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Statins, Neuromuscular Degenerative Disease and an Amyotrophic Lateral Sclerosis-Like Syndrome

An Analysis of Individual Case Safety Reports from Vigibase

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Abstract

Background: The WHO Foundation Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre [UMC]) has received many individual case safety reports (ICSRs) associating HMG-CoA reductase inhibitor drug (statin) use with the occurrence of muscle damage, including rhabdomyolysis, and also peripheral neuropathy. A new signal has now appeared of disproportionally high reporting of upper motor neurone lesions.

Aim and Scope: The aim of this paper is to present the upper motor neurone lesion cases, with other evidence, as a signal of a relationship between statins and an amyotrophic lateral sclerosis (ALS)-like syndrome. The paper also presents some arguments for considering that a spectrum of severe neuromuscular damage may be associated with statin use, albeit rarely. The paper does not do more than raise the signal for further work and analysis of what must be regarded as a potentially very serious and perhaps avoidable or reversible adverse reaction, though it also suggests action to be taken if an ALS-like syndrome should occur in a patient using statins.

Methods: The 43 reports accounting for the disproportional reports in Vigibase (the database of the WHO Programme for International Drug Monitoring) are summarised and analysed for the diagnosis of an ALS-like syndrome. The issues of data quality and potential reporting bias are considered.

Results: 'Upper motor neurone lesion' is a rare adverse event reported in relationship to drugs in Vigibase (a database containing nearly 4 million ICSRs). Of the total of 172 ICSRs on this reported term, 43 were related to statins, of which 40 were considered further: all but one case was reported as ALS. In 34/40 reports a statin was the sole reported suspected drug. The diagnostic criteria were variable, and seven of the statin cases also had features of peripheral neuropathy. Of a total of 5534 ICSRs of peripheral neuropathy related to any drug in Vigibase,

547 were on statins. The disproportional reporting of statins and upper motor neurone lesion persisted after age stratification, and such disproportionality was not seen for statins and Parkinson's disease, Alzheimer's disease, extrapyramidal disorders, or multiple sclerosis-like syndromes.

Discussion: Because the cases were sometimes atypical we propose the use of the term 'ALS-like syndrome' and speculate whether this is part of a spectrum of rare neuromuscular damage. The diagnosis of ALS is often problematic, and the insidiousness and chronicity of the disease make causality with a drug difficult to assess. The disproportionally high reporting makes this an important signal nevertheless, since ALS is serious clinically and statins are so widely used. Wide use of the statins also makes a chance finding more probable, but is unlikely to cause disproportional reporting when there are no obvious biases identified.

Conclusion: We emphasise the rarity of this possible association, and also the need for further study to establish whether a causal relationship exists. We do advocate that trial discontinuation of a statin should be considered in patients with serious neuromuscular disease such as the ALS-like syndrome, given the poor prognosis and a possibility that progression of the disease may be halted or even reversed.

Background

The HMG-CoA reductase inhibitors or 'statins' are one of the most widely used classes of drugs. They have been studied in many clinical trials and have been prescribed for millions of patients. The effectiveness of statins in the treatment of dyslipidaemia has been extensively documented.

Statins are associated with a range of adverse effects. The possibility of peripheral neuropathy in association with statins has been reviewed and appears real, but rare.[1-3]

Statins are also known to be associated with myalgia and myopathy. These adverse effects are noted in the individual Summary of Product Characteristics of each statin, although one recent systematic review of controlled trials failed to show any increased risk of muscle disorders with statins.[4] Rhabdomyolysis has been a highly publicised adverse effect of statins but is rare, with a reported incidence of about 0.3–13.5 cases/million statin prescriptions.[5] The possible mechanisms by which statins may cause muscle damage are under investigation, and no single mechanism is yet agreed upon,[6,7] but one paper emphasises the potential for serious muscular damage from statins, as well as suggesting a mechanism and treatment.[7]

A new signal has now appeared of disproportionally high reporting of upper motor neurone lesions and statins in Vigibase (the database of the WHO Programme for International Drug Monitoring). The signal showed statistically, based on the data mining and clinical triage used by the Uppsala Monitoring Centre. In light of this possible connection, we reviewed individual case safety reports (ICSRs) in Vigibase with the WHO-Adverse Reaction Terminology (ART) preferred term 'upper motor neurone lesion' with the subordinated term 'amyotrophic lateral sclerosis'. The details of the cases found are presented here.

