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Bibliometric analysis of the scientific production as regards statin use for ophthalmological symptoms of myasthenia gravis☆

S.M. Salado-Font[a,*], F. López-Muñoz[b,c,d], F.J. Povedano-Montero[e], F. Labella Quesada[f]

[a] Vicerrectorado de Innovación, Universidad Camilo José Cela, Madrid, Spain
[b] Facultad de Salud, Universidad Camilo José Cela, Madrid, Spain
[c] Instituto de Investigación, Hospital 12 de Octubre, Madrid, Spain
[d] Red de Investigación Cooperativa en Salud (RETICS-Red de Trastornos Adictivos), Instituto de Salud Carlos III, Madrid, Spain
[e] Centro Óptico Montero, Madrid, Spain
[f] Vicedecanato de Ordenación Académica y Estudiantes, Facultad de Medicina, Universidad de Córdoba, Córdoba, Spain

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ABSTRACT

Introduction: The first symptoms of myasthenia gravis (MG) usually involve weakness of the ocular muscles, making it relevant that ophthalmologists have updated information on studies as regards its relationship with the consumption of drugs, such as statins.

Materials and methods: A bibliometric analysis was performed using the Scopus database and by a search strategy in the selection of documents containing descriptors related to statins in the «Title» («TI») field and the descriptors «ophthalm *», «myast *», «visual *» in other fields of the document (period 1986–2015).

Results: The results showed that, while the number of scientific publications on ocular effects of statins has grown lineally (n = 838; $y = 2.267x - 4507.1$; $r = 0.7221$; time of duplication: 4.66 years, and rate of annual growth: 50.06%), the specific publications about MG have experienced an exponential growth (n = 38; $y = 2E - 262e^{0.3001x}$; $r = 0.3892$; time of duplication: 2.95 years, and rate of annual growth: 46.25%) without reaching the saturation postulated in Price theory of the expansion of the scientific literature. The majority of publications relating to MG are reports of cases linked to a worsening of the MG symptoms, and simvastatin and atorvastatin are the agents mentioned in most of the publications.

Conclusions: These results should enable ophthalmologists to expand their knowledge concerning the evolution of studies on statins and MG, pointing out the relevance of such causal relationships.

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* *Corresponding author.*
E-mail address: smsalado@ucjc.edu (S.M. Salado-Font).

Análisis bibliométrico de la producción científica sobre el efecto del consumo de estatinas en las manifestaciones oftalmológicas de la miastenia gravis

Palabras clave:
Miatenia gravis
Estatinas
Manifestaciones otftalmológicas
Bibliometría

RESUMEN

Introducción: Los pacientes con miastenia gravis (MG) suelen empezar con afectación de la musculatura ocular. Es relevante que el oftalmólogo disponga de información actualizada del estado de la investigación respecto a la relación de esta enfermedad con el consumo de fármacos, como las estatinas.

Material y métodos: Se realizó un análisis bibliométrico, utilizando la base de datos Scopus y aplicando una estrategia de búsqueda consistente en la selección de documentos que contuvieran los descriptores referidos a estatinas en el campo «Título» («TI») y los descriptores «ophthalm*», «myast*», «visual*» en cualquier otro campo del documento (de 1986 a 2015).

Resultados: Los resultados confirman que, mientras el número de publicaciones científicas sobre efectos oftalmológicos de las estatinas ha crecido linealmente (n = 838; $y = 2{,}267x - 4507{,}1$; r = 0,7221; tiempo de duplicación: 4,66 años y tasa de crecimiento anual: 50,06%), las publicaciones específicas sobre MG han experimentado un crecimiento exponencial (n = 38; $y = 2E\text{-}262e^{0{,}3001x}$; r = 0,3892; tiempo de duplicación: 2,95 años y tasa de crecimiento anual: 46,25%), sin que se haya alcanzado la saturación postulada en la teoría de Price de la expansión de la literatura científica. La mayor parte de las publicaciones relativas a la MG son reportes de casos vinculados a un empeoramiento de la sintomatología de la MG, y los agentes que más publicaciones aportan son simvastatina y atorvastatina.

