The Effect of Statins in Epilepsy: A Systematic Review

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Abstract

Background and Objectives: Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, used for the management of hypercholesterolemia and related atherosclerotic diseases. Several studies have indicated the neuroprotective effects of statins on several neuropathological conditions. However, the role of these medications in epilepsy is still unclear. The purpose is to evaluate and summarize the level of evidence on the efficacy of statins in neuronal hyperexcitability and the neuroinflammatory processes of epilepsy. Methods: A systematic review was performed. Eligibility Criteria: This review involved studies conducted in humans and nonhuman experimental models, covering the use of an inhibitor of HMG-CoA reductase, alone or accompanied by another medication, in epilepsy. Information Sources: A systematic literature search was performed in PubMed, Embase, Ebsco Host, Scopus, Science Direct, Medline, and LILACS. Risk of Bias: It was evaluated with the Newcastle–Ottawa Scale and the experimental studies were evaluated using the GRADE tool. Results: Twenty articles of the 183 evaluated were included. Sixteen studies were conducted in animal models and four studies in humans. Most studies in mice reported a reduction in epileptiform activity and reduction in systemic inflammation with the treatment of statins, potentially influencing epilepsy control. Few studies in humans were performed in the geriatric population with variable results (neuroinflammation, seizure prevention, cell death, prevention of kindling, increase in convulsive threshold, increase in latency, decrease in frequency of crisis, and reduction in mortality) related to reduction in the rate of hospitalizations, mortality, and prevention of epilepsy. Studies in mice found a decrease in interleukin-1β (IL-1β), IL-6, and tumor necrosis factor alpha and an increase in IL-10 and endothelial nitric oxide synthase. Conclusions: The possible antiepileptic mechanism of statins may be related to the reduction in neuroinflammation mediated by a decrease in pro-inflammatory cytokines and action in the nitricergic system. Further studies evaluating the impact of statins on seizure control are necessary.

Keywords: Brain, epilepsy, seizure, statins

Introduction

Epilepsy is a neurological disease generated by an abnormal brain electrical activity in certain regions of the brain that predisposes to recurrent unprovoked attacks. Worldwide, a prevalence of 1%–2% is estimated, affecting between 50 and 65 million people, with 50,000–100,000 new cases per year. In addition, it is estimated that 30%–40% are refractory to seizure treatment.1-3 Epilepsy is considered a public health problem worldwide and is one of the most frequent neurological disorders.3 Statins are inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase, used for the management of hypercholesterolemia and related atherosclerotic diseases, such as coronary artery

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The enzyme HMG-CoA reductase catalyzes the conversion of HMG-CoA to L-mevalonate; statins prevent the biological activities of L-mevalonate due to the aforementioned inhibitory effect. Statins perform pleiotropic actions on the endothelium, the inflammatory response, or the production of free radicals. The inhibition of obtaining endogenous cholesterol induces a positive regulation of low-density lipoprotein (LDL) receptors on the cell surface. Obtaining a higher absorption of LDL from the blood and therefore a decrease in its concentration. In addition, high-density lipoprotein levels increase and triglyceride levels decrease.

Several studies have indicated the neuroprotective effects of statins on several neuropathological conditions. The anticonvulsive activity has been explained by suppressing reactive astrogliosis with neuroinflammation in the crises; by stimulating GABAergic activity and inhibiting glutamatergic; by modulating the glycogen synthase kinase-3β pathway; and by decreasing the infiltration of monocytes in the neuronal death of the hippocampus and pro-inflammatory gene expression. The lipophilic statins (atorvastatin [ATV], lovastatin, fluvasatin, pitavastatin, and simvastatin) can passively pass through the blood–brain barrier (BBB); in addition, the hydrophilic statins can also enter the neuroparenchyma. All statins are substrates for organic anion transporter polypeptides (OATPs), of which OATP1A2 and OATP1C1 are expressed in the brain. Despite this, the selectivity of hydrophilic statins for these subtypes has not been explored to determine their mechanism of entry to the central nervous system (CNS). In addition, the existence of monocarboxylic acid transporters in the BBB can constitute an alternate route of entry to the CNS although there are no specific studies for the CNS either. Independently of the specific transporters, it is feasible that statins are deposited at different speeds and concentrations within the CNS according to their different lipid solubility alone.

