Systematic review of the efficacy of statins for the treatment of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most common type of dementia. Recent studies have assessed the possibility of using statins as treatment for AD. However, their efficacy is not clear. In this study, we collected the most relevant information about the efficacy of statins for the treatment of AD. We conducted a systematic literature search using MEDLINE, EMBASE and The Cochrane Library. We included clinical trials, meta-analyses and systematic reviews that analysed the efficacy of statins in AD. We also extracted the characteristics and efficacy results of the studies selected. Of the 304 articles identified, 13 complied with the inclusion criteria. The scientific quality of studies was high and their results indicated that there were no significant differences in the main efficacy variables between statins and placebo treatment for AD. Therefore, according to the available scientific evidence, statins have not shown an improvement in cognition and do not appear to offer significant benefits to patients with AD.

KEYWORDS: Alzheimer's disease, statins, efficacy, systematic review

Introduction

Alzheimer's disease (AD) is the most common type of dementia. It is a neurodegenerative pathology, whose incidence has increased in the past few years. With an estimated prevalence of 46.8 million cases worldwide in 2015, the number of patients with AD is expected to continue to increase in the coming years.[1]

There are two main manifestations of AD: early-onset AD, which especially affects young people, and late-onset AD, which is more common and occurs mainly in older people, usually patients over 65 years old; therefore, ageing is considered to be the main risk factor for the disease.[2]

Pathologically, AD is associated with pronounced brain atrophy and an excessive amount of neuritic plaques, which contain neurofibrillary tangles comprising highly phosphorylated tau protein and extracellular deposits of β-amyloid (Aβ).[3] When these deposits accumulate in the cerebral cortex, they cause neurotoxic effects.

Aβ peptides derive from the amyloid precursor protein (APP) in response to the activity of secretases (α-SAPP, β-SAPP and γ-SAPP), which cleave the APP into different fragments.[4] These secretases have been the subject of scientific research because of their role in the regulation of Aβ.[5]

Aβ deposits contain apolipoprotein E (apoE), a peptide found in the chylomicron, and very low-density lipoprotein (VLDL), which travels through the plasma transporting cholesterol to its receptors. In addition, apoE promotes the conversion of Aβ into its insoluble form, generating neuritic plaques in patients with AD. Hence, the appearance of plaques should be directly proportional to the levels of apoE in the central nervous system.[6] Therefore, polymorphism of the gene encoding apoE could indicate a risk of developing late-onset AD, given that apoE4 is associated with higher LDL cholesterol levels, which are involved in the accumulation of Aβ.[7]

Currently, there is no effective curative treatment for AD and the management of the disease is aimed at improving its symptoms. Drugs such as cholinesterase inhibitors (galantamine or rivastigmine) manage to slow the progression of the disease, but are only useful during the early stages of the disease. Memantine, a *N*-methyl-D-aspartic (NMDA) receptor antagonist, is effective during the advanced stages of the disease, protecting nerve cells in the brain from glutamate, a neurotransmitter that is released in excessive amounts in AD.[8]

Statins are hydroxymethylglutaryl coenzyme A reductase inhibitors that reduce cholesterol synthesis and increase the number of LDL receptors in hepatocyte membranes, enabling greater clearance of LDL from the bloodstream and lowering the level of lipoproteins.[9] These are the drugs of choice for the treatment of hypercholesterolemia.

According to previous studies, patients treated with statins have a lower risk of developing AD.[10,11] In addition, some experimental studies have shown that statins treatment delays the progression of AD because they reduce the production of Aβ and, therefore, the decrease in cholesterol levels appears to inhibit the formation of the same.[6,12]

However, the efficacy of such drugs is not clear, given that the results of the latest clinical trials did not reflect an improvement on the parameters that are used to measure the cognitive impairment of patients. Nevertheless, some clinical guidelines for the treatment of AD consider the use of statins as a possible

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treatment option for this pathology and some studies suggest its efficacy as treatment for certain subpopulations with AD.[13,14]

Given the above, and because of the high prevalence of AD and high frequency of publications respect to the use of statins in patients with AD, it would be necessary to perform a systematic assessment of its efficacy to identify possible subpopulations of patients who could benefit most from statin therapy.