Conclusiones: Estos resultados permitirán al oftalmólogo ampliar su conocimiento respecto a la evolución de la investigación sobre estatinas y MG y reflejan un interés creciente por la relación entre el consumo de ambas, señal de la relevancia de dicha relación causal.

Introduction

Myasthenia gravis (MG) is an infrequent malady with a worldwide prevalence estimated at 15–179 per million inhabitants.[1] MG is a self-immune disease in which the presence of autoantibodies against acetylcholine receptors in the post-synaptic membrane causes a reduction in the number of receptors in the motor Plate[2] compromising neuromuscular transmission. This gives rise to fluctuating proximal muscular weakness which worsens with activity in the course of the day. Muscle fatigue is a typical clinic sign of this malady.[3] In addition, bulbar symptoms may appear such as dysphony, dysphagia, facial musculature weakness or a combination thereof.[3,4]

In the majority of MG patients, the disease begins with ocular musculature compromise,[5,6] with intermittent diplopia and palpebral ptosis. Accordingly, the Ophthalmology practice would be the first stop for undiagnosed patients.

Statins, i.e., 3-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are medicaments with demonstrated capacity to diminish concentration in blood and therefore prevent cardiovascular morbidity and mortality.[7] The use of statins in primary as well as secondary care is supported by international reference therapeutic guides.[8–11] For this reason, statins are routinely prescribed and their consumption is continuously increasing.[12] However, a side effect reported in scientific literature is the induction of self-immune diseases, including MG. The pathway through which statins induce the development of self-immune diseases seems to be related to its ability to enhance T-cell phenotypes that reduce cellular immunity but increase humor immunity regulated by antibodies.[13]

As in the majority of patients MG debuted with ophthalmological symptoms,[5,6] in many cases the ophthalmologist will be the first specialist to perform anamnesis and obtain their clinical records. Accordingly, it is advisable for said specialist to be familiar not only with MG-related symptoms but also with the possibility of the adverse reactions related to the therapeutic use of statins.

The results of scientific research are difficult to assess, giving rise to the need of analysis methods allowing us to study different aspects of said research. The parameters utilized to evaluate any activity can be defined as indicators. A set of indicators is applied to bring out one aspect of the object being assessed.[14] At present, scientific policy reviews would not be understood without recourse to existing indicators.

By means of its indicators, bibliometry focuses precisely on calculating and analyzing quantifiable values of scientific consumption and production.[15,16] Bibliometry can be defined as the science that studies the nature and cause of a discipline that gives rise to publications by computing and analyzing different aspects of written communications.[17] Bibliometry involves obtaining, processing and managing quantitative reference data from scientific publications.[18] The Organization for Economic Cooperation and Development (OECD) referred to bibliometry as a tool enabling the observation of the state

of science and technology through the global production of scientific literature at a given level of specialization.[19]

Accordingly, due to the huge increase in the prescription and consumption of statins and the interest in establishing its relationship with a disease with the onset of which it is involved in the majority of cases, it becomes relevant to carry out a bibliometric analysis of scientific literature on the connection between statins, self-immunity and MG to enable the ophthalmologist to increase his/her knowledge on the evolution of research about said relationship in recent years in order to point out the interest of said causal relationship among the scientific community.

Material and method

For a documental search the study utilized the Scopus database, the largest database comprising summaries and peer-reviewed scientific literature references comprising scientific journals, books and summaries of meetings. Said database covers approximately 22,000 titles of over 5000 publishers, 20,000 of which are specialized in medical and social sciences and technology (including arts and human sciences).

The Scopus database enables searches by fields, one of which is «TI» i.e., the title of an article. With remote downloading techniques the articles published in the period comprised between 1986 (year of the first records) and 2015 that included in the «TI» fields the following main descriptors: «statin», «atorvastatin», «fluvastatin», «lovastatin», «pitavastatin», «pravastatin», «rosuvastatin», «simvastatin» and «cerivastatin», joined by the OR prefix, were identified. The search was linked with the AND tab to the search made with specific descriptors «ophthalm*», «myast*», «visual*», utilizing the wildcard option with the * symbol to obtain all words including said prefixes. In this case, the search was not restricted to any field in the database. In addition, a subanalysis was made to determine the number of registries for the specific «myast*» descriptor. The study included all original articles, short articles, reviews, editors notes, letters to the editor, etc., and omitted all duplicate documents. After collecting all the files as described in the methodology, the following stage involved computer processing and statistical analysis. For this purpose the SPSS application was used (version 20.0) (IBM SPSS Statistics 20.0.1 – International Business Machines Corp, Armonk, NY, USA).