As well as reporting the details of the ALS-like cases found on Vigibase, this study also considers information on both nervous and muscle tissue damage for the following reasons, each of which is

important as a signal on this very widely used group of drugs:

- Neurological and muscular damage may present with weakness and pain in the limbs (though the pathology may be different), therefore clinical diagnosis may be confusing early on.[8] (ALS is one of the neurological disorders in which serum creatine phosphokinase levels may be moderately increased, which may lead to confusion with myopathies.)
- Confusion may be carried over into the words used to convey the meaning of the free text in health professional or consumer case reports and into searchable database terms.
- Muscle wasting may occur after neural damage and may appear acutely with peripheral neuropathy. One paper has proposed mechanisms for muscle and nerve damage with statins as well as reporting four cases of severe neuromuscular degeneration.[9] In one of the cases there was tongue atrophy, muscle twitching and weakness, and evidence of muscle denervation and re-innervation 4 months after stopping statin therapy. This is perhaps the first report of a patient with ALS-like syndrome while receiving statin therapy, to which we now add a case series of similar reports.
- ALS is a rare, fatal, progressive, degenerative motor neurone disease with an overall prevalence of about 5 in 100 000 individuals.[10] There is a need to investigate both the incidence and aetiology further, with particular consideration given to the fact that central neurotoxicity may occur in some patients using statins.
- Recently, it has been suggested that statins may be protective of neurodegenerative disease, although experimental evidence, from *in vivo* and *in vitro* studies, points in both directions.[11-14]

All of the above reasons and the varying results of the experimental studies on neurons make it important that the following clinical cases of ALS are reported here as suspected ICSRs. They may represent a signal that, in rare instances, statins may cause or provoke ALS or a severe, chronic neuromuscular damage with ALS-like features, or they may be a signal of a difficult diagnostic problem, where a chance relationship cannot be ruled out.

There are several internet sites with queries and discussions from the public about a possible connection between statins and ALS from 2006,[15,16] where many referrals are to Dr Duane Graveline and his website on the adverse effects on statins.[17] Public concern raises the question of potential reporting bias, which has been considered in this paper.

Methods

In screening Vigibase for disproportional reporting rates, a data mining method was used based on a robust statistical measure, the Information Component (IC).[18] Positive IC values represent drug-adverse reaction pairs that are reported together more frequently than expected based on the overall reporting of the drug and adverse reactions in Vigibase. For clarity, we also calculated observed and expected values. We searched Vigibase for ICSRs where the WHO-ART preferred term 'upper motor neurone lesion', with the subordinated term 'amyotrophic lateral sclerosis', was reported for drugs in the HMG-CoA reductase inhibitors group (according to the anatomical therapeutic chemical (ATC) classification).

Duplicate reports are randomly distributed in Vigibase therefore they were not excluded from calculations of the observed and expected reporting rates against the Vigibase report background but they are excluded in the detailed clinical review. We did not make any comparison between drugs, since such comparisons from ICSRs should be considered very cautiously, particularly when small numbers are involved.

We investigated the potential for disproportional reporting against all statins of other nervous system

degenerative disease, such as Parkinson's disease, extrapyramidal disorder, multiple sclerosis-like syndromes, Alzheimer's disease, as well as tongue disorders in general. This acted as some check against age bias and as a control for reporting disproportionality compared with other, common, neurodegenerative syndromes (or a typical ALS feature in the case of tongue disorder). Also, due to discussions about ALS and statins on the Internet, we reviewed when the ICSRs were sent to the national pharmacovigilance centre as a check for potential reporting bias.

Results

Following our search, 43 cases reporting a statin and the preferred WHO-ART term 'upper motor neurone lesion' were extracted from Vigibase. The actual reported term was 'amyotrophic lateral sclerosis' for all but one report, where the coded term was 'upper motor neurone lesion'. One report included both atorvastatin and simvastatin as the suspected drugs. Three reports (all involving atorvastatin) were excluded from the detailed case review because two were considered to be possible duplicates and the third report listed 61 adverse reactions, which made it unfeasible to evaluate.

Table I is a 'line listing' of some essential information mentioned in the 40 reports included in the detailed case review, particularly the reporting terms. There was a great deal more free text information available on many of the reports, but this could not be included here for reasons of patient confidentiality.

