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Role of Medium Chain Triglycerides (Axona®) in the Treatment of Mild to Moderate Alzheimer's Disease

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Abstract

Treatment of Alzheimer's disease (AD) with acetylcholinesterase inhibitors or N-methyl-D-aspartate (NMDA) receptor antagonists provides symptomatic relief but do not prevent its progression. Thus, additional approaches aimed at slowing the progression of the disease have been investigated. Reports detailing reduced brain glucose metabolism in the early stages of AD led to the hypothesis that alternate energy sources aimed at increasing neuronal metabolism may protect neurons and thus benefit patients with AD. Medium-chain triglycerides (MCTs) are metabolized to ketone bodies that serve as an alternative source of energy for neurons. Data from clinical trials suggest that MCTs improve cognition in patients with mild to moderate AD in apolipoprotein E4–negative patients. Adverse events observed were mild and included minor gastrointestinal problems such as diarrhea, dyspepsia, and flatulence. However, since genomic profiles are not routinely conducted in patients with AD in a clinical setting, the role of MCTs in clinical practice seems to be minimal.

Keywords

APOE4, Axona®, Alzheimer's disease, β-hydroxybutyrate, caprylidene, ketasyn, medium-chain triglycerides, ketogenic agents

Introduction

Currently, there are over 5.2 million Americans aged 65 years and older who are having Alzheimer's disease (AD).[1] The present incidence of AD is estimated at 1270/day and is expected to rise to 2618/day by the year 2050.[1] Pharmacotherapy with acetylcholinesterase inhibitors (AChEIs) alone or in combination with NMDA antagonist (memantine) provides some symptomatic relief but do not arrest the progressive cognitive decline in the patients.[1] Efficacy of AChEIs with or without memantine is meager but measurable, improving the Mini-Mental State Examination (MMSE) score by 1 to 1.5 points within the first 6 months of therapy.[2] This corresponds to a reduction in only 2.5 to 3.75 points on the Alzheimer's disease Assessment Score–Cognitive (ADAS-Cog) scale.[3] Thus, additional approaches designed to elicit a more robust treatment response in patients with AD need to be designed and investigated.

The prognosis of AD is worse for individuals homozygous for apolipoprotein E4 (APOE4) allele or those harboring certain genetic polymorphisms of insulin-degrading enzyme (IDE) or of interleukin 1β (IL-1β). Individuals homozygous for APOE4 allele have a heightened risk and severity of AD characterized by earlier age of onset, lower survival rate, and poor response to current medications.[4-6] IDE is responsible for degradation of insulin and amyloid-β, whereas IL-1β is a proinflammatory cytokine that is shown to increase in the brain following AD. Hence, loss-of-function mutations of IDE and gain-of-function mutations of IL-1β increase the risk of AD.[7,8] Therefore, approaches that are effective in patients homozygous for APOE4 allele or mutations of IDE or IL-1β that increase AD risk need to be designed and tested to improve the prognosis of these individuals.

Neuronal metabolism is a novel and an attractive target to treat AD since reports suggest that brain glucose metabolism is reduced in early stages of AD.[9,10] Reduced glucose concentration may adversely affect the hippocampus that is responsible for consolidation of memory.[11,12] Thus, it has been hypothesized that increasing energy supply for neuronal metabolism may benefit patients having AD. Although increasing glucose intake may potentially increase neuronal metabolism,[13-15] the hyperglycemia that may result in this population precludes using oral or intravenous glucose as an option for treating AD. Moreover, evidence points to a reduced expression of glucose transporters in the brain of patients with AD,[16,17] indicating that glucose utilization is insufficient despite high concentration. However, medium-chain triglycerides (MCTs) may be an option, since

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Table 1. Assessment Tools Used in Trials.

Tool	Purpose	Score	Interpretation
ADAS-Cog	Estimates levels of cognitive impairment	0-70	Higher score indicates worse cognition
MMSE	Estimates levels of cognitive impairment	0-30	Higher score indicates better cognition
ADCS-CGIC	Measures clinical changes in cognitive, behavioral and functional performance over time	0-7	Higher score indicates worsening condition
MHIS	Evaluates likelihood of dementia due to vascular causes	0-18	Higher score indicates increased likelihood of vascular related dementia
Paragraph Recall test	Evaluates immediate or delayed recall of information from a paragraph read to the patient	0-18	Higher score indicates better cognition
Stroop Color Word Interference Task	Evaluates effects of interference on reading ability	0-20	Higher score indicates better cognition (less interference on reading ability)

Abbreviations: ADAS-Cog, Alzheimer Disease Assessment Scale-Cognitive subscale; MMSE, Mini-Mental State Examination; ADCS-CGIC, Alzheimer Disease Cooperative Study—Clinical Global Impression of Change; MHIS, Modified Hachinski Ischemia Scale.

they are oxidized by the liver to ketone bodies.[18-20] These ketone bodies cross the blood–brain barrier, enter the neuronal mitochondria, and serve as an alternative energy source.[18-20] This increase in energy may improve neuronal metabolism, survival, and, therefore, improve cognitive functioning in patients with AD. Axona® is composed of MCTs and is a Food and Drug Administration–approved medical food for the treatment of AD. This review will evaluate the safety and efficacy of MCTs (Axona®) and therefore elucidate its role in the treatment of mild to moderate AD.