The bibliometric analysis comprised the most usual indicators: Price index, duplication time and annual growth rate, Lotka productivity rate, Price transient level, Bradford zones and coauthorship index.

The bibliometric production indicators included the application of the Price law.[20] This law is the most widely utilized indicator for analyzing scientific production in a specific discipline or country, and shows a fundamental aspect of scientific production such as exponential growth. In order to determine whether the growth of scientific literature about the ophthalmological effects of statins follows the exponential growth Price law, a linear adjustment of data obtained was carried out in accordance with the $and = 2.267x - 4507.1$ equation, and another adjustment to an exponential curve in accordance with the $and = 1E - 82e^{0.0958x}$ equation (where *and* is the number of publications and *x* the number of years from year zero).

Duplication time[21] and annual growth rate are related to growth. The former is the time, expressed in years, that must elapse for the subject being studied to duplicate its production, while the annual growth rate shows the percentage of growth compared to the previous year. The equation that calculates the duplication time (D) is represented by the following expression: $D = Ln^2/b$, with b being the constant that relates growth rate with the already acquired size of the science. For calculating the annual growth rate the following equation was utilized: $R = 100\ (e^b - 1)$.

Lotka formulated the authorship distribution law according to the number of published papers, also known as the «quadratic inverse of scientific production».[22] This law studies the volume of publication of authors and found that there are more authors who publish a few articles than those who publish many.[23] This law establishes that in the entire scientific community, the number (A) of authors who publish a number (n) of studies in the course of a period comprising several years of activity, i.e. $A(n)$ authors, equals the amount of those who have published a single study, $A(1)$, in the same period of time, divided by the square of n. In mathematical terms, the original law is expressed with the following formula: $A(n) = A(1)/n^2$. According to this index, authors are distributed in 3 productivity levels: small producers who publish a single study, middle producers who publish between 2 and 9 studies and large producers who publish 10 or more papers. The productivity index, also known as productivity level (PL), is one of the fundamental indicators that corresponds to the logarithm of the number of contributions of an offer. It is also interesting to determine the number of authors with a single publication. This is also known as the transient or Price rating.[24] It is calculated as a percentage of the quotient of authors with a single publication among all authors. Mathematically, it would be expressed as follows: $IT = (Authors\ with\ a\ single\ publication/Total\ of\ authors) \times 100$.

Bradford's law was applied as the bibliometric indicator of dissemination of scientific information. In order to show the distribution of scientific literature in an individual discipline, Bradford proposed a model based on concentric productivity zones (the Bradford zones) according to diminishing information density.[25] Accordingly, each in his own would contain a similar number of publications but the number of journals in which these are published will increase when going from one zone to the other. This model enables the identification of the most widely used journals and those having lower weight in a given scientific production field.

Results

Overall, 838 results were obtained for the period 1986–2015 using the above-mentioned search criteria, including original articles, reviews, editorials, letters to the editor, etc.). Fig. 1 illustrates the chronological distribution. Said figure also illustrates that the mathematical adjustment to a linear curve provides a correlation coefficient of $r = 0.7221$, which indicates that 27.79% of the variability is not explained with said adjustment. On the other hand, the exponential adjustment of

