantamine were favored as well (p = 0.041).

Although this is a very recent study using galantamine, the first major double-blind and randomized study analyzing the efficacy of galantamine in probable vascular dementia and mixed dementia was the GAL-INT-6.[23] In this study, 396 patients with probable vascular dementia or mixed dementia were managed with 24 mg/day of galantamine in a period of 6 months, and 196 patients with the same diagnostic hypothesis were given placebo. The primary outcomes were cognition, assessed with the ADAS-cog, and global function, assessed with the Clinician's Interview-Based Impression of Change-plus (CIBIC-plus). Galantamine was shown to be more efficient than the placebo. The group of galantamine had a significant improvement, the treatment efficacy was shown in a difference of 2.7 points between the galantamine group and the placebo in the ADAS-cog scale (p < 0.0001). In the CIBIC-plus, 213 patients (74%) of the galantamine group remained stable or obtained some improvement, while only 95 patients (59%) of the placebo group had a clinical stability. The daily life activities and behavioral symptoms were secondary outcomes and also improved significantly in the group that received galantamine (p = 0.002 and p = 0.016, respectively.

We also found an open study, which was an extension of the one carried out with galantamine. This new study aimed at continuing the treatment of patients randomized in the previous study.[24] In this new follow-up, patients who were given galantamine and placebo were given 24 mg/day of galantamine for 6 months more. The primary parameter used to measure efficacy was change in cognition assessed by the ADAS-cog. Secondary assessments included

changes in the functional ability, measured with the instrument of evaluation of disability for dementia, and changes in behavior, assessed with the neuropsychiatric inventory. After 12 months, there were improvements with relation to the admission values found in the group of galantamine, both in the group that was given placebo during the double-blind phase (placebo/galantamine group: -0.3 points, CI 95%, -1.64 to 1.06) and in the group coming from the previous study using galantamine (group galantamine/galantamine: -0.3 points; 95% CI, -1.73 to 0.03); p = 0.001. Improvements in the functional abilities were demonstrated through statistically significant changes with relation to the scores of the instrument baseline used for the assessment of disability for dementia (*Disability Assessment for Dementia* – DAD), which showed an improvement in the scores of both groups: placebo/galantamine (-7.4; p = 0.01) and galantamine/galantamine (-3.6; p = 0.01). There was no significant change in the means of the neuropsychiatric inventory scores.

With relation to studies about the efficacy of rivastigmine in the treatment of vascular dementia, we found a study developed in 2000 that did not test exactly rivastigmine in the vascular dementia, but analyzed its efficacy making a comparison between patients with AD and risk factor for cardiovascular diseases and patients with AD without this risk factor.[25]

This study randomized 235 patients with AD to receive rivastigmine or placebo, which were analyzed as for vascular risk with the Modified Hachinski Ischemic Score (MHIS) and classified into two groups: with MHIS > 0, which means presence of vascular risk, and with MHIS = 0, which means absence of vascular risk. In a 26-weeks follow-up, patients treated with rivastigmine were shown to have a higher response than those who received placebo, with statistically significant difference. However, those with vascular risk (MHIS > 0) had a higher response in the scores of the ADAS-cog than those without vascular risk (p = 0.002).

An open and comparative study carried out with rivastigmine, published in April 2004, analyzed and compared the effect of rivastigmine against aspirin plus nimopidine in the subcortical vascular dementia.[26] Patients with a diagnosis of probable vascular dementia received 3-6 mg/day of rivastigmine (n = 32) or aspirin plus nimopidine (n = 32). They were assessed through an open

study for 16 months. Patients treated with rivastigmine showed to have improvements when analyzed with instruments for the assessment of attention, execution functions, instrumental activities of everyday life and behavioral symptoms.

DISCUSSION

Results found in this review about the efficacy of AChEIs in pre-morbid conditions and other cognition diseases but Alzheimer answered many questions that patients and families impose to healthcare providers who face, in the clinical practice, vascular dementia and MCI.

There is a lot of research on drugs for treatment of cognitive disorders in general, but most of studies regarding AChEIs are aimed at the treatment of AD. We found, however, in the surveyed database, a significant number of works that study the efficacy of this group of drugs in the treatment of vascular dementia, mixed dementia and MCI.

The first clinical trial with an AChEI in patients with MCI was published in 2003. It assessed donepezil, and showed a not very significant cognitive enhancement. However, the impact of the evidence found in this study was affected by the short follow-up (only 6 months) and small sample size. It was neither adequately designed to assess the progression of mild cognitive impairment for AD.[16]

With relation to the use of rivastigmine in the treatment of MCI, we found a study comparing patients with mild AD treated with rivastigmine against those with mild AD or MCI who were not given the drug. This way, although the study suggested a possible positive effect in the treatment of MCI with rivastigmine, it does not reveal if there is an impact of this drug on the symptom enhancement of MCI and prevention against the progression of AD, once the drug was not used in patients with MCI and mixed patients with mild AD and MCI, so that the power of evidence was weakened for such reasons.[17]

Although the scientific literature is poor on studies published with significant statistical reliability to answer questionings about AChEI in the treatment of MCI, there are many ongoing

clinical trials that have not been concluded yet. These studies approach not only the use of AChEI, but also other pharmacologic strategies for the treatment of MCI.

In this review about the impact of AChEIs in the MCI, findings show that the MIS is the only published study that shows more concrete information about the effect of an AChEI (donepezil) in the treatment of MCI, as the follow-up period (3 years) and the number of patients studied (n = 769) give a good power of evidence to this study, which showed a progressive decrease in AD in the first 12 months, but without supported response after this period.[18,19] This study, however, does not answer some questions about symptoms improvement, once it was not designed with such a purpose.