Evidence

A literature search was performed through EMBASE (1974 to October Week 2, 2013) and Medline (1946 to October week 2, 2013) using the key words Axona®, Alzheimer's disease, β-Hydroxybutyrate, Caprylidene, Ketasyn, Medium-chain triglycerides, and Ketogenic agents. The search was limited to English language, humans, and clinical trials. Three articles were deemed relevant and therefore used in this review.[21-23]

The first 2 studies evaluated the efficacy and safety of MCTs in the treatment of Alzheimer's disease.[21,22] Since APOE4 status is known to affect the response to ketogenic agents,[24] both studies performed genotyping of patients to determine their APOE4 status (positive or negative). Whether IDE or IL-1β contribute to/interact with APOE4 status to affect the response toward MCTs was investigated in the post hoc analysis[23] of the larger trial.[22]

Table 1 shows the assessment tools used in these clinical trials assessing the efficacy and safety of Axona® in AD. The first study[21] (Table 2) evaluated whether hyperketonemia improved cognitive functioning in patients with Alzheimer's disease (n = 15) or mild cognitive impairment (n = 5). Patients had a mean age and MMSE score of 74.7 years and 22 years, respectively. Five patients were receiving AChEIs and 4 were receiving antidepressants prior to study entry. Patients were evaluated at 2 visits following an overnight fast prior to each visit. The patients received either emulsified MCTs or placebo (isocaloric long chain triglycerides; LCTs). A 30-minute neuropsychological test was performed by trained professionals 90 minutes after administration of MCTs or placebo and included the ADAS-Cog, MMSE, paragraph recall test, and Stroop Color Word Interference Task. Blood tests were also performed in order to determine APOE4 status and levels of β-hydroxybutarate (BHB) to assess the ketogenic state.

Treatment of APOE4 (−) patients with MCTs showed a significant improvement in the ADAS-Cog when compared to placebo-treated patients ($P = .04$). However, treatment of APOE4 (+) patients with MCTs showed significant worsening in ADAS-Cog when compared to APOE4 (−) patients treated with MCTs ($P = .039$). A statistically significant correlation between BHB levels and ADAS-Cog scores among APOE4 (−) patients who were treated with MCTs was not found, but this could be due to low power. However, higher BHB levels were correlated with greater improvement in the groups treated with MCTs with respect to paragraph recall when the population was not stratified based on APOE4 status. Treatment by MCTs did not have any significant effects on the Stroop Color Word Test as compared to placebo. No difference was found between patients taking antidepressants or AChEIs.

There are many limitations to this study, which make application of results to practice nearly impossible. Although it is apparent that this was meant to be a pilot study, the small patient population and the 2-visit evaluation design limit the applications for a long-term treatment. Further, the authors omit important details concerning the methodology of the study as it is unclear how far apart the 2 visits were. They also do not disclose the number of patients who received placebo versus the active drug. Moreover, the results are reported only as those who received active medication rather than a comparison between active drug and placebo with respect to baseline values. Also, although the authors report that they utilized the MMSE to evaluate efficacy, those results are not reported. While these limitations severely restrict the results from this study for long-term treatment, the clear benefit observed in APOE4 (−) patients provided the rationale to conduct a larger trial to evaluate efficacy of MCTs.

In a multicentered, double-blinded, randomized, placebo-controlled, parallel group trial, 140 patients were evaluated to determine whether treatment with MCTs improved cognitive functioning in patients with mild to moderate AD (Table 2).[22]

Table 2. Summary of Trials Assessing the Safety and Efficacy of Medium-Chain Triglycerides (MCTs) in Alzheimer's Disease.

