SHORT COMMUNICATION

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Amyotrophic Lateral Sclerosis-Like Conditions in Possible Association with Cholesterol-Lowering Drugs

An Analysis of Patient Reports to the University of California, San Diego (UCSD) Statin Effects Study

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Abstract

Background: While cases of amyotrophic lateral sclerosis (ALS) or ALS-like conditions have arisen in apparent association with HMG-CoA reductase inhibitors ('statins') and/or other lipid-lowering drugs (collectively termed 'statins' in this paper for brevity), additional information is needed to understand whether the connection may be causal. The University of California, San Diego (UCSD) Statin Effects Study is a patient-targeted adverse event surveillance project focused on lipid-lowering agents, whose aim is to capitalize on patient reporting to further define characteristics and natural history of statin adverse effects (AEs), and to ascertain whether a patient-targeted surveillance system might lead to presumptive identification of previously unrecognized AEs. ALS was a candidate 'new' AE identified through this process. The aim of the analysis presented here was to examine characteristics and natural history of reported statin-associated ALS-like conditions with attention to factors that may bear on the issue of causality.

Methods: For the present analysis, we focused on cases of statin-associated ALS that were reported to our study group prior to publication of a possible statin-ALS association. Of 35 identified subjects who had contacted the UCSD Statin Effects Study group to report ALS or an ALS-like condition, 18 could not be reached (e.g. contact information was no longer valid). Six were unable to participate (e.g. due to progression of their disease). Of the 11 who could be contacted and were able to participate, one declined to give informed consent. The remaining ten, with either a formal or probable diagnosis of ALS in the context of progressive muscle wasting/weakness arising in association with lipid-lowering drug therapy, completed a mail or phone survey eliciting information about ALS symptom onset and change in association with drug use/modification and development of statin-associated AEs. We reviewed

findings in the context of literature on statin antioxidant/pro-oxidant balance, as well as ALS mechanisms involving oxidative stress and mitochondrial dysfunction.

Results: All ten subjects reported amelioration of symptoms with drug discontinuation and/or onset or exacerbation of symptoms with drug change, rechallenge or dose increase. Three subjects initiated coenzyme Q10 supplementation; all reported initial benefit. All subjects reportedly developed statin AEs (not indicative of ALS) prior to ALS symptom onset, strongly disproportionate to expectation ($p < 0.001$). Since this reflects induction of pro-oxidant effects from statins, these findings lend weight to a literature-supported mechanism by which induction by statins of oxidative stress with amplification of mitochondrial dysfunction, arising in a vulnerable subgroup, may propel mechanisms underlying both AEs and, more rarely, ALS.

Conclusion: A theoretical foundation and preliminary clinical observations suggest that statins (and other lipid-lowering drugs) may rarely be associated with ALS in vulnerable individuals in whom pro-oxidant effects of statins predominate. Our observations have explanatory relevance extending to ALS causes that are not statin associated and to statin-associated neurodegenerative conditions that are not ALS. They suggest means for identification of a possible vulnerable subgroup. Indeed whether statins may, in contrast, confer ALS protection when antioxidant effects predominate merits examination.

Background

Amyotrophic lateral sclerosis (ALS) is a rare, progressive and usually fatal degenerative motor neuron disease that is increasing in incidence faster than accounted for by aging of the population alone.[1] HMG-CoA reductase inhibitors ('statins') are widely prescribed lipid-lowering drugs that are often well tolerated. Based on a patient-targeted drug adverse effect (AE) surveillance system, we previously identified and reported on an apparent signal of excess ALS or ALS-like cases (together designated as 'ALS' in this paper for brevity) in association with statins.[2,3] Subsequently, in 2007, a WHO pharmacovigilance report identified an apparently high number of ALS cases arising among statin users and called for additional studies exploring a causal relationship.[4] However, disproportionate reporting need not mean disproportionate or causal occurrence.