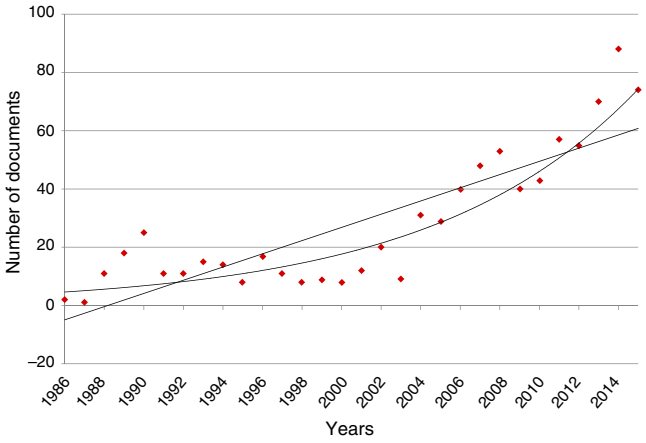

Fig. 1 – Growth of scientific production on the ophthalmological expressions of statins. Data were linearly and exponentially adjusted in accordance with Price law. Linear adjustment: *and* = 2.267*x* – 4507.1 (*r* = 0.7221). Exponential adjustment: *and* = 1*E* – 82$e^{0.0958x}$ (*r* = 0.6645).

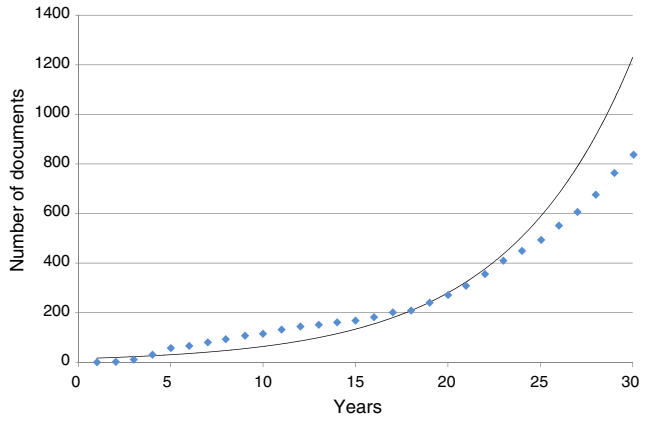

Fig. 2 – dispersion of scientific production according to time-based evolution. Tendency line: *and* = 14.533$e^{0.148x}$ (r^2 = 0.7991).

measured values gives *r* = 0.6645 and therefore a residual variability percentage of 33.55%. On the basis of these data, it can be concluded that the analyzed database is better adapted to a linear adjustment and that the Price law postulates are not fulfilled.

For calculating the duplication time, the temporal production of contributions is represented in a dispersion graph, with the trendline adjusted to the *and* = 14.533$e^{0.148x}$ equation and a determination coefficient of 0.7991 (Fig. 2). Said production covers 30 years. Utilizing the equation for calculating the duplication time, the result is 4.66 years and the annual growth rate is 50.06%.

Distribution in 5-year periods shows a significant increase in the 2011–2015 period, which exhibited a growth above 40% compared to the previous period. This demonstrates the increased scientific interest in the subject in recent years.

As can be seen in Fig. 3, the statins that have the highest number of documents are atorvastatin and simvastatin, whereas pitavastatin and cerivastatin attracted the lowest number of documents.

As regards the origin of scientific production, the most productive countries are the United States with 276 contributions, China with 72 and the United Kingdom with 71. As regards institutions, the most productive ones are Merck Research Laboratories (16 documents), VA Medical Center (14 documents) and University of California, San Francisco (12 documents) (Fig. 4).

After applying Lotka's law, distribution by authors is highly concentrated in small producers (n = 3.813), with a transient index (occasional authors) of 88.02% and the absence of large producers (medium producers amount to 519 (11.98%). The overall number of authors is 4332 which, for the 838 search results, gives a coauthorship index of 5.16.

The Bradford model was applied for analyzing the scientific journals in which articles about the effects of statins at the ocular level were published. The mean number of articles per Bradford zone was 279.3. Table 1 shows the division in Bradford areas of the articles included in this analysis. The total number of journals that published about the subject is 482, whereas the nuclear zone includes 26 journals. Table 2 indicates the impact factor data as well as other data of interests all the journals concentrating the highest number of documents.

