

**SAFETY ANALYSIS INSIGHT**

## Statin-Associated Myasthenia Gravis

### A postmarketing study in WHO's pharmacovigilance database

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## Abstract

The aim of this study was to measure the disproportionality of the combination of exposure to statins and the occurrence of myasthenia gravis recorded in the World Health Organization (WHO)'s global individual case safety report database (VigiBase®).

**Methods:** We conducted a retrospective analysis of Individual Case Safety Reports (ICSRs), with 2022Q4 cut-off dates in the VigiBase®, in which statins were associated with myasthenia gravis events. We used the Multiitem Gamma Poison Shrinker (MGPS) Bayesian data mining method for signal generation. Besides that, we calculated the Information component (IC) with 95% confidence interval, frequently applied disproportionality analysis method.

**Results:** A total of 358 cases were retrieved from VigiBase®. The results revealed statistically significant signals for the following combinations: PT: Ocular myasthenia and atorvastatin ( $EB05=2.375$ ) and myasthenia gravis and rosuvastatin ( $EB05=2.138$ ), using EBGm and its lower 90% confidence bound (i.e.,  $EB05$ ) as a parameter of disproportionality. However, when  $IC025$  was considered as a disproportionality measure, additional drug-event combinations satisfied criteria for statistically significant signals: myasthenia gravis and atorvastatin ( $IC025=0.704$ ), neuromuscular blockade and atorvastatin ( $IC025=0.109$ ), myasthenia gravis and fluvastatin ( $IC025=0.339$ ), neuromuscular blockade and lovastatin ( $IC025=0.555$ ), myasthenia gravis and pravastatin ( $IC025=0.466$ ), myasthenia gravis and simvastatin ( $IC025=0.833$ ).

**Conclusion:** Our findings suggest an increased risk for myasthenia gravis in patients receiving statins. Although this risk seems to be low, considering statins are increasingly prescribed, close monitoring of patients for symptoms of myasthenia gravis should be considered during long-term treatment with statins.



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## Introduction

Statins block the rate limiting step of cholesterol synthesis in which 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) is transformed to mevalonate by the enzyme HMGCR. However, the cholesterol biosynthetic pathway is also involved in the synthesis of dolichols, the production of ubiquinone (coenzyme Q10), and in the process of prenylation, an important post-transcriptional protein modification. Of note, dolichols are required for glycoprotein synthesis and ubiquinone plays an important role in muscle cell energy<sup>1</sup>.

The main beneficial effect of statins is lipid-lowering effect. A large body of evidence from randomized, controlled trials shows that statins reduce the risk of major vascular events<sup>2</sup>. Since cardiovascular disease is currently one of the most important health problems in the world, statins are increasingly prescribed.

Despite the benefits of statins in patients at risk for cardiovascular events that are without a doubt present, they also have the potential to cause side effects. One of the best documented side effects in observational studies and clinical trials is an increased risk of myopathy, due to the direct effect of statins in the muscle, or an autoimmune myopathy associated with autoantibodies targeting HMGCR<sup>1</sup>. More rarely, statins have been linked to autoimmune diseases such as lupus-like syndrome, dermatomyositis, polymyositis, and immune-mediated necrotizing myopathy<sup>3,4</sup>.

Even though statin-induced myopathy is well-known, the effect of cholesterol-lowering agents on myasthenia gravis has not been studied in detail. In literature, several case reports indicated possible association of statins and the induction or exacerbation of myasthenia gravis<sup>5,6,7,8</sup>. In addition, one prospective study investigated statin use and its effects among patients with baseline myasthenia gravis, and the results indicated worsening of myasthenia gravis in 11% of patients<sup>9</sup>.

In view of the small number of cases of statin-associated myasthenia gravis in literature (relative to huge number of statin prescriptions), the risk of myasthenia gravis is probably low. However, the incidence has probably been underestimated since statin-induced myasthenia gravis is not widely known among healthcare professionals and is not mentioned in the SmPC for the various statins on the market<sup>9</sup>. However, according to the

recent PRAC recommendations on signals from 12th January 2023, for all statins: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin and other relevant fixed dose combinations; pravastatin, fenofibrate; simvastatin, fenofibrate, labelling documents should be updated to reflect that statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia.