The University of California, San Diego (UCSD) Statin Effects Study is a patient-targeted lipid-therapy AE surveillance effort, developed with the goal to capitalize on patient reporting of possible statin-associated AEs. The aim was to examine characteristics, natural history (e.g. time-course, effect of discontinuation and rechallenge, relation of recurrence to drug and potency) and impact of statin AEs, and to ascertain whether a patient-targeted surveillance system might lead to identification of signals of previously unrecognized AEs. In 2005, we designated ALS as the first such possible AE for investigation.[2,3] This followed an analysis of a sample of 500 e-mails to our group citing statin AEs. A tally of reported AEs showed nine cases of reported ALS attributed by patients to statins; for comparison, there were eight cases of erectile dysfunction, which is a well documented statin AE in the literature.[5-19] Although disproportionate reporting need not imply disproportionate incidence, ALS was notable among reported conditions for having (at that time) no prior literature documentation of a statin association, and the disproportionate

reporting of this rare condition, relative to more common conditions, provided a possible 'signal' meriting additional follow-up. As continued reports of ALS and ALS-like conditions were received by our group, we sought to look more carefully at patient reports of possible statin-associated ALS.

Our aim was to collate information on reported cases of ALS-like conditions attributed by patients to lipid drug use, focused on those with the least prospect for external influence in their original inference regarding a statin association, i.e. those patients who had contacted us prior to published reports of a potential ALS-statin association, and to evaluate characteristics relevant to potential drug causality in the context of the literature relevant to potential mechanisms.

We relay a series of cases of ALS-like conditions arising in apparent association with statins, and present triangulating evidence, which we believe supports a hypothesized mechanism.

Methods

Subjects were men and women citing either a formal ALS diagnosis or consideration of an ALS diagnosis in the context of progressive muscle weakness/wasting arising in perceived association with statins and/or other drugs used for management of hyperlipidaemia (collectively termed 'statins' in this paper for brevity). Thirty-five subjects were identified who had contacted our patient-targeted AE surveillance group (the UCSD Statin Effects Study group) during an approximate 3-year period prior to scientific and media attention to a possible link between statin therapy and ALS.[4] A number of additional cases have come to our attention since that time, but our focus here is on those for whom prior publication could not have influenced their inference about a statin association to their ALS-like symptoms.

Of the 35 subjects, 18 could not be reached (e.g. contact information was no longer valid). Six were unable to participate (e.g. due to progression of their disease). Of the 11 subjects who could be contacted and were able to participate, one declined to give informed consent, providing ten subjects for whom data are shown. No prospective subject who could be contacted, and was willing and able to provide the requested information, was excluded from analysis. All subjects gave written informed consent. Subjects completed surveys approved by the UCSD Human Research Protections Program.

Information was elicited regarding the following: statin(s) used; symptom time-course relative to drug use (symptom onset, effect of dose change or discontinuation); character of symptoms including those culminating in concern for ALS; diagnostic testing and diagnosis; occurrence of other recognized AEs of statins, including muscle/fatigue,[20] cognitive symptoms[21-24] or neuropathy[25-27] (and response of these symptoms to statin discontinuation); and impact of coenzyme Q10 (Q10) supplementation if tried (statins reduce Q10[28,29] and it has been proposed that Q10 may benefit ALS[30-32]). The apparent disproportionate co-occurrence of other statin AEs in these patients contributes to the case for the mechanism proposed (see Discussion section). To show that this co-occurrence is indeed disproportionate (relative to expectation) we employed the binomial test to assess whether the proportion citing statin AEs (not attributable to ALS) is statistically consistent with literature-based rates of AEs among statin users more generally.

Potential risk factors (family history of ALS, heavy metal or pesticide exposure[33,34]) and protective factors (smoking[35]) for neurodegeneration were collated. Medical records were secured complementing survey information for five subjects. The categories of information sought are summarized in table I.

We reviewed findings in the context of literature on statin antioxidant/pro-oxidant balance, as well as ALS mechanisms involving oxidative stress and mitochondrial dysfunction.

Results

All subjects had received a diagnosis of ALS or probable ALS in the context of progressive muscle wasting/weakness arising in association with statin drug therapy.

Table I. Information elicited from patients in surveys

Name of subject
Date of survey
Date of birth
Sex
Ethnicity
Other health and exposure history
Nonlipid medications
Lipid medications
dosage
usage period
lipid values (if known)
symptoms with each medication
time-course of symptom onset, progression, recovery vs drug initiation, change, discontinuation
change (improvement/recovery, worsening, change in character) with each dose change or medication change
Tests done
Diagnoses given
Treatments given
Story/narrative

Table II provides a summary of each case, including statin use, apparent non-ALS statin AEs, development of symptoms culminating in the ALS or related diagnosis, medical tests performed and response to statin discontinuation or Q10 supplementation. Case details are reported in the supplementary material (see Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A12).