Of the 40 reports, 36 originated from the US, and one report each originated from the UK (simvastatin), Denmark (atorvastatin), France (simvastatin) and The Netherlands (rosuvastatin).

The reports involved 24 men and 15 women (sex was not specified in one report). The median age of the patients in the reports was 69 years (range 40–80 years); age was not specified for 7 reports. In 23 reports, the ICSR was supported by information from a physician, in four cases by a pharmacist and in two cases by a nurse. Ten ICSRs were consumer reports and in one report the notifier was unspecified

For 34 of the 40 reports, the statin was reported as the single suspected drug. Five of the atorvastatin reports included co-suspected drugs: doxycycline, fenofibrate, losartan and nicotinic acid, and one report with the co-reported term thrombosis listed both sotalol and warfarin. One of the cerivastatin reports included gemfibrozil as a co-suspected drug with co-reported rhabdomyolysis. The full list of co-reported drugs is shown in table I.

Table I also details the co-morbidities reported in the ICSRs. These indicate the varying clinical pictures amplified in the free text. Co-reported neurological terms atypical for ALS were (with number of reports within parenthesis): ataxia (3), dyskinesia (1), coordination abnormal (1), hypoaesthesia (2), paraesthesia (1) and peripheral neuropathy (4). On the other hand, for ten cases, speech disorder was co-reported, of which four cases also reported dysphagia and two cases reported tongue disorders. A third report of tongue disorder was co-reported as a single event with ALS. Abnormal electromyograms were reported for 11 cases, eight of which were consistent with ALS.

Because of the unusual occurrence of motor and sensory peripheral neuropathy in seven cases, it is worth noting that statins were overall the most frequently reported suspected cause of 'upper motor neurone lesion' (43 of a total of 172 cases in the database) and were also high among reports of the preferred term 'peripheral neuropathy' (547 of a total of 5534 cases in Vigibase).

In 14 reports the time to onset (start of statin therapy until ALS onset) could be determined and varied from 1 to 3 months (six reports), 8–14 months (six reports) and 2 years or more (two reports).

The clinical outcomes were assessed from information on the reports; seven patients died (although one patient may have died from causes unrelated to

Table I. Forty individual case safety reports from Vigibase (the database of the WHO Programme for International Drug Monitoring) with HMG-CoA reductase inhibitors and the WHO-Adverse Reaction Terminology preferred term 'upper motor neurone lesion'. The reports are listed in the order of when they were entered in Vigibase and Vigibase data is complemented with details from the original reports on notifier and outcome

Age (y)/ gender	Year received by the national centre	Notifier	Adverse reactions	Outcome	Suspected drugs	Concomitant drugs
71/female	1997	P	Amyotrophic lateral sclerosis; death; dysarthria	D	Simvastatin	Aspirin (acetylsalicylic acid [ASA]); amlodipine/benazepril hydrochloride; riluzole
69/female	1998	P	Amyotrophic lateral sclerosis; asthenia; electromyogram-brachial plexopathy; muscle contractions involuntary; paraesthesia	NR	Simvastatin	Atenolol
58/male	1999	P	Amyotrophic lateral sclerosis; diabetes mellitus; laboratory test abnormality	NR	Simvastatin	Diltiazem
67/male	1998	P	Amyotrophic lateral sclerosis; asthenia; confusion; dysarthria; fall; myocardial infarction	NR	Atorvastatin; losartan	ASA; fluticasone; lovastatin
58/male	2000	C	Amyotrophic lateral sclerosis; dysarthria; dysphagia; fatigue; joint stiffness; Lyme's disease	NR	Atorvastatin; doxycycline	Baclofen
70/male	1999	C	Amyotrophic lateral sclerosis; calcaneal spur; muscle weakness; myalgia	NR	Atorvastatin	
74/female	1999	PH	Amyotrophic lateral sclerosis; tongue disorder	NR	Simvastatin	Insulin
69/male	1999	P	Amyotrophic lateral sclerosis; asthenia; balance difficulty; enzyme abnormality; fall; myopathy	NR	Atorvastatin	ASA; dilitazem
44/male	1999	P	Amyotrophic lateral sclerosis; back pain; coordination abnormal; creatine phosphokinase increased; dysarthria; neuropathy peripheral	R+S	Atorvastatin	
70/male	1999	C	Amyotrophic lateral sclerosis	NK	Simvastatin	
74/female	2000	P	Amyotrophic lateral sclerosis	NR	Atorvastatin	Metoprolol
72/female	2001	N	Amyotrophic lateral sclerosis; balance difficulty; dysarthria; dyskinesia; dysphagia	NR	Cerivastatin	ASA; atenolol/chlortalidone
54/male	2001	P	Amyotrophic lateral sclerosis	NR	Atorvastatin; fenofibrate	Levothyroxine
66/male	2001	N	Amyotrophic lateral sclerosis	D	Cerivastatin	