For the above-mentioned reasons, the main objective of this review was to compile the most relevant information about the efficacy of the use of statins for the treatment of patients with AD.

Methods

Selection criteria

In concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines,[15] we conducted a systematic search of the literature published between January 2010 and April 2016 in the main biomedical databases MEDLINE (PubMed), EMBASE and The Cochrane Library. The search strategy is detailed as supplementary material.

We complemented our literature search by consulting different websites of drug regulatory agencies and scientific societies, and looking for new references within the documents found.

We included clinical trials, meta-analyses and systematic reviews that determined the efficacy of statins in AD, using parameters associated with the cause or the evaluation of the pathology, in patients diagnosed with AD and aged 18 or older.

Articles based on a different study design, those that evaluated the efficacy of the use of statins for the prevention of AD, and those written in languages other than English or Spanish were excluded.

Study selection and quality assessment

In a first phase, duplicates were eliminated. Then, eligible articles were selected based on information obtained from the title, abstract or full text, if necessary.

To ensure reproducibility and minimise bias, discrepancies were resolved by a second researcher. Subsequently, a critical reading of the selected articles was performed.

To assess the quality and validity of the clinical trials, we used the Spanish version of the Critical Appraisal Skills Programme (CASP) scale: the CASPe scale.[16] The quality of the studies was scored on a 0–6 scale, where 0 = negative or doubtful (no explicit information) and >1 = positive response; more specifically: <3 = low quality, 3 = medium–low quality, 4 = medium quality, 5 = medium–high quality, 6 = high quality. We used the AMSTAR tool to assess the quality of systematic reviews and meta-analyses.[17] The score percentage was divided by 10 instead of 11 if the systematic review was rated as 'not applicable' on item 10, related to publication bias. The AMSTAR score percentage was used to classify the methodological quality of the study. A percentage of 0–33% was classified as low quality; 34–66%, as medium quality; and 67–100%, as high quality.

Data extraction and outcomes

A descriptive analysis of the main characteristics of the studies selected was captured in an ad hoc table, considering the following variables: study design, number of patients included, selection criteria, characteristics of pathology and treatment regimens evaluated.

The following efficacy variables were considered:

- Mini-Mental State Examination (MMSE) score
- AD Assessment Scale - Cognitive Portion (ADAS-Cog) score
- Change in Neuropsychiatric Inventory (NPI) total score
- AD Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC) score
- Analytical variables indicating AD: levels of Aβ40 and Aβ42 in plasma and in cerebrospinal fluid (CSF), total tau protein and phosphorylated tau protein levels, soluble amyloid precursor protein-beta (sAPP-b), soluble amyloid precursor protein-alpha (sAPP-a) and plasma levels of 24S-hydroxycholesterol.

Statistical analysis

The statistical analysis was carried out using Microsoft Excel 2007® and IBM SPSS Statistics 21®. Qualitative variables were represented as percentages and quantitative variables were represented by measures of central tendency (mean) and measures of dispersion (standard deviation and range).

Results

Literature search

We identified a total of 304 articles within the databases consulted (52 in PubMed-MEDLINE, 218 in EMBASE, and 34 in the Cochrane Library).

Finally, 13 articles passed through the selection process: six clinical trials, six meta-analyses and one systematic review. Figure 1 shows the flowchart of the selection process for the systematic review.

The main reasons for excluding studies were: the study focused on the use of statins for the prevention of AD (48%); the study design was different from that required (41%); and the study analysed different variables from those considered (8%).