All ten subjects reported having experienced recognized statin AEs prior to onset of the symptoms that culminated in the ALS-related diagnosis. In all cases these included non-muscle symptoms and/or muscle symptoms that reversed with statin discontinuation, sometimes with repeated dechallenge/rechallenge. Muscle AE rates of 10% have been found with 'high dose' statins,[45] reflecting among the higher reported estimates. Assuming a rate of 20% for *combined* statin AEs (although compatible with some studies,[46] this is higher than rates often given and thus conservative *vis-à-vis* our comparison), the occurrence of statin AEs prior to development of ALS in ten of ten subjects departs significantly from expectation: $p < 0.000001$, binomial test (departure from expectation becomes still more strongly significant if a lower statin AE comparator rate is employed).

In many, the symptoms ultimately diagnosed as ALS first emerged, or accelerated, with statin dose increase or rechallenge. Many subjects noted marked temporary abatement of symptoms, or a subset of symptoms, with statin discontinuation – generally followed by re-emergence of disease progression. Three subjects tried Q10 supplementation; all reported initial benefit/symptom amelioration. A range of statins (and also ezetimibe) were involved in the ten cases (table III). Three subjects have since died from ALS complications.

Discussion

Although a recent report originating from the US FDA has suggested that analyses of statin *clinical trials* did not reveal an increased incidence of ALS in subjects treated with a statin compared with placebo,[47] we have noted disproportionate reporting of ALS-like cases in our patient-targeted statin AE reporting database,[2,3] independently of and previous to reporting of the same observation by the WHO Programme for International Drug Monitoring.[4] (Rhabdomyolysis, a condition well accepted to bear a relation to statins, had not been found to be increased with statins in statin clinical trials either;[48,49] other data sources were required to establish a connection.) Even rare problems can be seen incidentally with common drugs, so existence of reports alone does not constitute evidence for causality. However, in our study, other factors provide a basis for concern that an association between statin use and ALS may be causal. These include a supportive theoretical foundation, and factors in the natural history of the ALS presentations in these cases such as response to statin dose increase and/or discontinuation, as well as the striking preponderance of antecedent and concurrent non-ALS statin AEs, beyond that attributable to chance. Since occurrence of statin AEs has been linked to statins conferring net pro-oxidant effects (vs their more typical antioxidant effects), this finding fuels a hypothesis by which statins may be causal to ALS in some persons, via

Table II. Characteristics of the ten patients who took part in the survey

Case	Age at ALS diagnosis (y)	Sex	Lipid drugs	Non-ALS AEs occurred on lipid drug	ALS symptoms occurred on lipid drug[a]	Neurologist evaluation	Medical record information on file	Medical testing	Formal diagnosis	Benefit with lipid drug cessation	Worsening with dose increase/ rechallenge	Tried Q10/if tried-benefit with Q10?	Identified other possible risk factors
1	68	F	L	Yes	Yes	Yes	No	EMG (×2) MRI, SOD gene test (negative result)	ALS	Yes[b]	NA	Yes/Yes	No
2	55	M	S	Yes	Yes	Yes	Yes	EMG/NCV, MRI (brain, spine)	ALS	Yes	Yes	No	Yes[c]
3	71	F	A	Yes	Yes	Yes	No	EMG, speech and swallow study	Atypical ALS	Yes	NA	No	No
4	50	M	A	Yes	Yes	Yes	Yes[d]	EMG (multiple), MRI, LP, swallow study	ALS and frontotemporal degeneration	No	Yes	No	Yes[e]
5	71	M	A, S, V	Yes	Yes[f]	Yes	No	EMG (×4), MRI (×5), MRA	Probable ALS	No	Yes	No	No
6	59	M	A, E	Yes	Yes[g]	Yes	No[h]	EMG	ALS	Yes[b]	No	No	No
7	70	M	A, C, E, Fl, P, R, S	Yes	Yes[g]	Yes	Yes[d]	EMG (×2), MRI (C-spine)	ALS	Yes[b]	Yes	No	Yes[i]
8	62	F	R	Yes	Yes	Yes	No	EMG/NCV, brain CT, CK	Motor neuron disease, Possible ALS	Yes	NA	No	No
9	48	F	E, Fl, L, S, V	Yes	Yes[j]	Yes	No	EMG	ALS	No	NA	Yes/Yes	No
10	63	M	A, S	Yes	Yes	Yes	Yes[d]	EMG/NCV, MRI (spine)	Possible ALS	Yes	Yes	Yes/Yes	Yes[k]

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induction of oxidative stress and propagation of mitochondrial injury.