**METHODS**

**Objectives**

The objective of this review is to answer the following question: What is the level of evidence on the efficacy of statins to decrease neuronal hyperexcitability and neuroinflammatory processes of epilepsy?

To develop the review, the steps of the patients, intervention, comparison, outcomes, and study design strategy were followed.

**Inclusion criteria**

**Types of participants**

This review involved studies conducted in humans and nonhuman experimental models.

**Type of intervention**

It covered the use of inhibitors of HMG-CoA reductase, alone or accompanied by another medication.

**Types of studies**

The qualitative component of the review included studies that described the molecular mechanisms of statins in the CNS, the pharmacokinetic aspects, and the changes derived from the use of these drugs in neurotransmitters and cerebral cholesterol. The quantitative component included randomized and nonrandomized controlled trials, quasi-experimental designs, prospective or retrospective cohort studies, and nested case–control studies.

**Types of results**

The benefit of the therapy was defined as the decrease in neuroinflammation derived from seizures, decrease in neuronal death after the seizure, prevention of seizures, decrease in mortality after a seizure episode, increase in seizure threshold, reduction in the frequency, and increase in the latency of the crises.

**Search and selection of studies strategy**

This systematic review followed the recommendations of the Cochrane Collaboration (PRISMA). A bibliographic search was carried out in the databases: PubMed, Embase, Ebsco Host, Scopus, ScienceDirect, Medline, and LILACS, considering all the publications made up to February 2, 2018. The search was carried out in five steps: First, the keywords using the Medical Subject Headings and DeCs (Health Descriptors), then proceeded to use the descriptors of the subject (hydroxymethyl glutaryl-CoA reductase inhibitors, statins, epilepsy, epileptogenesis) in the databases mentioned. Subsequently, the duplicate records were eliminated (Step 2) and an analysis of the titles and abstracts thrown by the search was continued (Step 3), then the full-text review of the selected articles was proceeded (Step 4), and finally, the references were reviewed of the included articles to identify those studies that also met the eligibility criteria (Step 5). Letters to the editor and studies with a language other than English or Spanish were excluded.

**Method of revision**

The search strategy and selected studies were evaluated by two independent reviewers (LM and ZC). The discrepancies were discussed with a third reviewer (RM).
Data collection
The following data were extracted from the studies that met the eligibility criteria: authors, year of publication, number of participants, type of study, study objective, statin used, statin dose, epilepsy inducer used, route of administration of the statin, duration of treatment, and results of the study. These data were compiled in Microsoft Excel and were divided into two: collection of human studies and collection of non-human studies.

Assessment of quality and risk of study sessions
The assessment of the risk of bias in human studies was performed using the Newcastle–Ottawa Scale [Figures 1 and 2], while experimental studies in animal models were evaluated using the GRADE tool [Figure 3].

Data synthesis and additional analysis
An analysis of the studies was carried out in nonhuman experimental models that only involved the use of statins, excluding from this analysis those studies that applied a drug or substantial addition to the statin and the studies that did not specify the duration of the treatment. With the Epi-info 7.2 programs, (CDC, Atlanta, Georgia, USA) the median duration of treatment, absolute and relative frequency of the variables were determined:

Results
Selection of studies
The selection process of the studies was based on the PRISMA foundations as shown in Figure 4. Twenty articles of the 183 included in the bibliographic search were considered.

Characteristics of the studies
Studies in animal models
We identified 16 studies in animal models (mice), of this total only 10 studies (n = 626 mice) met the criteria for descriptive analysis [Table 1]. We excluded three studies that used an additional substance to the statin; one study that did not clearly specify the duration of the treatment and two studies that did not clarify the number of participants. The median duration of treatment with statins was 14 days (IQR = 7–15), the inducers of epilepsy used were pilocarpine, kainic acid, quinolinic acid, pentylenetetrazole (PTZ), and electroshock test, as shown in Figure 5. Sehar et al.’s study was performed in two phases: acute and chronic, for statistical analysis were taken as two studies. On the other hand, as can be seen Figure 6, the most used route of administration was

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Figure 1: PRISMA flow diagram of our search mechanism
oral. In addition, the most commonly used statin dose was 10 mg of ATV [Figure 7]. In Table 2, it is observed that most of the studies reported a positive change of statin treatment.

