Amyotrophic lateral sclerosis associated with statins. A disproportionality analysis of the WHO Program for International Drug Monitoring database (VigiBase)

Diego Macías Saint-Gerons¹ · José Luis Castro¹

Received: 18 May 2018 / Accepted: 22 May 2018 / Published online: 23 November 2018
© Pan American Health Organisation (PAHO) 2018

Statins have been found to be associated with peripheral neuropathy and muscle adverse reactions such as weakness, increased fatigability, myopathy, and rhabdomyolysis [1]. In addition, sporadic cases of amyotrophic lateral sclerosis (ALS) with statins have been also reported and disproportionality for the ALS and statins has been observed in a recent analysis of the FAERS database [1–3].

We searched in VigiBase for individual case reports (ICSRs) in which the MedDRA preferred term “Amyotrophic lateral sclerosis (ALS)” was reported for HMG-CoA reductase inhibitors according to the anatomical therapeutic chemical (ATC) classification. A de-duplicated dataset version of VigiBase with 16,619,231 ICSR was used to minimize the risk of identifying duplicate reports. Disproportional reporting was investigated through frequentist and Bayesian approaches by the calculation of the reporting odds ratio and the information component (IC) respectively. Cumulative RORs by year were also calculated.

Following our search, 903 ICSR of ALS were found. From these, 220 ICSR reported a statin and ALS. The median age of the patients in the reports was 63 years old (range 32–84). The reports involved 140 (63.6%) men and 67 (30.5%) women; sex was not specified in 13 (5.9%) reports. Of the 220 ICSR, 107 (49%) were reported by health professionals and 48 (22%) by consumers or lawyers; reporting source was not specified in 59 (27%) reports. By regions, the reports originated in America 188 (85.5%), Europe 28 (12.7%), Asia 3 (1.4%), and Africa 1 (0.5%). From

the 15 different countries in where the reports were originated, the USA contributed the most with 183 ICSR (83.2%). For 77 (35.0%) ICSR, there was available information on the outcome at the time of reporting: 13 died, 41 did not recover, 8 seemed to have made some recovery though with sequelae, 8 were recovering, and 7 recovered.

A statistically significant disproportionality was found for most individual statins (Table 1). The signal of ALS and statins has been strengthened for the drug-class over time. Nevertheless, the cumulative analysis of the RORs (Fig. 1) suggest a potential notoriety bias in 2008 (and 2009) consistent with the concerns and discussions from the public about a possible connection between statins and ALS published in previous data mining studies [2, 3].

Causal associations cannot (and should not) be made using data from spontaneous reports. Signals coming from spontaneous report warrant additional epidemiological and clinical investigations and a further confirmation in controlled studies are usually required [3]. However, the evidence available from controlled clinical studies has yielded conflicting results. In 2008, a pooled analysis from data provided by the drug manufacturers to the FDA (not publicly available) found an overall incidence rate of ALS of 4.2 per 100,000 person-years and 5.0 per 100,000 person-years for statin and placebo respectively (rate ratio 0.85, 95% CI 0.34–2.08) [4]. On the other hand, a population-based case-control study in the Netherlands including 722 sporadic ALS found a protective effect of statins (odds ratio 0.45, 95% CI 0.35–0.59) [5]. The pooled analysis of three observational studies (128,405 patients) included in a systematic review was inconclusive for the comparison of ALS risk for statin versus non-statin groups (rate ratio 0.89, 95% CI 0.55–1.42).

The analyses carried out to date could be statistically underpowered to detect risk differences for ALS whose

✉ Diego Macías Saint-Gerons
dmacias.sg@gmail.com

¹ Unit of Medicines and Health Technologies (MT); Dep. of Health Systems and Services (HSS), Pan American Health Organization (PAHO/WHO), 525 23rd St NW, Washington DC 20037, USA

Table 1 Information component (IC) and reporting odds ratio (ROR) values for statins and ALS