First, statins reduce total cholesterol, which (including low-density lipoprotein [LDL] cholesterol) transports key antioxidants such as vitamin E, Q10 and carotenoids.[50-53] Lipid levels increase in some settings of oxidative stress and are improved with many antioxidant interventions (including fruits, vegetables, nuts, Q10 and exercise) suggesting adaptive regulation. Statins, by lowering cholesterol, may reduce antioxidant transport, in some cases lowering adaptively upregulated antioxidant transport.

Second, neurodegenerative disease occurrence is conditioned by the balance of oxidant stressors to antioxidant defenses.[54] This is germane to the observation that higher total and LDL cholesterol are observationally linked to a lower risk of Parkinson's disease[55,56] (a condition with close pathophysiological connections to ALS) and higher survival time within ALS.[57] Those with ALS are twice as likely to have hyperlipidaemia as a control group; however, the hyperlipidaemia may be a protective adaptation to the triggering oxidative stress and mitochondrial dysfunction[58] rather than be causal to ALS, as suggested by evidence that ALS patients with hyperlipidaemia live longer than those without hyperlipidaemia.[57]

Third, Q10 is transported by cholesterol (as noted above) and is also a product of the mevalonate pathway inhibited by statins, thus statins reduce Q10 in a dose-dependent fashion.[28,29,59] Q10 has key antioxidant functions,[60,61] as the primary endogenous lipophilic antioxidant, and in particular as a vital mitochondrial antioxidant. This is important because mitochondria are a major source of reactive oxygen species (free radicals) – and, through proximity, a major target of free radicals.[62] In addition, Q10 has pivotal cell-energy supportive effects (serving in the electron transport chain)[60,63,64] and antiapoptotic effects.[65-68] Patients with familial low Q10 exhibit increased muscle apoptosis that abates with Q10 administration.[30] Q10 confers benefit to ALS in animal models;[31] in humans, Q10 retards progression of Parkinson's disease[69] and clinical trials for its use in ALS are underway.[32]

Table II. Contd

a In these patients, ALS symptoms were classified as muscle weakness (including problems from bulbar weakening).

b Muscle *pain* improved/resolved with cessation of statin (case #1, 6, 7). However, *weakness* progressed off statin (case #1) or with switch to ezetimibe (case #6). Pain recurred, and weakness occurred and progressed with initiation of ezetimibe (case #7).

c Family history of statin sensitivity.

d Partial records secured.

e Played competitive football. Competitive football[36] and soccer[37-41] have been linked to increased risk of ALS. Although theories abound, we speculate the association may rest in part on pesticides/herbicide exposure in grass fields.

f Weakness first arose on statins, but accelerated with subsequent simvastatin/ezetimibe treatment.

g ALS symptoms arose on ezetimibe (non-statin).

h Subject gave permission for records to be secured, but requested records were not received.

i Heavy metal exposure (an oxidative stressor that has presumptive ties to ALS.[34])

j ALS symptoms arose on simvastatin/ezetimibe treatment.

k Family history of Parkinson's disease in two paternal uncles. Parkinson's disease is a neurodegenerative condition linked to ALS by common pathophysiological mechanisms, risk factors and in some instances co-occurrence.[42-44]

A = atorvastatin; **AE** = adverse effect; **ALS** = amyotrophic lateral sclerosis; **C** = cerivastatin; **CK** = creatine kinase; **E** = ezitemibe; **EMG** = electromyogram; **F** = female; **Fl** = fluvastatin; **L** = lovastatin; **LP** = lumbar puncture; **M** = male; **MRA** = magnetic resonance angiography; **MRI** = magnetic resonance imaging; **NA** = not applicable; **NCV** = nerve conduction velocity; **P** = pravastatin; **Q10** = coenzyme Q10; **R** = rosuvastatin; **S** = simvastatin; **SOD** = superoxide dismutase; **V** = simvastatin/ezetimibe (Vytorin™).