The aim of our study was to measure the disproportionality of the combination of exposure to statins and the occurrence of myasthenia gravis recorded in the World Health Organization (WHO)'s global individual case safety report database (VigiBase®).

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## Methods

### Source Data

The Oracle Health Sciences Empirica Signal application was used to retrieve the source data and perform the statistical evaluation of retrieved data. The events of interest were retrieved at PT level of the MedDRA (version 25.0) with 2022Q4 cut-off dates. VigiBase, the WHO global database of reported potential side effects of medicinal products, developed, and maintained by the Uppsala Monitoring Centre was selected as the primary data source to assess the risk of myasthenia gravis in patients on therapy with statins.

### Database Query

Data was retrieved for the following drugs: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, and fixed combinations: fenofibrate and pravastatin, fenofibrate and simvastatin.

The data mining strategy included the following MedDRA Preferred terms (PTs): Myasthenia gravis, Myasthenia gravis crisis, Myasthenia gravis neonatal, Ocular myasthenia, Neuromuscular blockade, and Recurrence of neuromuscular blockade.

Data mining runs were created to retrieve drug event combinations related to the categories of either “suspected/interacting” or “concomitant” to reveal potential associations unsuspected by the reporter. Only drug-event combinations with at least three adverse events reported, were included in the analysis.

### Statistical Evaluation

In this case/non-case study, a quantitative review of the VigiBase was performed using Empirica Signal, data-mining software (version 9.1, ORACLE).

Disproportionality analysis was used to assess associations between drug-event combinations. This method compares observed adverse event counts to the count that would be expected if occurrence of drugs and events in reporting were independent. Taking the ratio of the observed to expected count reflects a relative rate of reporting. We used the multiitem gamma poison shrinker (MGPS)<sup>10,11</sup> to smooth the relative rate value. The MGPS is an empirical Bayesian data mining method that uses data on all drugs and events in a database to compute relative reporting frequencies. To prevent confounding of drug-event associations and associations due to patient demographics or secular characteristics, MGPS internally stratifies on age, gender, and year of report and then computes an estimate of the relative rate. The estimate of relative rate obtained with MGPS is the statistic known as the empiric Bayes geometric mean (EBGM) and corresponding 2-sided 90% confidence interval (EB05, EB95). The EBGM values represent adjusted relative reporting rates (observed/expected) after Bayesian shrinkage is applied to minimize the variability that occurs in large, sparsely populated databases.

An EBG value of 5 is interpreted to mean that a drug-event pair has been reported 5 times as frequently as would be expected if reports involving the drug and reports of the event were independent (i.e., no association). A high relative reporting rate does not necessarily indicate a high incidence of the event or suggest a causal relationship between the drug and the event. For purposes of signal detection, we applied a lower 90% confidence bound (i.e., EBO5) 2 as a signal threshold. This threshold ensures with a high degree of confidence that regardless of the number of reports, a particular drug event pair is being reported at least twice as often as it would be if there were no association between the drug and the event<sup>12</sup>.

Besides that, we calculated the Information component (IC) with 95% confidence interval, frequently applied disproportionality analysis method<sup>13</sup>. A signal was shown when the lower limit of the 95% confidence interval of IC (IC025) exceeded 0.

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## **PRIMEVIGILANCE SIGNAL MANAGEMENT**

*Our approach: risk-based but proportionate, focused on 'unearthing' concerning safety patterns.*

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## Results and Discussion

Data mining runs were performed based on the search strategy described. Data mining results for each combination of MedDRA PT and drug are presented in Table 1. The results revealed statistically significant signals for the following combinations: PT: Ocular myasthenia and atorvastatin (EB05=2.375) and myasthenia gravis and rosuvastatin (EB05=2.138), using EBG as parameter of disproportionality. The remaining combinations did not have an EB05 value that exceeded our predetermined threshold of 2. However, when IC025 was considered as a disproportionality measure, additional drug-event combinations satisfied criteria for statistically significant signals: myasthenia gravis and atorvastatin (IC025=0.704), neuromuscular blockade and atorvastatin (IC025=0.109), myasthenia gravis and fluvastatin (IC025=0.339), neuromuscular blockade and lovastatin (IC025=0.555), myasthenia gravis and pravastatin (IC025=0.466), myasthenia gravis and simvastatin (IC025=0.833).