In what concerns the sub-analysis on the correlation of statins with MG, the number of search results was 38. The chronological distribution of these results is shown in Fig. 5. In accordance with the Price science growth law, the determination coefficient is higher for the exponential curve, *r* = 0.3892 against the linear adjustment, with *r* = 0.3368. Accordingly, research activity is in an exponential growth phase. However, the high degree of variability must be taken into account, as the correlation coefficient is well below 1. In this case, production doubles every 2.95 years and the annual growth rate is of 46.25% (Table 3).

According to the Bradford model, the nuclear zone comprises 5 journals, i.e., Canadian Journal of Cardiology, Canadian Journal of Neurological Sciences, Molecular and Cellular Neuroscience, Muscle and Nerve and Neuromuscular Disorders.

In the author productivity study, the number of occasional authors is higher than in the previous analysis (146), amounting to 94.41%, without any large producer and only 12 median producers (7.59%). The overall number of authors is 158, representing a coauthorship index of 4.15 authors per document.

As in the previous analysis, the most productive countries are the United States with 15 documents, followed by Canada and China with the 6 documents each. The most productive institutions are the McMaster University with 5 documents, and Pfizer and Shandong University with 3 documents each.

Discussion

The use of bibliometric indicators for studying research activity in a specific field is based on the premise that scientific publications are the essential results of said activity.[26] Accordingly, bibliometric studies have consolidated as useful tools for assessing the social and scientific relevance of a given discipline or field of study.[27] As shown in Fig. 1, the present analysis

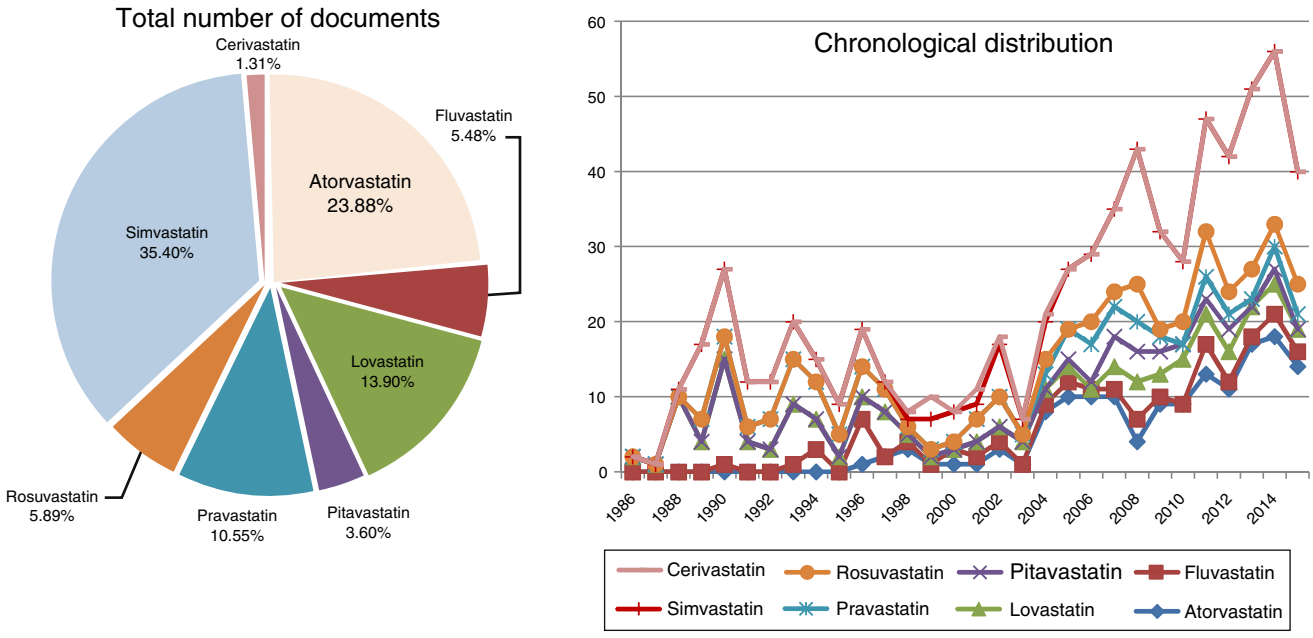

Fig. 3 – Evolution of scientific studies on different statins and distribution of all documents for each.