Table III. Cholesterol-modifying drug use in reported cases of amyotrophic lateral sclerosis (ALS)-like conditions

Drug	Number of subjects on this drug at one point in their lipid drug history[a]	Number of subjects on this drug at time of development of symptoms diagnosed as ALS
Atorvastatin	6	4
Simvastatin	5	1
Lovastatin	2	1
Fluvastatin	2	0
Pravastatin	1	0
Simvastatin/ezetimibe (Vytorin™ preparation)	2	1[b]
Rosuvastatin	2	1
Cerivastatin	1	0
Ezetimibe	3	2

a These are the lipid drugs taken throughout the course of cholesterol therapy for the ten subjects. The total number exceeds the number of subjects (ten) because some subjects reported use of more than one drug.

b In one additional subject, weakness first arose on statins, but accelerated with subsequent statin/ezetimibe (Vytorin™) treatment.

Q10 supplementation can 'bypass' a range of respiratory chain disorders[70-72] – thus adequate Q10 can render mild mitochondrial pathology clinically silent. Conversely, Q10 reductions may unmask previously silent mitochondrial vulnerabilities, with increased cell energy deficits, oxidative stress and apoptosis among predicted consequences. Elevated oxidative stress may in turn promote further mitochondrial protein, lipid, RNA and DNA injury[73,74] (since mitochondria are both a primary source and target of reactive oxygen species[62]), in unfortunate cases triggering a vicious cycle that is believed to underlie neurodegeneration.[75,76]

Reported risk factors for statin AEs include mild and previously clinically silent mitochondrial pathology or vulnerability and mutations affecting Q10 production.[48,77,78] These are expected to amplify oxidative stress and mitochondrial dysfunction (also diminishing energy and promoting apoptosis) in settings of statin-induced Q10 reduction.[48] In turn, persons experiencing statin AEs – a group enriched in subjects with mitochondrial pathology – show typical *increases in oxidative damage when placed on statins*.[48,79,80] Statins have themselves been found to promote mitochondrial compromise, particularly in settings of statin AEs.[20,48,78,81-95] Like statin AEs, neurodegenerative diseases including ALS show a mitochondrial predisposition[96,97] and involve mitochondrial dysfunction[96,98-100] along with an unfavourable balance of oxidative stress to antioxidant defense (both of which are promoted by statins in persons with AEs).[101-104]

Together, the above evidence suggests that in some patients subclinical mitochondrial pathology, which had been successfully 'bypassed' by adequate Q10/antioxidant activity[70,71] (perhaps driven up by mevalonate upregulation), is 'unmasked' (and/or advanced) by statin-induced reductions in Q10 and antioxidant transport. This increases prospects for clinical symptoms of mitochondrial impairment (e.g. muscle, cognitive) and for both development and acceleration of degenerative conditions such as ALS.[48] Thus, statin AEs may signal predisposition for ALS in general – and particularly for statin-induced ALS – as oxidative stress triggers new mitochondrial injury, which may lead to further elaboration of reactive oxygen species, propelling a vicious cycle. Thus too, statin AEs may signal a predisposition to unmasking or acceleration of previously triggered ALS, via statin-induced withdrawal of antioxidant, energetic and antiapoptotic protections afforded by Q10 and other fat-soluble antioxidants.

By this hypothesis, the variable time to onset of symptoms is related to several factors, including the severity of the statin-induced excess of oxidative stress in the relevant tissue (for subjects in whom pro-oxidant effects dominate); the character and severity of the mitochondrial vulnerability that was 'unmasked' or accelerated by loss of antioxidant protections; how close the organ is to a clinical threshold (how much more pathology must progress before clinical signs are evident); and whether (probabilistic) triggering of an additional mitochondrial DNA mutation is needed for induction of the ALS-promoting process in that subject (vs amplification or unmasking of existing processes that were adequately compensated, or were progressing but still preclinical).

Recently, it has been found that at least some ALS patients exhibit pathology beyond the

motor neuron *per se* – including mitochondrial pathology in muscle,[105] brain pathology,[106] and cognitive effects.[1] Our hypothesis seamlessly accounts for these 'unexpected' findings. In our statin-associated cases, muscle and cognitive symptoms linked to statins typically preceded evidence of ALS. We have previously indicated that muscle and cognitive AEs have a probable foundation in oxidative stress and mitochondrial dysfunction.[48] We suggest this may reflect a broader pattern applicable to ALS triggered by (nonstatin) oxidative stressors, and/or arising on a background of mitochondrial vulnerability, in which the same underlying processes may lead to muscle and brain pathology as well as ALS.