The remaining combinations did not have an IC025 value that exceeded our predetermined threshold of 0. Our results indicated there is a relationship between statins and myasthenia gravis. There are three plausible pathophysiological explanations for the association between statins and myasthenia gravis onset/exacerbation<sup>14</sup>. Firstly, the primary myotoxicity of statins might exacerbate muscle weakness in patients with underlying myasthenia gravis<sup>14</sup>. Secondly, statins might induce mitochondrial dysfunction via depletion of coenzyme Q10 (ubiquinone), leading to dysfunction of the pre- and postsynaptic motor end-plate interfaces (which are very rich in mitochondria); this might impair transmission in the neuromuscular junction<sup>15</sup>. Third proposed mechanism is that statins might induce antibodies against the neuromuscular junction<sup>14</sup>.

**Table 1.** Data mining results for the paired (MedDRA PT – statin) analysis

| Generic Name | PT                       | N   | EBGM  | EB05  | EB95  | IC     | IC025  | IC975  |
|--------------|--------------------------|-----|-------|-------|-------|--------|--------|--------|
| Atorvastatin | Myasthenia gravis        | 115 | 1.963 | 1.68  | 2.282 | 0.979  | 0.704  | 1.231  |
| Atorvastatin | Myasthenia gravis crisis | 7   | 1.102 | 0.579 | 1.946 | 0.216  | -1.049 | 1.089  |
| Atorvastatin | Neuromuscular blockade   | 35  | 1.525 | 1.148 | 1.995 | 0.627  | 0.109  | 1.065  |
| Atorvastatin | Ocular myasthenia        | 17  | 3.583 | 2.375 | 5.232 | 1.903  | 1.136  | 2.508  |
| Fluvastatin  | Myasthenia gravis        | 7   | 2.786 | 1.463 | 4.921 | 1.603  | 0.339  | 2.477  |
| Lovastatin   | Myasthenia gravis        | 8   | 1.383 | 0.757 | 2.362 | 0.541  | -0.631 | 1.37   |
| Lovastatin   | Neuromuscular blockade   | 8   | 3.053 | 1.671 | 5.216 | 1.727  | 0.555  | 2.556  |
| Pravastatin  | Myasthenia gravis        | 26  | 2.064 | 1.482 | 2.813 | 1.074  | 0.466  | 1.575  |
| Rosuvastatin | Myasthenia gravis        | 59  | 2.66  | 2.138 | 3.277 | 1.426  | 1.034  | 1.771  |
| Rosuvastatin | Myasthenia gravis crisis | 6   | 2.192 | 1.093 | 4.029 | 1.257  | -0.125 | 2.185  |
| Rosuvastatin | Neuromuscular blockade   | 3   | 0.364 | 0.137 | 0.823 | -1.343 | -3.418 | -0.149 |
| Rosuvastatin | Ocular myasthenia        | 5   | 2.399 | 1.12  | 4.638 | 1.419  | -0.117 | 2.414  |
| Simvastatin  | Myasthenia gravis        | 83  | 2.22  | 1.848 | 2.649 | 1.16   | 0.833  | 1.454  |
| Simvastatin  | Myasthenia gravis crisis | 5   | 1.192 | 0.556 | 2.305 | 0.361  | -1.175 | 1.356  |
| Simvastatin  | Ocular myasthenia        | 6   | 1.905 | 0.95  | 3.502 | 1.044  | -0.338 | 1.972  |

A total of 358 cases were retrieved from Vigibase, using the described data mining strategy. The main characteristics of reporters, patients and case seriousness are detailed in Table 2.