Study characteristics

Table 1 shows the quality score of each study, according to the CASPe scale and the AMSTAR tool. Generally, all the studies included were of high quality, with the exception of those conducted by Sjogren *et al*[19] and Serrano-Pozo *et al*[21] because of their non-randomised open-label design. All the meta-analyses were of high scientific quality and three of them obtained the maximum score on the AMSTAR scale.[24,25,28]

Tables 2 and 3 show the characteristics and the efficacy outcomes of the clinical trials and meta-analyses selected, respectively. In general, the study populations comprised older patients diagnosed with mild–moderate AD and MMSE scores between 12 and 26, in most cases.

The systematic review performed by Xiong *et al* included a total of nine randomised, crossover and placebo-controlled clinical trials that studied the cognitive effects of statins.[29]

Clinical outcomes

Simons *et al* did not find any significant differences in ADAS-Cog score between patients treated with simvastatin and those treated with placebo.[18] However, they found significant differences between both groups in terms of the MMSE score. Differences in the variation

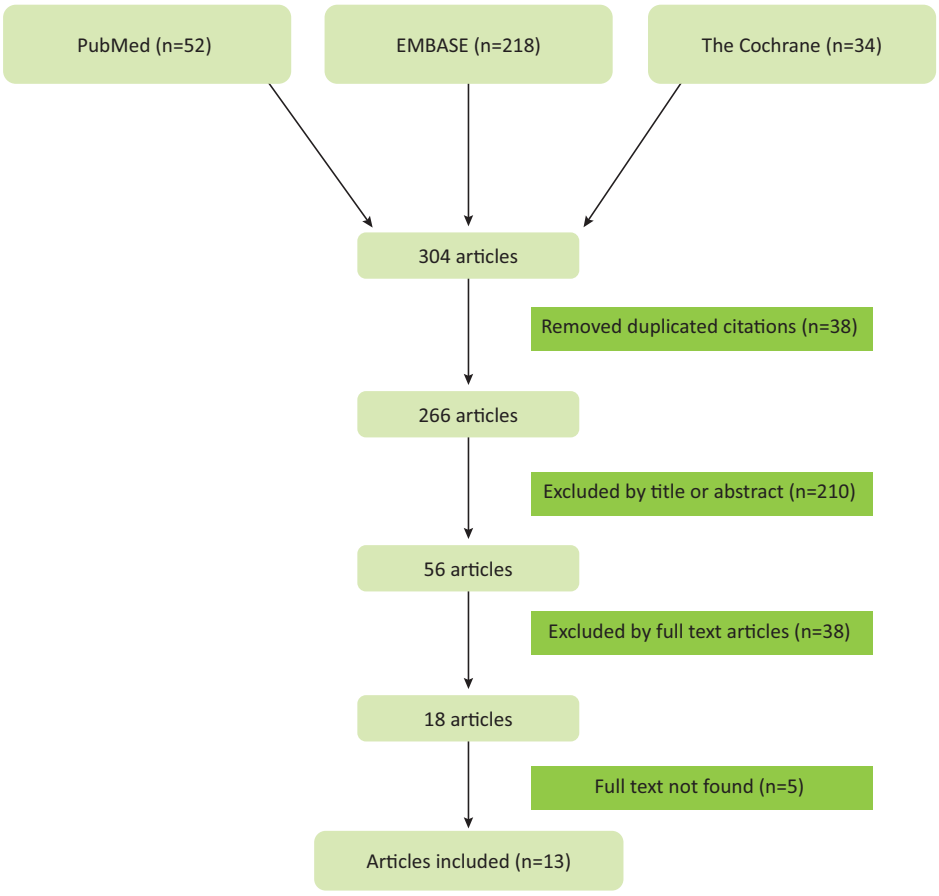

Fig 1. Flowchart of the selection process for the systematic review.

of Aβ40 and 24S-hydroxycholesterol levels in favour of simvastatin were detected in patients with MMSE scores between 20 and 26.