	Observed no. of reports	Expected no. of reports	IC	IC 025	ROR (CI 95%)	ROR (CI 95%) excluding reports from the USA
Atorvastatin	115	5.21	4.34	4.06	25.17 (20.51–30.74)	10.18 (5.35–17.74)
Simvastatin	57	3.32	3.91	3.51	18.28 (13.72–23.92)	7.25 (3.28–13.99)
Lovastatin	18	0.9	3.72	2.98	20.29 (11.97–32.27)	
Rosuvastatin	33	2.62	3.42	2.89	13.03 (8.91–18.43)	
Ezetimibe; simvastatin	9	0.32	3.54	2.45	28.64 (13.05–54.65)	
Pravastatin	8	0.96	2.54	1.37	8.37 (3.60–16.57)	13.07 (3.53–33.87)
Cerivastatin	7	0.78	2.55	1.29	9.08 (3.64–18.79)	
Fluvastatin	5	0.39	2.63	1.10	12.86 (4.16–30.14)	5.71 (0.14–32.10)
Lovastatin; nicotinic acid	1	0.03	1.51	–2.29	35.84 (0.90–201.10)	
Pitavastatin	1	0.23	1.04	–2.76	4.32(0.11–24.13)	

IC 025: Lower credibility interval of the IC; note: positive IC values (including the lower 95% credibility interval) represent drug-adverse reaction pairs that are reported more frequently than expected. Similarly, ROR (with their 95% confidence interval) results > 1.0 indicate a higher than expected reporting rate. ICSRs can include reports of several suspected statins

Fig. 1 Cumulative RORs of statins and ALS by year. **a** Analysis for all the ICSRs included in Vigibase (on top). **b** Analysis excluding the ICSRs from the USA

worldwide annual incidence has been estimated to be 1.9 per 100,000 [6]. Despite big population samples and longer follow-up could be available in the so-called *statinization era* [7], large pharmacoepidemiological studies based on electronic health care databases analyzing the risk of ALS associated to statins are lacking. Moreover, there is much evidence already existent from large RCTs that has not yet be considered and critically assessed [8].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the Pan American Health Organisation (PAHO), its Board of Directors, or the countries they represent.

Open Access This article is licensed under the terms of the Creative Commons Attribution 3.0 IGO License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the Pan American Health Organisation, provide a link to the Creative Commons licence and indicate if changes were made.

The use of the Pan American Health Organisation's name, and the use of the Pan American Health Organisation's logo, shall be subject to a separate written licence agreement between the Pan American Health Organisation and the user and is not authorized as part of this CC-IGO licence. Note that the link provided above includes additional terms and conditions of the licence.

The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.

To view a copy of this licence, visit <http://creativecommons.org/licenses/by/3.0/igo/>

References

1. Golomb BA, Verden A, Messner AK, Koslik HJ, Hoffman KB (2018) Amyotrophic lateral sclerosis associated with statin use: a disproportionality analysis of the FDA's Adverse Event Reporting System. *Drug Saf* 41:403–413. <https://doi.org/10.1007/s40264-017-0620-4>
2. Edwards IR, Star K, Kiuru A (2007) Statins, neuromuscular degenerative disease and an amyotrophic lateral sclerosis-like syndrome: an analysis of individual case safety reports from vigibase. *Drug Saf* 30:515–525
3. Colman E, Szarfman A, Wyeth J, Mosholder A, Jillapalli D, Levine J, Avigan M (2008) An evaluation of a data mining signal for amyotrophic lateral sclerosis and statins detected in FDA's spontaneous adverse event reporting system. *Pharmacoepidemiol Drug Saf* 17: 1068–1076
4. Seelen M, van Doormaal PT, Visser AE, Huisman MH, Roozkrans MH, de Jong SW, van der Kooij AJ, de Visser M, Voermans NC, Veldink JH, van den Berg LH (2014) Prior medical conditions and the risk of amyotrophic lateral sclerosis. *J Neurol* 261(10):1949–1956
5. Zheng Z, Sheng L, Shang H (2013) Statins and amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Amyotroph Lateral Scler Frontotemporal Degener* 14:241–245
6. Chiò A, Logroscino G, Traynor BJ, Collins J, Simeone JC, Goldstein LA, White LA (2013) Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. *Neuroepidemiology* 41(2):118–130
7. Ioannidis JP (2014) More than a billion people taking statins? Potential implications of the new cardiovascular guidelines. *JAMA* 311:463–464
8. Yusuf S, Lonn E, Pais P, Bosch J, López-Jaramillo P, Zhu J et al (2016) Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 374(21):2021–2031