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Featured Article

The effect of statins on rate of cognitive decline in mild cognitive impairment

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Abstract

Introduction: This study's aims are to identify whether a relationship between statin use and rate of cognitive decline exists. The relationship between statins and mild cognitive impairment (MCI) has been investigated in the past with the evidence showing mixed results.

Methods: Seven hundred sixty-eight subjects were identified with MCI. Subjects were stratified into six possible groups according to ApoE4 status and statin use and assessed for decline in cognitive function.

Results: All cognitive assessments trended toward less decline with statin use. Alzheimer's Disease Assessment Scale 11 (ADAS 11) showed the biggest difference in mean change between statin users and nonusers (−0.82 vs. −1.22, respectively). Change reached marginal significance on the ADAS 11 when stratified by ApoE4-negative subjects.

Discussion: All cognitive assessments trended toward less decline when subjects were concurrently treated with a statin, supporting the position that statins do not have a net negative effect on cognitive assessment and suggests a potential treatment benefit.

Keywords: Statin; Alzheimer's disease; Mild cognitive impairment; ADAS; ADNI

1. Introduction

Alzheimer's disease (AD) is increasingly prevalent in the United States. As of 2015, there are an estimated 5.3 million individuals in the United States suffering from AD. It also affects approximately 10% of the population over the age of 65 years [1]. The rate of mild cognitive impairment (MCI) progressing to dementia when thought to be of neurodegenerative origin is approximately 10% per year. The rate of decline on Mini-Mental State Examination (MMSE) in

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[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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AD is approximated at 3 to 3.5 points per year. In rapidly progressive cases, decline can reach 5–6 points annually [2]. Mean survival after diagnosis of AD ranges from 3–8 years [2].

The direct effects of plasma cholesterol and related lipoproteins on the incidence of dementia and cognitive decline have long been controversial. Senile neuritic plaques and neurofibrillary tangles are the pathogenic hallmarks of AD, and increasing evidence links brain cholesterol with both plaques and tangles [3]. Recent studies have shown a positive correlation between high-density lipoprotein (HDL) levels and MMSE performance and a negative correlation between low-density lipoprotein (LDL) levels and immediate and delayed recall [4]. Several epidemiological studies also showed that elevated total serum cholesterol was a significant risk factor for AD, independent of ApoE status [2]. Lowering cholesterol levels via statins is associated with decreased β-amyloid [5].

Past studies noted that subjects with incident dementia had higher total cholesterol at their first visit [6]. Cholesterol levels and atherosclerosis have also been found to correlate with AD [7]. Increased glucose levels and decreased HDL levels increase risk of incident MCI [6]. High midlife total cholesterol has been associated with decreased memory and fluency later in life [8]. For this reason, statins have long been purported to play a role in cognitive decline; however, the general consensus on this role is mixed. Recent studies have shown that statin use is associated with a reduced risk of dementia. Specifically, lipophilic statins were found to have the greatest reduction in risk [9].

Evidence that statins decrease the risk of incident dementia is convincing from an epidemiological standpoint. Some studies show that statin users had a 5-fold lower risk of incident AD and a 3-fold lower risk of MCI [6]. Statins have also been shown to decrease the risk of AD in subjects under 80 years old, after controlling for sex, education level, and self-rated health [10]. There have been three major clinical trials investigating the role of statins in cognitive decline. The CLASP study in 2011 assessed the use of simvastatin in probable AD. It showed no significant difference in cognitive decline between statin therapy and a placebo when measured by Alzheimer's Disease Assessment Scale—Cognitive (ADAS-Cog) [11]. The LEADe trial in 2010 studied atorvastatin therapy in mild-to-moderate AD and showed no net benefit of statin therapy to placebo over 72 weeks [12]. This study focused on ADAS-Cog and ADAS-Clinical Global Impression of Change as benchmarks. These two clinical trials contradict the initial findings by Sparks in 2005 that displayed a significantly decreased rate of cognitive decline by atorvastatin on ADAS-Cog and MMSE over 6 months [13]. These values were also near significant at the 12-month mark [13]. All three of these trials focused on subjects with AD. The PROSPER trial also showed that pravastatin had no significant effect on cognitive function in the elderly [14]. Clinical trial data on subjects with MCI do not exist. The severity of disease progression among the selected subject population may play a role. By focusing on individuals categorized as MCI, any relationship between progression of cognitive impairment and statin use should be teased out more easily.

The ADNI database has the unique attribute of possessing prospectively collected data, which have not been analyzed in past studies. Past epidemiological studies have focused on utilizing retrospectively gathered data. The focus of this study will be to assess whether or not cognitive decline is affected by a statin regimen. Randomized controlled trials suggest that the dementia stage of AD may be too late for significant benefits of statin therapy [15]. To assess cognitive decline at an earlier time point in disease progression, it is necessary to study subjects that have not progressed to AD. MCI is an ideal population to assess whether or not early intervention with a statin will be beneficial.

2. Methods

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by principal investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

ADNI's data requisition Web site was the source of all data. The analysis focused on information contained within a summary file that ADNI had compiled and a medication file containing home medications for each subject. These files were the ADNIMERGE and RECCMEDS data files, respectively. This list was used to isolate any subject that had been prescribed a statin. Each subject was included in the database regardless of statin type or dose. No other lipid-lowering medications were considered when data were being collected; however, patients concurrently on other lipid-lowering agents were not excluded from analysis. Of the 1737 subjects contained within the ADNIMERGE file, 939 were identified as statin users after cross-referencing with the RECCMEDS file. Statins queried include atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin.

ADNI's summary file was then used to isolate any subject within the database that was labeled as having a diagnosis of MCI. ADNI has broken down each subject into various levels of cognition based on the Petersen criteria for MCI [16]. The two levels of progression that we decided to include in our definition of MCI were the early and late MCI subjects. Within these categories, 872 subjects were identified with a diagnosis of MCI. These two parameters (statin status and MCI status) formed the major categorical parameters for isolating data. MCI status formed our