**Human studies**

We identified four studies in humans \((n = 1,071,422)\): 3 (75%) of retrospective cohort and 1 (25%) of nested cases and controls. The results are shown in Table 3.

**Evaluation of the risk of bias**

The results of the evaluation of the bias are shown in Figures 2-4.

**Statins and brain cholesterol**

One study quantified sterol levels in the hippocampus of an animal model with unilateral hippocampal lesion induced by kainic acid. The lovastatin treatment was performed 3 days before and 3 days after the induction of status epilepticus (SE). There were no significant changes in the levels of sterols (lanosterol and desmosterol) at 24 h after the SE, but it did detect a bilateral reduction in the hippocampus of the metabolite 24-OHC and cholesterol levels at 48 h and 14 days \((P < 0.001 \text{ and } P < 0.01, \text{ respectively})\). These periods in which changes were identified corresponded to the preepileptogenic and to the appearance of daily seizures. On the other hand, lovastatin was not associated with alteration of seizures during status.\(^8\)

**Statins and neuroinflammation**

We identified three studies related to the role of statins in neuroinflammation mediated by cytokines. Two studies used lovastatin and one study used ATV. All three studies administered postinduction statin with pilocarpine. The study by Oliveira et al. found a reduction of the pro-inflammatory cytokines: interleukin-1β (IL-1β), IL-6, tumor necrosis factor alpha (TNF-α), and interferon-γ in cortex and hippocampus, 14 days after induction \((P < 0.05)\) together with an increase in the levels of the anti-inflammatory cytokine IL-10. These results were better with the dose of ATV 100 mg/kg compared to the dose of 10 mg/kg. In addition, the control group of ATV without induction with pilocarpine also showed a reduction in pro-inflammatory cytokines. In this same study, it was found that mice needed higher doses of the statin to achieve an increase in IL-10, unlike rats, which in turn had higher levels of pro-inflammatory cytokines.\(^5,9\) Gouveia et al. found similar results in both 2011 and 2014.\(^3\) The two

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**Figure 2:** Risk of bias for experimental studies in animal models using GRADE

**Figure 3:** Risk of bias using Newcastle–Ottawa Scale for cohort studies

**Figure 4:** Risk of bias using Newcastle–Ottawa Scale for case–control studies

**Figure 5:** Epilepsy inducers
| Authors            | Year | Number of animals | Statin | Number of times per day | Inductor | Start of statin | Duration of treatment | Evaluations                                                                 | Results                                                                                           |
|--------------------|------|-------------------|--------|-------------------------|----------|-----------------|-----------------------|----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Sehar et al. [1]   | 2015 | 24                | Controls=6 ATV 20 mg, 40 mg and 80 mg=6 for group | Once a day | PTZ (60 mg/kg) | 1 h before PTZ administration | 7 days | ICES test, elevated plus maze and forced swim test | ATV 80 mg/kg increased seizure threshold current significantly compared with the control group (22±0.00); did not significantly increase the latency of seizures ATV 40, and 80 mg/kg suppressed the development of PTZ kindling significantly in a dose-dependent manner (P<0.05, P<0.01, and P<0.001, respectively) |
|                    |      |                   | 60     | Controls=12 Only PTZ=12 ATV 20 mg + PTZ, 40 mg + PTZ y 80 mg + PTZ=12 for group | PTZ (25 mg/kg) | 1 h before PTZ administration | 7 weeks | Racine scale and assessment of dopamine, glutamate, and GABA levels |                                                                                                 |
| Van Vliet et al. [18] | 2011 | 13+               | Control with ATV=5, ATV 10 mg/kg + ES=8, vehicle+ ES=8 | Once a day | ES | 7 before the induction of epilepsy and 7 days after | 14 days | Video-EEG monitoring-Racine scale, blood-brain barrier permeability, and fluorescent immunocytochemistry EEG telemetry units, sterol analysis, and histopathology | ATV did not affect the duration of SE or the development of epilepsy, had not reduced inflammation, neuronal death, or synaptic reorganization |
| Heverin et al. [8] | 2012 | 96                | 4 mg/kg | Once a day | KA (0.3 µg) | 1 h before and 1 h after the KA | 7 days |                                                                 | LVT did not alter seizures during SE or seizure-induced neuronal death. Changes in hippocampal cholesterol homeostasis occur bi-laterally ATP dose-dependently decreased basal and SE-induced levels of (IL-1β), (IL-6), (TNF-α), (INF-γ) and increased (IL-10) levels in the hippocampus and cerebral cortex LVT induced an increased expression of the IL-10 and the picrocaine plus lovastatin group showed a significant decrease in the levels of IL-1β and TNF-α during the latent and chronic phase |                                                                                                 |
| Oliveira et al. [3] | 2018 | 108               | Saline=22, ATV 10=17, ATV 100=13 | Once a day | Pilocarpine (100 mg/kg) after methylscopolamine 1 mg/kg | 3 h after diazepam injection | 14 days | Cytokine analysis and Behavioral tests |                                                                                                 |
| Gouveia et al. [5] | 2014 | 26                | Control=5; LVT (20 mg/kg)=5; Pilocarpine=8 and Pilocarpine plus LVT=8 | Twice daily | Pilocarpine (350 mg/kg) | After 2 h of SE onset | 15 days | Real-time PCR analysis for cytokines and Immunohistochemistry |                                                                                                 |
| Piermartiri et al. [10] | 2009 | 71                | Saline + QA=22 ATV 1 mg/kg + QA=15 ATV 10 mg/kg + QA=34 | Once a day | Quinolinic Acid (36.8 nmol) | Before QA administration | 7 days | L-[3H] glutamate Uptake, Cell death (Propidium Iodide Staining) | ATM 10 mg/kg prevented seizures induced by QA in 29.41% of the mice. (P=0.004), ATM prevented QA induced cell death in the hippocampus and prevented the reduction in glutamate uptake into the hippocampus |                                                                                                 |