**Table 2.** Main characteristics of 358 analysed cases

| <b>N</b>                                      | <b>358</b> | <b>%</b> |
|-----------------------------------------------|------------|----------|
| <b>Region</b>                                 |            |          |
| Region of the Americas                        | 239        | 66.76%   |
| European Region                               | 98         | 27.37%   |
| Western Pacific Region                        | 21         | 5.87%    |
| <b>Report type</b>                            |            |          |
| Spontaneous                                   | 262        | 73.18%   |
| Report from study                             | 49         | 13.69%   |
| Post marketing study/Special monitoring       | 39         | 10.89%   |
| Other                                         | 5          | 1.40%    |
| Not provided                                  | 3          | 0.84%    |
| <b>Gender</b>                                 |            |          |
| Male                                          | 197        | 55.03%   |
| Female                                        | 149        | 41.62%   |
| Unspecified                                   | 12         | 3.35%    |
| <b>Age group</b>                              |            |          |
| 18-44                                         | 9          | 2.51%    |
| 45-64                                         | 111        | 31.01%   |
| 65-74                                         | 99         | 27.65%   |
| Above 75                                      | 66         | 18.44%   |
| Unspecified                                   | 73         | 20.39%   |
| <b>Source</b>                                 |            |          |
| Physician                                     | 165        | 46.09%   |
| Consumer or other non-health professional     | 80         | 22.35%   |
| Other Health Professional                     | 74         | 20.67%   |
| Pharmacist                                    | 22         | 6.15%    |
| Lawyer                                        | 1          | 0.28%    |
| Unknown                                       | 16         | 4.47%    |
| <b>Seriousness</b>                            |            |          |
| Y (serious)                                   | 295        | 82.40%   |
| N (non-serious)                               | 23         | 6.42%    |
| Not provided                                  | 40         | 11.17%   |
| <b>Seriousness criteria for serious cases</b> |            |          |
| Other medically significant conditions        | 116        | 39.32%   |
| Caused/Prolonged Hospitalization              | 103        | 34.92%   |
| Death                                         | 28         | 9.49%    |
| Disabling/Incapacitating                      | 16         | 5.42%    |
| Life threatening                              | 14         | 4.75%    |

Majority of cases came from Region of the Americas (66.76%) and European region (27.37%). There were 73.18% cases from spontaneous reporters, 13.69% reports from the studies and 10.89% reports from Post marketing studies/Special monitoring. It is important to highlight that vast majority of the reports was reported by health care professionals (physicians 46.09%, other health care professionals 20.67%, pharmacists 6.15%). Most of the case reports were assessed as serious (82.40%); out of them, 39.32% reports were assessed as serious due to being medically significant, 34.92% due to hospitalisation, 9.49% due to death, 5.42% due to being disabling/incapacitating and 4.75% were assessed as life threatening. Patients were male in 41.62% and female in 55.03%, while in other reports gender was not provided. Most of patients were between 45 and 74 years (58.68%). This finding reflects trends in statin treatment because these medications are mostly prescribed to older patients with cardiovascular disease.

In the retrieved 358 cases, atorvastatin was coded in 181 cases, simvastatin was coded in 103 cases, rosuvastatin in 76 cases, pravastatin in 26 cases, lovastatin in 16 cases and fluvastatin in 9 cases (in some cases more than one drug was coded). This finding is in accordance with the fact that simvastatin, atorvastatin and rosuvastatin are three most frequently prescribed statins. Details regarding indications for drug use in retrieved cases are presented in Table 3, for each drug separately. In 91 of reported cases, treatment with statins was withdrawn in response to the event, which resulted in positive dechallenge in 71 cases. This finding is in accordance with cases described in the literature <sup>7,9</sup>, and further confirms association between use of statins and myasthenia gravis occurrence. In 35 cases, patients were rechallenged with the statin drug, however, information whether the event reoccurred was not provided in the vast majority of cases (only one case was reported with a positive rechallenge).