Sparks *et al* observed results that favoured atorvastatin against placebo, according to ADAS-Cog, MMSE and CGIC scores.[20]

Table 1. The quality and CASPe/AMSTAR scores of the studies examined

Study	CASPe[16]	AMSTAR tool[17]	Study quality
Sano *et al*[7]	6/6		High
Simons *et al*[18]	6/6		High
Sjogren *et al*[19]	3/6		Medium–low
Sparks *et al*[20]	6/6		High
Serrano *et al*[21]	3/6		Medium–low
Feldman *et al*[22]	6/6		High
Zhou *et al*[23]		9/11	High
Gizachew *et al*[24]		11/11	High
Sun *et al*[25]		11/11	High
Pandey *et al*[26]		9/11	High
Richardson *et al*[27]		9/11	High
McGuiness *et al*[28]		11/11	High
Xiong *et al*[29]		7/10[a]	High

[a]Question number 9 not applicable.

According to the open-label clinical trials performed by Sjogren *et al*[19] and by Serrano-Pozo *et al*,[21] there were no changes in AD markers in plasma or CSF after 12 weeks of simvastatin treatment (Aβ40-plasma, Aβ40-CSF, Aβ42-CSF, total tau-CSF, and phosphorylated tau-CSF). ADAs-Cog score and soluble amyloid precursor protein levels were significantly lower at the end of Sjogren *et al* study.[19]

In the latest clinical trials conducted by Sano *et al*[7] and by Feldman *et al*,[22] ADAS-Cog, MMSE, CGIC and NPI results were similar in statins (simvastatin and atorvastatin, respectively) and placebo patients.

Based on the outcomes of the meta-analyses included in this review, there were no differences in ADAS-Cog, MMSE, CGIC or NPI scores between placebo and treatment groups.[23–25,27,28] Gizachew *et al* analysed four clinical trials and did not detect any variation in ADAS-Cog;[24] they also included nine observational studies, one of which analysed the effect of the use of statins in MMSE without detecting any differences between treatments.

Xiong *et al* in their systematic review concluded that, although one study showed a slight improvement in patients treated with lovastatin versus placebo patients, the remaining trials did not show any significant differences in cognitive tests.[29]

Discussion

Here, we present an updated systematic review of available high-quality evidence on the efficacy of statins in AD given that, over the past few years, many of the investigations published

Table 2. Characteristics and efficacy results of clinical trials included in this study

Study	Design	Study population	Therapy: study arm / control arm	Number of patients (n)	Efficacy results, N (SD)			p-value
Simons *et al*[18]	Randomised, double-blind, placebo-controlled, clinical trial; phase III	Patients with diagnosis of probable AD, with MMSE 12–26	Simvastatin 40 mg/24 h orally for 4 weeks followed by 80 mg/24 h until 26 weeks/ placebo/24 h orally for 22 weeks	44 (simvastatin, 24; placebo, 20)		Simvastatin	Placebo	
					ADAS-Cog	4.1 (6.5)	3.4 (7.0)	ns
					MMSE	–0.6 (0.2)	–2.7 (0.7)	<0.02
					Change from baseline levels (pmol/L):			
					MMSE 12–20			
					Aβ40 (CSF)	–2.8 (10.3)	4.3 (14.2)	ns
					Aβ42 (CSF)	2.3 (15.2)	4.0 (9.0)	ns
					24S-hydroxycholesterol (CSF)	–7.8 (13.5)	1.7 (10.1)	ns
					MMSE 20–26			
					Aβ40 (CSF)	–5.7 (6.5)	6.8 (13.2)	<0.05[b]
					Aβ42 (CSF)	–5.6 (9.5)	–0.9 (9.7)	ns
					24S-hydroxycholesterol (CSF)	–15.2 (12.6)	6.2 (16.3)	<0.01[b]
Sjogren *et al*[19]	Open-label clinical trial	Patients with AD; 64–84-years old; MMSE 12–26	Simvastatin 20 mg/24 h orally for 12 weeks	19	Levels (pmol/L)	Before	After	
					α-SAPP (CSF)	2264 (543)	1986 (557)	<0.001[b]
					β-SAPP (CSF)	945 (133)	830 (83)	<0.001[b]
					Total tau (CSF)	658 (352)	638 (306)	ns
					Phosphorylated tau (CSF)	95 (43)	92 (37)	ns
					Aβ42 (CSF)	460 (172)	472 (160)	ns
					Aβ42 (plasma)	75 (80)	80 (88)	ns
					ADAS-Cog	16.6 (7.8)	19.3 (8.0)	<0.05[b]
Sparks *et al*[20] ADCLT study	Randomised, double-blind, placebo-controlled, clinical trial, phase II	Patients with mild to moderate AD; MMSE 12–28	Atorvastatin 80 mg/24 h orally for 1 year/placebo 24 h orally for 1 year	63 (atorvastatin, 32; placebo, 31)		Atorvastatin	Placebo	
					ADAS-Cog	0.5 (5.9)	–3.7 (6.7)	0.019[b]
					MMSE	–0.77 (2.7)	–2.42 (3.2)	0.009[b]
					CGIC	0.40 (1.81)[a]		0.037
					NPI	6.99 (6.85)	2.69 (6.68)	0.120