Reference	Study Design	Duration	Inclusion and Exclusion Criteria	Primary Outcomes	Interventions	Results	Adverse Events
Henderson(2009)[22]	R;DB; PC	104 days	Inclusion: MMSE 14-24; MHIS score < 4 MRI or CT within 2 years; No other reasons for dementia Exclusion: Major depression; Hypothyroidism; B_{12} deficiency; renal insufficiency; hepatic insufficiency; or diabetes 1 or 2	Change from baseline at day 90 in: ADAS-Cog[a] ADCS-CGIC[a]	MCTs (n=77) Placebo (n=63) MCTs (n=64) Placebo (n=60)	−0.312 1.227 p=NS 4.41 4.62 p=NS	GI effects were the most common, occurring in 48.8% and 27.3% of patients receiving MCTs and placebo, respectively. Further, diarrhea occurred in 24.4% and13.6% of patients receiving MCTs and placebo, respectively.Generally, no significant differences were found between groups for changes in serum chemistry and hematology values, vital signs or electrocardiograms. However, though they did not reach clinical significance, mean values in renal function increased in those receiving MCTs.
Reger(2004)[21]	R, DB, PC	2 days	Inclusion: Probable AD with NINCDS-ADRDA criteria (mean MMSE 22) Exclusion: Significant medical or psychiatric illness other than mild depression	Change in cognitive function ADAS-Cog	MCTs APOE4 (+) APOE4 (-) Placebo	 −1.7[b] 0.9[b] Numerical Values not reported	None Reported

Abbreviations: APOE, apolipoprotein E allele; CT, computed tomography Scan; DB, double blind; ITT, intention to treat; LOCF, last observation carried forward; MHIS, Modified Hachinski Ischemia Scale; MRI, magnetic resonance imagaing; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NS, no significance; PC, placebo controlled; GI, gastrointestinal.

[a]ITT population with LOCF (patients receiving at least 1 dose and completing at least 1 follow-up visit following baseline).

[b]Numerical values estimated from figure.

Patients taking approved AD medications were included as long as they were on stable doses at least 3 months prior to enrollment and could continue on this dose for the duration of the study. Patients were randomized to receive either 10 g of MCTs (n = 77) or isocaloric placebo (n = 63) via a powder packet; the dose was increased to 20 g on day 8 of the study and continued up to day 90. Patients were assessed via the ADAS-Cog and ADCS-CGIC at baseline, day 45, 90, and 2 weeks after the last dose (day 104; washout visit). The primary outcome of this study was improvement in these assessment scales (ADAS-Cog and ADCS-CGIC) at day 90. Secondary outcomes included changes in MMSE scores and cognitive improvement in patients with AD with differing *APOE* genotypes.

In this intention to treat with last observation carried forward (ITT w/LOCF) group, mean change in ADAS-Cog or ADCS-CGIC scores at day 90 was not significantly different between the placebo-treated group and those treated with MCTs (Table 2). However, when the patients were classified based on their genotype, a significant difference in ADAS-Cog was observed in APOE4 (−) patients between placebo and the group treated with MCTs at days 45 and 90 but not at day 104. A significant change in the ADCS-CGIC scores in APOE4 (−) patients occurred at day 45 only. The MMSE scores were not significantly different at any point of time in this ITT w/LOCF group regardless of the APOE4 status.

Results from the post hoc analysis[23] found that certain single-nucleotide polymorphisms (SNPs) that provided gain of function to IDE or loss of function to *IL-1*β gene products conferred beneficial effects in patients treated with MCTs on day 45 and 90 but not on day 104. Patients who did not carry an APOE4 allele but possessed SNPs that provided gain of function to IDE or loss of function to *IL-1*β gene products experienced a statistically significant benefit in the ADAS-Cog on days 45, 90, and 104. This indicates that these SNPs provide added benefit in APOE4 (−) patients when treated with MCTs.

The most common adverse events (AEs) experienced by all participants were gastrointestinal complaints, with diarrhea being the most abundant. These AEs resulted in patient dropout from the trial, but this decreased markedly after the patients were instructed to administer each dose with food. Additional information on safety can be found in Table 2.

The short duration of 3 months and no observed benefit in primary end points are obvious limitations of this trial. Hence, their application to long-term treatment of patients with AD is questionable. It is possible, however, that a larger trial of longer duration using computerized neuropsychological test battery[25] that is more sensitive in measuring latency, speed of response, and recall accurately may have shown larger differences. However, several other points must also be noted. For example, the authors report that the proportion of patients taking multiple AD drugs was higher in the placebo group, possibly signifying a more advanced disease state in the placebo-treated group. Moreover, the level of education was higher in the group treated with MCTs. Although neither of these may be statistically significant differences between the groups, they do have a potential bias in favor of the population treated with MCTs as it is believed that earlier intervention and higher level of education has a better prognosis in the treatment of AD.[26-28] The authors also report that patients were allowed to ''interrupt or reduce the doses of investigational products with permission of principal investigators if necessitated by adverse events" (p. 6). This implies that the group treated with MCTs was not a homogeneous population in terms of the amount or number of doses received during the course of the study. In addition, although the authors report that the tests were conducted when the level of ketone bodies was high, they do not mention how long the elevated levels were maintained (as they dropped down to basal level in the morning) and whether the beneficial effects were correlated with the increase in levels of ketone bodies. Multiple inconsistencies in the values reported in table and text also exist.