Contd...
Table 1: Contd...

| Authors        | Year | Number of animals | Statin | Number of times per day | Inductor | Start of statin | Duration of treatment | Evaluations | Results                                                                 |
|----------------|------|-------------------|--------|-------------------------|----------|----------------|-----------------------|-------------|-------------------------------------------------------------------------|
| Lee et al. \[11\] | 2008 | 28                | Control=9 ATV 10 mg/kg pre-SE=11 ATV 10 mg/kg Post-SE=8 | Once a day | KA (10 mg/kg) | Before KA injection- ATV pre-SE group; 0.5 h after KA in ATV Post-SE group | 7 days | Racine scale | Treatment with ATV efficiently decreased convulsive events induced by KA, the neuronal death of the hippocampus, infiltration of monocytes and proinflammatory gene expression |
| Gouveia et al. \[9\] | 2011 | 20                | Control=5, Solo LVT 20 mg=5, Solo pilocarpine=5, pilocarpine plus LVT=5 | 2 h after the onset of SE and 12 h after the first dose | Pilocarpine (350 mg/kg) to 1 mg/kg before scopolamine methyl nitrate | After pilocarpine injection | 0,5 days | Quantitative real-time PCR (for cytokines and kinin B1 and B2 receptors) and corporal temperature | LVT significant decrease in mRNA expression of IL-1β, IL-6, TNF-α, and kinin B1 receptor, also reduced SE-induced hyperthermia |
| Campos et al. \[19\] | 2017 | 152               | Control=14, ATV 10 mg/kg=10, ATV 100 mg/kg=10, Solo SE=13, ATV 10 + SE=18, ATV 100 mg/kg + SE=15 | Once a day | Pilocarpine 100 mg/kg and Pilocarpine (30 mg/kg) | After pilocarpine injection | 14 days | Giemsa staining | The ATV regarded against tonic-clonic seizures caused by PTZ on the 14th post-SE. The protective effects were similar in female and male mice, requiring a higher amount of ATV in females (100 mg/kg versus 10 mg/kg in males) |

PTZ: Pentylenetetrazole, ICES: Increasing current electroshock, ATV: Atorvastatin, ES: Electrical stimulation, EEG: Electroencephalography, SE: Status epilepticus, LVT: Levetiracetam, PCR: Polymerase chain reaction, TNF-α: Tumor necrosis factor alpha, IL-1β: Interleukin-1β, INF γ: Interferon gamma, GABA: gamma-Aminobutyric acid, KA: Kainic acid, QA: Quinolinic acid
studies used ATV with a difference in the duration of treatment. However, both studies found a reduction in IL-1β and TNF-α.⁵,⁹