Table 2. (*Continued*)

Study	Design	Study population	Therapy: study arm / control arm	Number of patients (n)	Efficacy results, N (SD)			p-value
Serrano-Pozo *et al*[21]	Open-label clinical trial	Patients with probable AD or amnestic mild cognitive impairment; TC: 170–240 mg/dL	Simvastatin 20 mg/24 h orally for 6 weeks followed by 40 mg/24 h for 6 weeks	12	Levels (pmol/L) 24S-hydroxycholesterol (plasma)	Before 52.3 (11.8)	After 47.8 (12.5)	0.0368
					24S-hydroxycholesterol (CSF)	2.459 (1.966)	2.485 (1.805)	0.8225
					Aβ40 (plasma)	81.4 (22.0)	85.3 (17.3)	0.3700
					Aβ40 (CSF)	1573.1 (501.4)	1542.8 (531.0)	0.3016
					Aβ42 (CSF)	61.2 (29.9)	59.1 (26.2)	0.2624
					Total tau (CSF)	690.2 (312.2)	699.0 (322.4)	0.6072
					Phosphorylated tau (CSF)	87.1 (57.4)	90.0 (60.9)	0.1705
Feldman *et al*[22] LEADe study	Randomised, double-blind, placebo-controlled, multicentre and parallel clinical trial	Patients with mild to moderate probable AD; older than 50 years; taking donepezil 10 mg/24 h >3 months before screening; MMSE 13–25; LDL 95–195 mg/dL	Atorvastatin 80 mg/24 h orally for 72 weeks followed by 8-week withdrawal of treatment/ placebo 24 h for 72 weeks followed by 8-week withdrawal of treatment	640 (atorvastatin,314; placebo, 326)		Atorvastatin	Placebo	
					ADAS-Cog	2.77 (9.00)	3.3 (10.00)	0.73
					MMSE	–0.87 (2.9)	–1.11 (2.8)	ns
					CGIC	–0.02 (2.43)[a]		0.26
Sano *et al*[7]	Randomised, double-blind, placebo-controlled, multicentre clinical trial, phase III	Patients with probable AD and normal lipid levels; older than 50 years; MMSE 12–26	Simvastatin 20 mg/24 h orally for 6 weeks followed by 40 mg/24 h until 18 months; placebo/24 h orally for 18 months	406 (simvastatin, 204; placebo, 202)		Simvastatin	Placebo	
					ADAS-Cog	9.51 (9.48)	8.18 (8.70)	ns
					MMSE	–4.23 (4.77)	–3.75 (4.38)	ns
					NPI	3.21 (12.71)	3.78 (10.73)	ns

[a]Mean difference data were calculated as statin–placebo results;
*Significant values after regression analysis.
AD = Alzheimer's Disease; ADAS-Cog = Alzheimer's Disease Assessment Scale-cognitive; CGIC = Clinical Global Impressions of Change; CSF = cerebrospinal fluid; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; OR = odds ratio; RR = relative risk