In contrast to the induction of oxidative stress by statins that is typical in persons exhibiting statin AEs, modest statin doses produce 'net' antioxidant effects in many or most subjects (as indexed by blood and/or urine markers of lipid peroxidation[107]). This raises the prospect that statins might, in some cases, protect against neurodegenerative conditions.

This study has limitations inherent to all case series: there is not a defined base population so that rates cannot be calculated; however, our intent is not to estimate rates and we make no assumption that rates are increased. There is no control group, which precludes calculation of risk ratios; however, this study does not seek to calculate risk ratios, and again we make no assumption regarding whether ALS rates are increased overall. Rather, we wish to highlight that statins may promote ALS in individual cases even if overall rates of ALS are unaffected or reduced. Literature suggests bidirectional effects of statins on other AEs such as proteinuria[48,108] and muscle pain.[48,109] Progressive conditions such as ALS cannot adhere to strict drug AE causality criteria, which require resolution with drug discontinuation. Yet our subjects characteristically reported abatement of symptoms with statin discontinuation, and/or worsening with statin dose increase.

There is self-selection for participation, as in all passive pharmacovigilance databases. Subjects who identified our study group and contacted us may not reflect all those with this condition. As is true for research participants generally, subjects may be better educated. Additionally, since the internet was a common mode of learning about our study group, the sample may be younger – although family members not uncommonly directed subjects to our study. However, there is little rationale for assuming that these limitations will modify the major inferences drawn. Subjects included in this study could represent a healthier or less rapidly progressing subset of those statin-associated ALS cases that initially contacted us. Reasons for this include that those deceased or placed in assisted living following initial contact will disproportionately be among those who were lost to follow-up, and the most severely affected among those remaining were disproportionately unable to complete the survey. This is expected to reflect the stage of disease as opposed to risk associations. Since higher cholesterol is linked to longer survival in those with ALS,[57] the ten subjects we present here could reflect a higher cholesterol subgroup.

Patient reports were the primary mode of ascertainment of symptom and diagnosis information, and recall or reporting bias are issues general to self-report modalities and survey designs. These concerns are somewhat mitigated by focus on a severe neurological condition for which all subjects reported having received neurological evaluation. Additionally, most subjects provided written consent for medical record verification (although success in procuring records from medical facilities proved unexpectedly challenging in some cases). Moreover, patient reports of AEs have been reported to be relevant and reliable,[110-114] and patients are inherently the gold standard for symptom reporting. Subjects' reports of physician diagnoses have a history of use in epidemiological studies examining relationships of exposures to outcomes.[115] Supporting validity of this approach, where medical records were procured, subjects' reports – uniformly including the ALS-related diagnoses – were affirmed.

Existence of putative statin-associated ALS cases need not have implications for the general effect of statins on ALS: even a causal association in *some* statin users needn't imply that *average*

increases in ALS occur with statins. Indeed, it is possible that statin antioxidant effects may dominate over pro-oxidant effects at modest statin doses in many persons.[107] Favourable effects by statins on paraoxonase activity have been reported to arise (differentially by statin, by high-density lipoprotein level and by paraoxonase genotypes[116-121]) and could confer protection against neurodegenerative disease in some or most persons.

Conclusions

Excess reporting of ALS in apparent association with lipid-lowering drug use was identified in our patient-targeted AE surveillance study prior to the corroborating reports of others,[2,3] providing independent affirmation of elevated reporting. Information from this case series, viewed in the context of a body of science linking oxidative stress and mitochondrial dysfunction to ALS, fuels concerns that a statin concordance with ALS may in some instances reflect a causal association. We proffer a hypothesis regarding a mechanism that may have explanatory merit extending to ALS cases that are not statin-associated; and to statin-associated neurodegenerative conditions that are not ALS.[122] Additionally, our observations directly suggest the testable possibility of an identifiable vulnerable subgroup, an observation of high potential importance.

Additional studies are required. Three questions should be addressed. First, do statins increase ALS overall? Second, do statins increase the risk of ALS among subsets in whom statins induce pro-oxidant effects or AEs (related constructs)? This may occur even if statins do not increase or even if they reduce ALS risk overall. Finally, do statins accelerate ALS, hastening its clinical presentation or progression in general or only in individuals where statins have pro-oxidant effects?

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