Discussion

The basis of using MCTs to correct cerebral hypometabolism observed in AD arises from the fact that during periods of extended fasting (low-glucose conditions), the liver oxidizes fatty acids to produce ketone bodies that serve as an alternative source of energy for neuronal cells.[19,29-31] Although direct glucose supplementation may be thought of as an obvious choice to correct the cerebral hypometabolism, long-term therapy with glucose supplementation can lead to hyperglycemia, which is a risk factor for diabetes in old age. Some evidence also points to reduced expression of glucose transporters in the brain of patients with AD,[16,17] which is in perfect agreement with the fact that patients with diabetes (where glucose is present but not utilized appropriately) are more likely to have AD.[32,33] Thus, alternate means to increase neuronal metabolism and hence survival were investigated.

Medium-chain triglycerides are classified as medical foods, which are defined as substances that provide a specific nutritional need in a patient that cannot be satisfied by modification of a normal diet alone.[34] The MCTs are oxidized by the liver to ketone bodies that serve as an alternative energy source.[18-20] Although a low-carbohydrate, high-fat diet can also increase the levels of ketone bodies, patients with AD often have cravings for foods high in sugar and carbohydrate content, which may be due to their reduced ability to utilize glucose.[22] Thus, patients with AD may not be compliant to a low-carbohydrate, high-fat diet. The MCTs are remarkably convenient in this regard as they provide ketone bodies even in the presence of high carbohydrate diet, allowing for favorable compliance.[18] In addition, MCTs function by a pathway independent of glucose metabolism; hence, their efficacy is maintained even in the presence of the abundant glucose often found in patients with AD. Although MCTs are triglycerides, MCTs, unlike LCTs, neither are stored as fat nor raise blood cholesterol levels significantly.[35] This is advantageous as a high-fat diet to achieve high levels of ketone bodies is also not practical in the elderly population.

Besides serving as an alternate energy source, ketone bodies have also been shown to protect cultured neuronal cells from

β-amyloid peptide[36] and reduce the amount of β-amyloid levels in the brain of transgenic mouse models of AD.[37] In addition, ketone bodies have been shown to protect rodents from multiple insults such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP),[38] hypoxia,[39,40] traumatic brain injury,[41] and glutamate toxicity[42] and are hence believed to be neuroprotective via reduced production of reactive oxygen species and increasing the levels and activity of uncoupling proteins of mitochondria.[43] Whether MCTs provide a neuroprotective effect in humans remains to be determined.

Results from both the trials and the post hoc analysis indicate that MCTs may be a viable option to treat patients who are APOE4 (−) and/or possess SNPs of *IDE* or *IL-1*β genes that provide gain and loss of function, respectively. However, this benefit may be small, even though the authors report that 50% of APOE4 (−) MCTs dosage-compliant patients achieved the clinically significant 4-point change in ADAS-Cog as opposed to 10% of the placebo-treated APOE4 (−) patients. The SNPs that provided gain of function to IDE and loss of function to IL-1β interacted positively with APOE4 (−) status and offered greater beneficial effect of MCTs. However, no benefit was observed in APOE4 (+) patients upon administration of MCTs regardless of whether they possessed gain-of-function mutations in IDE or loss-of-function mutations in IL-1β. Thus, the benefit of MCTs to a very specific group of people as shown by the trials means that it will be necessary to obtain a genomic profile of the patients, which are not routinely obtained in a practice setting. Moreover, the fact remains that patients with AD are more likely to be APOE4 (+) or harbor SNPs providing loss-of-function mutations to IDE or gain-of-function mutations to *IL-1*β gene products and are therefore in greater need of interventions aimed to treat and slow the progression of their disease. Since MCTs do not seem to provide a benefit in these patients based on the current trials, the role of using MCTs in a general practice setting seems to be minimal.

There are several issues that must still be addressed before MCTs become standard of care in patients with AD. For example, since reduced neuronal metabolism is thought to be an early event in the disease, occurring prior to cognitive dysfunction and plaque deposition,[10] then it is reasonable to expect that earlier initiation of MCTs (before AD strikes) in at-risk populations may potentially yield more robust and beneficial effects in arresting neurodegeneration, especially in APOE4 (+) patients. Although the authors have mentioned that MCTs are safe,[22] the study was conducted only for 3 months. Therefore, long-term safety data based on this study alone is insufficient to gauge accurately. Also, as previously discussed, there is limited evidence to support the use of MCTs and therefore larger trials with more comprehensive assessment are needed to correctly identify the role of MCTs in the treatment of AD.

Declaration of Conflicting Interests

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