Table 3. Characteristics and efficacy results of meta-analyses included

Study	Studies included	Number of patients	Selection criteria	Efficacy results; n (95% CI)	p-value
Zhou *et al*[23]	Two clinical trials: Simons 2002; Sparks 2005	107	Patients with dementia or AD; randomised controlled trials	ADAS-Cog: 1.84 (–1.58, 5.27)	0.055
Gizachew *et al*[24]	Four clinical trials	1,153	Clinical trials and subjects with a history or risk of AD	ADAS-Cog: –0.57 (–1.39, 0.25)	0.17
				MMSE: 0.57 (–0.36, 1.50)	0.23
				NPI: –0.77 (–1.59, 0.06)	0.07
	Six observational studies	21,819	Patients diagnosed with AD or at risk for the disease	HR: 0.69 (0.542, 0.882) OR: 0.447 (0.229, 0.668)	0.003 <0.001
Sun *et al*[25]	Two clinical trials: Sparks 2005; Feldman 2010	710	Patients with probable AD; randomised placebo-controlled clinical trials. Sparks 2005: single-centre study; Feldman 2010: multi-centre study	ADAS-Cog: 1.05 (–3.06, 6.05) MMSE: 0.77 (–0.57, 2.10) CGIC: 0.13 (–0.15, 0.40) NPI: 2.07 (–1.59, 5.73)	0.52 0.26 0.38 0.27
Pandey *et al*[26]	Five clinical trials: PROSPER 2002; Simons 2002; Sparks 2005; Feldman 2008; Sano 2011	6,958	Randomised clinical trials; subjects with a history or risk of AD	ADAS-Cog: –0.18 (–1.03, 0.66)	ns
				MMSE: –0.921 (–1.84, 0.0055)	<0.05
				CGIC: –0.26 (–3.11, 2.58)	ns
Richardson *et al*[27]	14 AD studies		Patients; randomised controlled trials		
	10 cohort studies	759,553	Cohort study	RR: 0.79 (0.63, 0.99)	
	Three case-control studies	5,758	Case-control study	OR: 0.56 (0.41, 0.78)	
	One cross-sectional study	57,104	Cross-sectional study	OR: 0.45 (0.35, 0.58)	
McGuiness *et al*[28]	Four clinical trials: Sparks 2005; Feldman 2010; Simons 2002; Sano 2011	1154	Patients with probable AD; clinical trials placebo controlled, randomised, double blind	ADAS Cog: –0.26 (–1.05, 0.52)	0.51
				MMSE: –0.32 (–0.71, 0.06)	0.099
				CGIC: –0.02 (–0.14, 0.10)	0.74
				NPI: –0.84 (–1.64, –0.05)	0.034

AD = Alzheimer's disease; ADAS-Cog = Alzheimer's disease assessment scale-cognitive; CGIC = Clinical Global Impressions of Change; CI = confidence interval; HR = hazard ratio; MMSE = mini-mental state examination; NPI = neuropsychiatric inventory; ns = non-significant; OR = odds ratio; RR = relative risk

and some clinical guidelines have included these drugs as a possible treatment option for AD. The studies included in this work highlight the limited efficacy of the use of statins in AD when compared with placebo. In 2001, Friedhoff *et al* detected a decrease in serum Aβ levels after treatment with various doses of lovastatin in patients with elevated LDL cholesterol levels but not diagnosed with AD.[30] This finding opened the way to expand research on the use of statins in AD because, by reducing the formation of atheromatous plaque, the said treatment could prevent cognitive impairment.

In 2002, Simons *et al* detected a small decrease in Aβ40 and Aβ42 levels in patients with mild–moderate AD treated with simvastatin.[18] However, such results were only significant in patients with milder AD. In addition, an improvement in MMSE scores was observed. For their part, Sjogren *et al* performed a clinical trial with one active arm treated with simvastatin, and reported a reduction in CSF levels of α-SAPP and β-SAPP, in patients diagnosed with AD.[19] These results implied lower β-amyloid levels and, therefore, a decrease in the formation of atheromatous plaque, demonstrating that statins could interfere directly in the metabolism of secretases and in the accumulation of Aβ.