**Statins and nitric oxide**

Four studies evaluated the effect of statins on nitric oxide. Three studies used PTZ as an inducer and one used penicillin G ATV.¹³,¹⁶,¹⁷,²⁰ Akgün Dar et al, administered ATV 30 min before induction found that pretreatment with this statin reduced the inducible nitric oxide synthetase and matrix metalloproteinase 2 that have been related to a proconvulsant activity (P < 0.001) and also found a reduction in frequency and an increase in latency of seizures (P < 0.001).² These findings agree with the results of the study by Shafaroodi et al., who used PTZ and electrical stimulation as inductors and

**Table 2: Positive results reported in experimental studies**

| Study                | Neuro-inflammation | Seizure prevention | Cell death | Prevention of kindling | Increase in convulsive threshold | Increase in latency and decrease in frequency of crisis | Reduction in mortality |
|----------------------|--------------------|--------------------|------------|------------------------|---------------------------------|--------------------------------------------------------|------------------------|
| Sehar et al.¹¹        |                    |                    |            |                        |                                 |                                                        |                        |
| Oliveira et al.²      |                    |                    |            |                        |                                 |                                                        |                        |
| Akgün et al.⁹         |                    |                    |            |                        |                                 |                                                        |                        |
| Gouveia et al.⁹       |                    |                    |            |                        |                                 |                                                        |                        |
| Piermartiri et al.¹⁰  |                    |                    |            |                        |                                 |                                                        |                        |
| Lee et al.¹¹          |                    |                    |            |                        |                                 |                                                        |                        |
| Gouveia et al.⁹       |                    |                    |            |                        |                                 |                                                        |                        |
| Shafaroodi et al.¹²   |                    |                    |            |                        |                                 |                                                        |                        |
| Seker et al.¹³        |                    |                    |            |                        |                                 |                                                        |                        |
| Moezi et al.²¹        |                    |                    |            |                        |                                 |                                                        |                        |

*The study evaluated the respective parameter, finding positives results after the statin administration*

**Table 3: Statin studies in humans**

| Authors              | Year | Type of study       | Period evaluated       | Number of patients | Age               | Statin                                      | Objective                                           | Results                                                                 |
|----------------------|------|---------------------|------------------------|--------------------|-------------------|---------------------------------------------|-----------------------------------------------------|------------------------------------------------------------------------|
| Pugh et al.¹⁴        | 2009 | Retrospective cohort study | October 1999-September 2000 | Cohort of epilepsy (n=1847) cohort without epilepsy (n=1,023,376) | ≥65               | Unspecified                                | Identify risk factors for new-onset geriatric epilepsy                                    | The prescription of statins showed an OR=0.64, 95% CI=0.56-0.73 for the prevention of epilepsy |
| Etminan et al.¹⁵      | 2010 | Nested case-control study | 1995-2004              | 217 cases and 2117 controls | 69.4±12.3 (cases) 70.0±9.6 (controls) | Atorvastatin, lovastatin, cerivastatin, fluvastatin, pravastatin, simvastatin, and rosuvastatin | To assess the potential efficacy of statins in the prevention of epilepsy | The ARR in patients with current use of statins was 0.65 with 95% CI 0.46-0.92. The ARR for previous users of statins was 0.72 (95% CI 0.39-1.30) |
| Sierra-Marcos et al.¹⁶ | 2014 | Retrospective cohort study | April 2006-September 2012 | 427 patients       | 60.9±17.8         | Simvastatin, atorvastatin, and pravastatin | To evaluate the possible role modulator of statins in status epilepticus | Statins were associated with lower mortality (relative risk ratio 0.38, P=0.046) |
| Trivedi et al.¹⁷      | 2018 | Retrospective cohort study | October 2003-March 2012 | 43,438 patients    | 56.0±12.0          | Simvastatin, atorvastatin, and pravastatin | To examine the association between the use of statins and the risk of epilepsy | The OR of epilepsy in the general cohort was 0.91 (95% CI=0.67-1.23) and in the healthy cohort, it was 1.08 (95% CI=0.64-1.83). No significant beneficial or detrimental effect of the use of statins on the risk of epilepsy was demonstrated |