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Table I. Contd

Age (y)/ gender	Year received by the national centre	Notifier	Adverse reactions	Outcome	Suspected drugs	Concomitant drugs
78/female	2002	P	Amyotrophic lateral sclerosis; asthenia; joint dysfunction; muscle atrophy; myopathy toxic; neuromuscular disorder NOS; peroneal nerve palsy; upper motor neurone lesion; walking difficulty	NR	Lovastatin	Tocopherol (vitamin E); riluzole; Ascorbic acid (vitamin C); ASA; Candesartan; betacarotene
80/male	2002	P	Amyotrophic lateral sclerosis; asthenia; death; disease progression NOS; speech disorder	D	Cerivastatin	
74/female	2002	C	Amyotrophic lateral sclerosis; asthenia	NR	Simvastatin	
NK/female	2002	C	Amyotrophic lateral sclerosis	NR	Cerivastatin	
65/male	2002	PH	Amyotrophic lateral sclerosis; condition aggravated	NR	Atorvastatin	ASA
73/male	2002	P	Amyotrophic lateral sclerosis; abasia; asthenia; chest pain; creatine phosphokinase increased; dysstasia; electromyogram abnormal; muscle atrophy; pain in extremity; peroneal nerve palsy; polyneuropathy NOS; rhabdomyolysis	NR	Simvastatin	Hydrochlorothiazide
72/male	2002	P	Amyotrophic lateral sclerosis	NR	Cerivastatin	Quinapril; temazepam; ranitidine; hydrochlorothiazide; ibuprofen; finasteride; atenolol
68/female	2002	P	Amyotrophic lateral sclerosis; creatine phosphokinase increased; rhabdomyolysis	D	Gemfibrozil; cerivastatin	
NK/NK	2003	P	Amyotrophic lateral sclerosis; creatine phosphokinase increased; muscle atrophy	R+S	Atorvastatin	
NK/female	2003	PH	Amyotrophic lateral sclerosis	NR	Atorvastatin	
64/female	2004	NK	Amyotrophic lateral sclerosis; dysphagia; speech disorder; throat irritation	NR	Simvastatin	Dosulepin; isocarboxazid

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Table I. Contd

Age (y)/ gender	Year received by the national centre	Notifier	Adverse reactions	Outcome	Suspected drugs	Concomitant drugs
54/male	2003	P	Amyotrophic lateral sclerosis; antinuclear factor test positive; anxiety; bursitis; benign prostatic hyperplasia; back pain; creatine phosphokinase increased; dermatitis contact; demyelination; erectile dysfunction; hyperreflexia; intervertebral disc protrusion; injection site bullae; joint crepitation; muscle atrophy; myopathy; nerve root compression; neuropathy; osteoarthritis spinal; polytraumatism; penis disorder; pain; spondylosis	R+S	Simvastatin	Pneumococcal vaccine; influenza virus vaccine polyvalent; ASA; alprazolam; paracetamol (acetaminophen)/hydrocodone bitartrate; enalapril; fenofibrate; pravastatin; metoprolol; clonidine
NK/female	2003	P	Amyotrophic lateral sclerosis; muscle weakness; tongue pain; tongue dry; speech disorder	R+S	Atorvastatin	Terbutaline; budesonide
40/male	2004	C	Amyotrophic lateral sclerosis; asthenia; balance difficulty; creatine phosphokinase increased; electromyogram abnormal; fall; muscle cramp; spastic gait	NR	Atorvastatin; simvastatin	Quinapril
73/female	2004	C	Amyotrophic lateral sclerosis	D	Atorvastatin	
60/male	2004	P	Amyotrophic lateral sclerosis; creatine phosphokinase increased; drug interaction	NR	Atorvastatin; nicotinic acid	Metoprolol; hydrochlorothiazide/ triamterene
NK/male	2004	P	Amyotrophic lateral sclerosis	D	Atorvastatin	
71/male	2004	C	Amyotrophic lateral sclerosis; coughing; hypersensitivity; numbness oral; pain in extremity; weight decrease	D	Simvastatin	
46/male	2004	C	Amyotrophic lateral sclerosis; thrombosis; walking aid user	NR	Atorvastatin; warfarin; sotalol	
70/male	2005	PH	Amyotrophic lateral sclerosis; hypoaesthesia	NR	Rosuvastatin	Colecalciferol/calcium carbonate; amlodipine
64/male	2003	P	Upper motor neurone lesion; creatine phosphokinase increased	R+S	Simvastatin	
80/male	2005	P	Amyotrophic lateral sclerosis; dysarthria; dysphagia	NR	Atorvastatin	Amlodipine
68/female	2005	P	Amyotrophic lateral sclerosis; dysarthria; tongue oedema	NK	Rosuvastatin	
NK/female	2005	P	Amyotrophic lateral sclerosis	NR	Atorvastatin	