**Table 3.** Indications for use of statins in the retrieved cases

| Indication                  | Atorvastatin | Fluvastatin | Lovastatin | Pravastatin | Rosuvastatin | Simvastatin | Total |
|-----------------------------|--------------|-------------|------------|-------------|--------------|-------------|-------|
| Not provided                | 74           | 3           | 8          | 9           | 43           | 36          | 173   |
| Acute coronary syndrome     | 1            | 0           | 0          | 0           | 0            | 0           | 1     |
| Arterial occlusive disease  | 1            | 0           | 0          | 0           | 0            | 0           | 1     |
| Atrial fibrillation         | 1            | 0           | 0          | 0           | 0            | 0           | 1     |
| Blood cholesterol           | 4            | 0           | 0          | 0           | 1            | 0           | 5     |
| Blood cholesterol abnormal  | 1            | 0           | 0          | 0           | 1            | 0           | 2     |
| Blood cholesterol increased | 9            | 0           | 0          | 2           | 3            | 7           | 21    |
| Blood triglycerides         | 1            | 0           | 0          | 0           | 0            | 0           | 1     |
| Brain stem stroke           | 1            | 0           | 0          | 0           | 0            | 0           | 1     |
| Cardiomyopathy              | 1            | 0           | 0          | 0           | 0            | 0           | 1     |
| Cardiovascular disorder     | 1            | 0           | 0          | 0           | 0            | 0           | 1     |

**Table 3.** Indications for use of statins in the retrieved cases (continued)

| Indication                                      | Atorvastatin | Fluvastatin | Lovastatin | Pravastatin | Rosuvastatin | Simvastatin | Total |
|-------------------------------------------------|--------------|-------------|------------|-------------|--------------|-------------|-------|
| Cardiovascular event prophylaxis                | 0            | 0           | 0          | 0           | 0            | 1           | 1     |
| Cerebrovascular accident                        | 5            | 0           | 0          | 0           | 0            | 0           | 5     |
| Cholesterol                                     | 1            | 0           | 0          | 0           | 0            | 0           | 1     |
| Diabetes                                        | 0            | 1           | 0          | 0           | 0            | 0           | 1     |
| Diabetes mellitus                               | 1            | 0           | 0          | 0           | 0            | 0           | 1     |
| Disorder of lipoprotein metabolism, unspecified | 3            | 0           | 0          | 0           | 0            | 0           | 3     |
| Drug use for unknown indication                 | 6            | 1           | 0          | 1           | 3            | 2           | 13    |
| Dyslipidaemia                                   | 2            | 0           | 0          | 0           | 1            | 0           | 3     |
| Dyslipidemia                                    | 0            | 0           | 0          | 0           | 0            | 1           | 1     |
| Essential (primary) hypertension                | 5            | 0           | 0          | 0           | 0            | 0           | 5     |
| High cholesterol                                | 0            | 0           | 0          | 1           | 1            | 1           | 3     |
| Hyper Idl cholesterolemia                       | 0            | 0           | 0          | 0           | 1            | 0           | 1     |
| Hypercholesteremia                              | 1            | 0           | 0          | 0           | 0            | 1           | 2     |
| Hypercholesterolemia                            | 0            | 0           | 0          | 0           | 1            | 2           | 3     |
| Hypercholesterolaemia                           | 3            | 1           | 0          | 1           | 0            | 16          | 21    |
| Hypercholesterolemia                            | 0            | 0           | 0          | 0           | 0            | 2           | 2     |
| Hyperlipidaemia                                 | 7            | 0           | 1          | 0           | 2            | 6           | 16    |
| Hyperlipidaemia, unspecified                    | 13           | 0           | 2          | 0           | 0            | 0           | 15    |
| Hyperlipidemia                                  | 2            | 1           | 0          | 1           | 0            | 0           | 4     |
| Hypertension                                    | 2            | 0           | 0          | 0           | 1            | 1           | 4     |
| Hypertriglyceridaemia                           | 0            | 0           | 0          | 0           | 6            | 0           | 6     |
| Hypocholesterolaemia                            | 2            | 1           | 0          | 0           | 0            | 1           | 4     |
| Ill-defined disorder                            | 2            | 0           | 0          | 0           | 0            | 0           | 2     |
| Lipids increased                                | 0            | 0           | 0          | 0           | 0            | 1           | 1     |

In Table 4, we present the total number of retrieved cases per MedDRA PT and outcome of the event.