ARR: Adjusted rate ratio, OR: Odds ratio, CI: Confidence interval
administered ATV of 10 and 20 mg/kg; this treatment increased the threshold for tonic seizures caused by PTZ and decreased the appearance of tonic seizures and death in the induction model with electric current.\[12\] Similarly, the study by Moezi et al. found an increase in the seizure threshold for both intravenous and intraperitoneal PTZ models and a decrease in the appearance of tonic seizures and death in the chronically treated group with ATV and induction with intraperitoneal PTZ.\[21\] In the study by Seker et al., ATV, simvastatin, and rosuvastatin were used at a dose of 20 mg/kg; in this case, the group with rosuvastatin presented the best antiepileptic effect with a decrease in the expression of p53, Bax, and caspase 3 that are associated with cellular apoptosis, together with an increase in endothelial nitric oxide synthetase.\[13\] Three studies (Seker et al., Shafaroodi et al., and Moezi et al.) showed that inhibitors of nitric oxide synthetase (L-NAME and aminoguanidine) decreased the anticonvulsant effect of ATV.\[12,13,21\]

Statins and specific syndromes associated with epilepsy

We identified two studies that evaluated the use of statins in genetic syndromes with epileptogenic characteristics. In 2013, Osterweil et al. found that the administration of 100 mg/kg of lovastatin to genetically modified mice (fragile X syndrome) was able to correct the excessive synthesis of proteins and prevent the outbreak of epileptiform activity in the hippocampus in vitro, in addition to protecting the mice in vivo.\[1,22\] On the other hand, in 2018, it was postulated that lovastatin is capable of modulating upregulated protein functions in animal models with Angelman syndrome by a mechanism other than the inhibition of protein synthesis.\[23\] However, more research is needed to clarify this relationship.

**DISCUSSION**

The neuroprotective effects of statins have been observed in various neurological diseases. However, its protective effect on epilepsy continues to be debated and most studies have been conducted in rats. An association has been found between the use of statins and the reduction of the risk of epilepsy in older adults. Sierra-Marcos et al. demonstrated an antiepileptic role of statins in older adults, for which they used the registry of 427 patients with an epileptic episode in a period of 6 years and took into account different predictive items of prognosis, among which if they had used or they use statins. The use of statins was statistically significant, which correlated with a decrease in morbidity and mortality in these patients.\[16\]

Etminan et al. found that statins reduce the risk of hospitalization in patients with epilepsy focused on senile patients and stipulated that the result is directly related to the dose and the possible anti-inflammatory properties that statins confer.\[15\] The few studies conducted in humans focused on observing the properties of statins in terms of epilepsy have had an effect in elderly people who have been shown to have a certain risk of developing epilepsy associated with cerebrovascular diseases and dementia. Pugh et al., in their study on the risk factors of epilepsy of onset in old age, observed that in patients with prescription of statins, the development of epilepsies was lower.\[14\]

There is research in humans that suggests the neuroprotective benefit of statins that is generalized to the entire population. Trivedi et al. could not determine the benefit of statins in their study where they included healthy individuals or those with few comorbidities and who used statins or not; however, it is emphasized that they were not associated with an increase in the risk of statins. Development of epilepsies which allows establishing that the use of statins is safe in patients who have epilepsy.\[17\] All studies reviewed in humans agree on the need for more research on the subject to be able to define the beneficial effect of statins and be able to explain it.
Summary of evidence
This systematic review gives an overview of the available literature on the role of statins and its possible effect on epilepsy. This study only provides evidence 3b.

Limitations
Our study has some limitations. Most studies focused largely on an experimental level. All articles included in this review are peer-reviewed. There is a possibility of publication bias. Finally, the inclusion of only articles in English and Spanish could affect the generalization of our findings.

Conclusions
The role as anticonvulsant agents of statins is not completely known. Still, there is missing evidence to know how this type of mechanism works modulating the immune system. The participation of statins as reducing agents of neuroinflammation requires more studies.

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Conflicts of interest
There are no conflicts of interest.

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