Likewise, in 2005, Sparks *et al* conducted a trial to study the efficacy of a new statin (atorvastatin calcium) versus placebo in patients with mild–moderate AD.[20] This study measured ADAS-Cog, MMSE, CGIC and NPI scores, detecting differences between both treatment arms in the first three efficacy variables. Subsequently, the authors performed a post hoc analysis that showed that the efficacy of atorvastatin calcium was closely related to baseline cholesterol levels and to the apoE genotype.[31] Hence, patients with high cholesterol levels and those who are carriers of the apoE ε4 allele would be more likely to benefit from the use of statins early in their treatment. However, the limitations of this type of post hoc study make it difficult to generalise these findings.[14]

In 2010 and 2011, two clinical trials with larger sample sizes were carried out. Feldman *et al* studied the efficacy of atorvastatin in

patients with medium–moderate AD, detecting no significant differences between treatment and placebo groups in ADAS-Cog, MMSE and CGIC scores.[22] Later, Sano *et al* did not observe any cognitive improvement in ADAS-Cog and MMSE scores in patients with mild–moderate AD after treatment with simvastatin.[7] Although they identified a reduction in cholesterol levels in the statin treatment arm, their findings did not support the use of these drugs in AD.

After analysing the articles selected, we suggest that statins have not been proven to be of clear benefit for the treatment of AD. This claim relies on the fact that the main variables of the disease measured have not shown a significant improvement in patients treated with statins, compared with those who were administered a placebo.

Our review reinforces the findings of previous studies and meta-analyses carried out by Zhou *et al*,[23] Gizachew *et al*[24] and Richardson *et al*,[27] in which the main variables indicating cognitive impairment indicated negative results on the use of statins for the treatment of AD. The results of our review are supported by our inclusion of more, high-quality, articles compared with these previous reports.

Also, Miller *et al* performed a narrative review in which they included clinical trials investigating the use of statins and AD.[32] According to their study, evidence suggested that these drugs could offer a protective effect against the development of AD and had been proven to be useful as long-term therapy for hyperlipidaemia. However, the authors concluded that available studies assessing the use of statins had numerous confusing variables possibly skewing results and, therefore, they might not provide suitable clinical evidence as to whether these agents have an effect on the progression of AD. Hence, the authors did not recommend the use of statins as prophylaxis in patients with AD without hyperlipidaemia.

Additionally, patients diagnosed with AD are usually older and most have multimorbidities, frequently treated with polypharmacy.[33] It is essential to apply measures to reduce the number of drugs in these patients, with the purpose of preventing adverse reactions, improving adherence and reducing costs. Indeed, it is necessary to deprescribe drugs whose risk–benefit balance is controversial.[34] Given the efficacy demonstrated by statins for the treatment of AD, these drugs can be considered as susceptible to this process.

Among the limitations of our review is the delay between the date when the article search was finished (April 2016) and the date of its publication, which resulted from the high number of studies that were reviewed. Also, we have only considered studies that analyse the use of statins as treatment for AD and did not include those that analysed these drugs as prophylaxis against the disease. However, other systematic reviews on this topic have been recently published and, therefore, in this case, it would be difficult to provide relevant evidence in this regard.

Nevertheless, the present study includes updated information with a high level of evidence on the poor efficacy of the use of statins for the treatment of AD.

Conclusions

Although some previous studies suggest that the use of statins could offer a protective effect against AD, according to available evidence, the studies examined here do not provide enough evidence and do not show conclusive results that support the efficacy of statins for the treatment of AD. Therefore, the use of statins as treatment for this disease should not be recommended. ■

Author contributions

MM-T, MAP-M and MAF-A contributed to the design of the study; MM-T and MAP-M realised the acquisition and analysis of data, the peer-review process and the drafting of the manuscript; MM-T, MAP-M and MAF-A revised the manuscript critically for intellectual content and approved the final version to be submitted; MAP-M submitted the manuscript.

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