**Table 4.** Cases retrieved with the data mining run, presented per MedDRA PT and outcome of the event.

| MedDRA PT                | Not provided | Fatal | Not resolved | Resolved | Resolved with sequelae | Resolving | Unknown | Total |
|--------------------------|--------------|-------|--------------|----------|------------------------|-----------|---------|-------|
| Myasthenia gravis        | 37           | 14    | 58           | 50       | 3                      | 49        | 65      | 276   |
| Myasthenia gravis crisis | 2            | 1     | 0            | 9        | 0                      | 4         | 3       | 19    |
| Neuromuscular blockade   | 0            | 6     | 1            | 25       | 8                      | 1         | 5       | 46    |
| Ocular myasthenia        | 2            | 0     | 4            | 13       | 1                      | 3         | 3       | 26    |
| Total                    | 41           | 21    | 63           | 97       | 12                     | 57        | 76      | 367   |

The use of spontaneous reporting data has many well-known limitations, including under-reporting, lack of important clinical information (including information regarding relevant medical history and concomitant medications) and lack of information on number of drug users (denominator), which precludes estimation of the incidence rate of events. Despite the limitations, spontaneous reporting system remains an important tool for the early detection of drug safety signals.

## Conclusion

Our findings suggest an increased risk for myasthenia gravis in patients receiving statins. Although this risk seems to be low, considering statins are increasingly prescribed, close monitoring of patients for symptoms of myasthenia gravis should be considered during long-term treatment with statins.

## References

- Pinal-Fernandez I, Casal-Dominguez M, Mammen A L. Statins: pros and cons. Med Clin (Barc) 2018;150(10):398-402.
- Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016; 388:2532–61.
- Rudski L, Rabinovitch MA, Danoff D. Systemic immune reactions to HMG-CoA reductase inhibitors. Report of 4 cases and review of the literature. Medicine (Baltimore) 1998;77:378–83.
- Tiniakou E, Christopher-Stine L. Immune-mediated necrotizing myopathy associated with statins: history and recent developments. Curr Opin Rheumatol 2017; 29:604–11.
- Cartwright MS, Jeffery DR, Nuss GR, et al. Statin-associated exacerbation of myasthenia gravis. Neurology 2004; 63:2188.
- Gale J, Danesh-Meyer HV. Statins can induce myasthenia gravis. J Clin Neurosci Off J Neurosurg Soc Australas 2014; 21:195–197.
- Keogh MJ, Findlay JM, Leach S, et al. Statin-associated weakness in myasthenia gravis: a case report. J Med Case Reports 2010; 4:61.
- Khalid R, Ibad A, Thompson PD. Statins and Myasthenia Gravis. Muscle Nerve 2016; 54:509–509.
- Oh S J., Dhall R, Young A, Morgan MB, Lu L, Claussen GC. Statins may aggravate myasthenia gravis. Muscle & Nerve 2008; 38: 1101-1107.
- DuMouchel WPD. Bayesian data mining in large frequency tables, with an application to the FDA Spontaneous Reporting System. The American Statistician 1999; 53:177–202.
- DuMouchel WPD. Empirical Bayes screening for multi-item associations: Seventh ACM SIGKDD International Conference on Knowledge Discovery and Data Mining. San Francisco: ACM Press, 2001.
- Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Saf 2002; 25:381–392.
- Ang S.S., Chen Z., Chan C.L., Tai B.C. Data mining spontaneous adverse drug event reports for safety signals in Singapore - A comparison of three different disproportionality measures. Expert Opin. Drug Saf. 2016; 15:583–590.
- Sowa ML et al. Statin-associated myasthenia: A case report and literature review. Société française de pharmacologie et dethérapeutique 2019; 0040-5957.
- Hargreaves IP, Heales S. Statins, and myopathy. Lancet 2002; 359:711-2.

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