Continued next page

Table I. Contd

Age (y)/ gender	Year received by the national centre	Notifier	Adverse reactions	Outcome	Suspected drugs	Concomitant drugs
NK/male	2005	C	Amyotrophic lateral sclerosis; muscle weakness; muscle contractions involuntary; skin dry	NR	Atorvastatin	
68/male	2005	P	Amyotrophic lateral sclerosis; anaemia; anxiety; bronchitis chronic; cachexia; cervical myelopathy; denervation atrophy; drug ineffective; feeling cold; hepatic atrophy; impared self-care; inflammation; insomnia; leg pain; lymphadenopathy; muscle mass; myopathy; muscle atrophy; myositis; spinal osteoarthritis; pain; paraneoplastic syndrome; polymyalgia rheumatica; quadriplegia; respiratory disorder; spinal stenosis; tension	R	Rosuvastatin	Verapamil; tadalafil

C = consumer; **D** = died; **N** = nurse; **NK** = not known; **NOS** = not otherwise specified; **NR** = not recovered; **P** = physician; **PH** = pharmacist; **R** = recovered; **R+S** = recovered with sequelae.

the ALS-like disease); 25 patients had not recovered and appeared static clinically at the time of reporting; five patients seemed to have made some recovery though with sequelae, and one patient had recovered. The clinical outcomes of the remaining two patients were unknown/not assessable. It is noteworthy that four of five patients that made some recovery were among eight patients with an increased creatine phosphokinase level reported at some time during their illness.

The observed and expected number of reports and the corresponding IC values for the HMG-CoA reductase inhibitors ATC group for all the relevant neuromuscular terms reported to the database are reported in table II.

Table III gives the year when the 40 reports of ALS and the different statins were received at the relevant national pharmacovigilance centre.

We investigated the disproportional reporting for other nervous system degenerative diseases and in only the case of atorvastatin/Alzheimer's disease was there a significant disproportionality. For ALS, the disproportionality persisted after stratification for age.

In the review of when the national pharmacovigilance centres received the ICSRs, we found an irregular reporting pattern since the end of 1997, and 27 of the 40 reports were received before 2004 (table III). This reduces the possibility of reporting bias in more than half of the reports

Discussion

Although all severe neurological or muscular events after the use of statins seem to be rare in a group of commonly used and beneficial medicines, there is evidence for a range of muscle disorders that vary in severity from myalgia to rhabdomyolysis (table II), and there has already been much public concern over the rare rhabdomyolysis associated with the use of statins.[19]

Table II. Observed and expected reporting rates and information component (IC) values for statins with nervous (central and peripheral) and muscle disorders

WHO-ART preferred term	Observed no. of reports	Expected no. of reports	IC	IC025[a]
Upper motor neurone lesion	43	3.96	3.28	2.86
Peripheral neuropathy	547	127.56	2.10	1.97
Myalgia	14277	1415.14	3.33	3.31
Myopathy	3271	146.30	4.48	4.44
Rhabdomyolysis	8278	254.48	5.02	5.00

a Lower 95% credibility interval.

ART = Adverse Reaction Terminology.

Turning to neurological disorders, peripheral neuropathy is less frequently reported than myalgia and myopathy (table II).

The ICSRs presented in this investigation underline the possibility that severe, chronic and persistent neuromuscular problems may occur with a picture that may be difficult to distinguish from ALS, and that it seems likely to be a class effect. We are concerned that the long-term and very broad use of these drugs is likely to lead to their being overlooked as a possible cause of neuromuscular events by both patients and health professionals.