Concerning vascular dementia and the impact of AChEIs, some studies present strong evidence, which foster the impact of these drugs in the treatment of pure or mixed vascular dementia.[27] The field has been explored since the end of the 1990's, but the main publications, which we cited in this work, are from the early 2000's. Yet, there are many studies waiting to be published. They aim at correlating possible clinical outcomes to hystopathological findings and functional radiology, which show a deficit of up to 40% in the cholinergic transmission of these patients.

These studies have gathered findings that may provide backing for a possible inclusion of this class of drugs by organs such as the FDA in the list of drugs for the treatment of vascular dementia.

The main inhibitors of AChEIs were studied in the treatment of vascular dementia.

In 2000, a study with rivastigmine assessed AD patients with and without risk factors for cardiovascular diseases (not exactly vascular dementia).[25] The study revealed that patients with AD and risk factors for cardiovascular diseases had higher scores in the ADAS-cog score when treated with rivastigmine than patients without risk factors. It was a statistically significant study, but it did not study the use of rivastigmine in the treatment of vascular dementia. The authors only wanted to suggest that the cardiovascular risks could be a predictor of AChEI response in the AD. They

present only a few information concerning the questioning we made in the objective of the present review. Today, there is strong evidence that cardiovascular risks may be risks for Alzheimer dementia as well, and not only for vascular dementia. This may give room for the hypothesis that there is an intersection between vascular dementia and Alzheimer dementia, which will start from possible etiologic factors and extend to pathophysiologic mechanisms and the treatment.

In 2004, however, another study showed that rivastigmine presented better results than the association of aspirin and nimopidine in the treatment of subcortical vascular dementia.[26]

Different from the other study cited, this one tests rivastigmine in patients with vascular dementia and compares it with other therapeutic strategies already in use. It shows the benefits of this acethyl and BuChE inhibitor, however, we should not forget that the study was open and comparative, which does not provide the same evidence as a randomized, double-blind and placebo-controlled study.

With relation to donepezil as a therapeutic strategy for vascular dementia, there is more concrete evidence of its efficacy. The study presented a combined analysis of two randomized clinical trials and an adequate number of patients and follow-up period, where the use of donepezil in its optimized dose (10 mg/day) showed to have a statistically significant cognitive improvement of patients with vascular dementia.[20]

In what concerns galantamine for the treatment of vascular dementia, the GAL-INT-6, a major work published in 2002, points out a significant improvement as compared to placebo in the primary outcomes studied, which were cognition – assessed by ADAS-cog, and global function – assessed by CIBIC-plus. The extension of this work for 6 months more confirmed the supported efficacy.[23,24]

However, the GAL-INT-6 has some failures that decrease its power of evidence, because it mixes patients with vascular dementia and mixed dementia, which is certainly a negative factor in the assessment of galantamine for vascular dementia.

The randomized clinical trial published in 2004 was the main study carried out so far with galantamine for vascular dementia treatment. It had a higher follow-up period and the sample size was almost twice the size of GAL-INT-6. The exclusive participation of patients with vascular dementia in this study provides a strong power of evidence. The study presents an improvement of cognitive functions, everyday activities and execution functions, however, the only aspect that presented an improvement with statistic significance was cognition, assessed with ADAS-cog.

CONCLUSION

This review on the therapeutic impact of AChEI in the MCI and vascular dementia is intended to provide support and information to healthcare professionals that must manage such conditions in their daily clinical practice.

Concerning MCI, we conclude that the AChEIs do not prevent the development of AD, but decrease it within the first 12 months of treatment. After this period, the effect is dissipated. There is good evidence about the symptomatic improvement of patients with MCI using AChEI. Some studies showed a very modest effect in the improvement of cognitive functions, but they are very small studies and not very significant. The scientific community is still waiting for the conclusion of larger studies with adequate designs that can validate or not the real efficacy of such drugs in the cognitive symptoms of patients with MCI.

The use of AChEIs in the treatment of vascular dementia is more consistent than in MCI. Many studies analyzed the three main types of AChEI available in the market. Favorable results of these clinical trials for the treatment of vascular dementia are supported on a hypocholinergic substrate of this disease. Thus, these studies open the pathway for future approval of these drugs in the treatment of vascular and mixed dementia by regulatory organs.

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ABSTRACT

Introduction: *Acetylcholinesterase inhibitors constitute an effective class of drugs for the treatment of mild and moderate Alzheimer's disease and are allowed by the responsible agencies for this purpose only. However, concrete evidence is still necessary in what concerns the impact of the use of such drugs to treat a large variety of cognitive disorders not classified as Alzheimer's disease. The aim of this study was to review the medical literature in search for updated evidence of the impact of acetylcholinesterase inhibitors on mild cognitive impairment and vascular dementia.*

Methods: *The literature review was carried out in the Lilacs, MEDLINE and EBMR databases*.

Results and conclusions: *Assays using acetylcholinesterase inhibitors for the treatment of mild cognitive impairment are still small, present little power of evidence, and show only a modest improvement of symptoms. A recent study shows reduced progression of mild cognitive impairment to Alzheimer's disease in the first 12 months of treatment, but this effect was not continuous. On the other hand, clinical trials involving patients with vascular dementia show encouraging results associated with the use of these drugs.*

Key-words: *Acetylcholinesterase inhibitors, mild cognitive impairment, vascular dementia.*

Title: *Current evidence of the impact of acetylcholinesterase inhibitors on mild cognitive impairment and vascular dementia*

Correspondence:

Alexandre de Mattos Gomes

Rua Senador Soares Meireles, 71, Casa Amarela

CEP 52070-360 – Recife – PE – Brazil

E-mail: alexmtt@terra.com.br