The information we present is heterogeneous and incomplete, as it often is in ICSRs, but nevertheless important as a signal for the following reasons:

- The incidences of all neuromuscular events related to statins need to be properly ascertained.
- The current literature is unclear regarding serious events such as myopathy and neuropathy associated with statins, even to the extent of a mixed view of the pathophysiology.
- We now add information of a signal of an 'ALS-like syndrome', which may further add to the confusion. However, in general, muscle weakness is associated with a number of diseases with a relatively poor prognosis, and this is particularly true of ALS. The recognition of a possible causal link (and, if there is one, its nature) between statins and an ALS-like syndrome, neuropathy or myopathy may help avoid anxiety over diagnosis and even progression of the disease. Whether it would be possible to prevent the progression of the disease is likely to depend upon timely diagnosis and discontinuation of the statin.
- The limited information we present here is consistent with a statin-related 'ALS-like syndrome', which might be a primarily myopathic disorder presenting with an ALS-like picture, or a variant of ALS, despite the atypical nature of some of the cases. The finding of raised CPK values in five patients does not necessarily help in determining whether the patients had 'true' ALS or not, though a raised CPK may be an important prognostic indicator since four of the five showed some clinical improvement after discontinuing the statin.
- We also need to consider that the association between ALS-like syndrome and statins is a chance finding. However, the great disproportionality, lack of obvious reporting biases in our cases and some limited pathophysiological support[9] all make this less likely. We have tried to exclude some obvious biases by stratifying for age and by looking at the timing of the reports

Table III. Number of reports and year when the reports were received at the national centre (NC) with statins and 'upper motor neurone lesion'

Year at NC	No. of reports
1997	1
1998	2
1999	6
2000	2
2001	3
2002	8
2003	5
2004	7
2005	6

(67% of the cases were reported before the public debate started).

- The mechanism(s) causing the adverse effects will need to be elucidated to try to prevent some patients, possibly at risk by genetic predisposition and/or age, developing them. This must include consideration of the possible links between, and progression of, one type of neuromuscular damage to another, or that patients with early ALS may be worsened by the development of a myopathy.
- The clinical presentation of myopathy, and muscle changes related to neuropathies, may also confuse the picture and need more research. In one of the four published cases,[9] denervation and re-innervation were diagnosed by an electromyogram. In all four of the cases that had severe neuromuscular degeneration, serum creatine phosphokinase levels were increased, further confusing the diagnostic picture.

The signal itself may be regarded as somewhat speculative, because of the long duration between the statin administration and presentation of the disease, and because of consumer reports. However, consumer reports are very important when considering new, unexpected adverse events since there may be less likelihood both for a health professional to believe in the link, or to report a specific diagnosis. There are several instances where consumer reports have been critical in making such associations.[20,21]

There is a classic paradox in presenting this signal: we may be accused of raising an unsupported scare against a useful group of drugs. However, with rare and unexpected events and a long time lag between starting the medicine and the event, there is no alternative way of proceeding other than raising awareness of the possibility of an association between the drug and the disease. This is because healthcare databases are unlikely to be large enough or indeed have all the relevant information. Case control studies would also be very difficult for similar reasons of size and adequacy of data. Moreover, in our experience, funding for such a large study is unlikely to be forthcoming using the argument that the hypothesis is weak. In any case, considerable time is likely to elapse between starting a study and reaching conclusions, during which time more people may have been affected and information and misinformation that may be misleading or exaggerate the problem will continue to be posted on the Internet.

The reports referred mainly to ALS as the diagnosis, but at this stage it may be better to use the term ‘ALS-like syndrome’. The case details we have vary in quality and quantity, though several were very descriptive. It seems clear that there are features that are not typical of ALS in some of the cases, as already mentioned, but this detracts neither from the possibility of an important consideration in differential diagnosis nor from the seriousness of the patient’s state with progression of the condition while using statins.

Conclusion

The very high use of statins mandates that the possibility of serious neuromuscular adverse reactions be clarified urgently. In the meantime, it seems wise that patients using statins with severe neuromuscular symptoms should consider stopping the statin, under medical supervision, and in the absence of an urgent clinical need for their continuation.

However, we hope that this signal will be accepted not as anything more than a hypothesis that needs to be followed up to ensure the safer use of an important group of medicines.

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