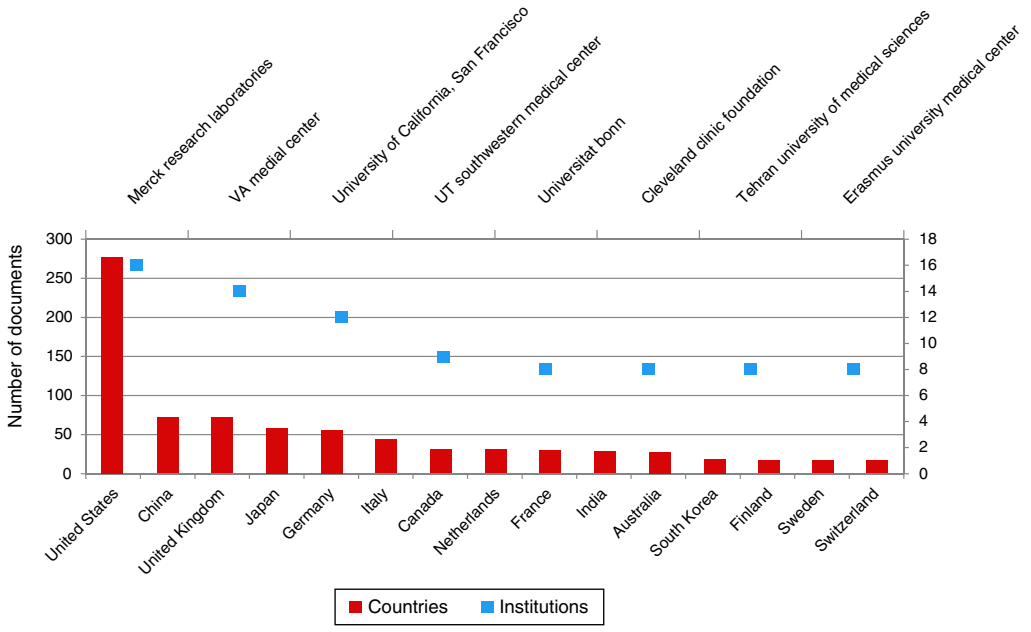

Fig. 4 – Contribution of countries and institution to the production of articles on the visual effects of statins.

Table 1 – Bradford zone distribution of journals.

	# Of journals	% Of journals	# Of articles	% Of articles	Bradford multiplier
Core	26	5.39	220	26.25	
Zone 1	110	22.82	272	32.46	4.23
Zone 2	346	71.78	346	41.29	3.14
Total	482	100.00	838	100.00	3.68

confirms that the number of scientific publications on the visual effects of statins has increased linearly in the past 20 years, mainly after 2004, whereas publications on the relationship between said drugs and MG have grown exponentially in the past 15 years. This shows that MG and its relationship with statins has aroused great interest concerning the ocular effects of said drugs. In addition, it is interesting to see how at the end of this study said growth did not reach the

Table 2 – Journals with highest number of publications on statins and ophthalmological effects.

Journal	# Of publications	%	FI	FI at 5 years	Eigenfactor® score	Article influence® score	Country	Short name
PLoS ONE	21	2.51	3.234	3.702	1.53341	1.209	United States	Plos One
American Journal of Cardiology	18	2.15	3.276	3.345	0.06237	1.296	United States	Am J Cardiol
Investigative Ophthalmology and Visual Science	18	2.15	3.404	3.673	0.07624	0.996	United States	Invest Ophth Vis Sci
Atherosclerosis	12	1.43	3.994	4.013	0.04689	1.167	Ireland	Atherosclerosis
American Journal of Ophthalmology	10	1.19	3.871	4.225	0.02767	1.337	United States	Am J Ophthalmol
European Journal of Pharmacology	10	1.19	2.532	2.672	0.03469	0.659	Holland	Eur J Pharmacol

Table 3 – Bradford zone distribution of journals for the sub-analysis on miastenia gravis and statins.

	# Of journals	% Of journals	# Of articles	% Of articles	Bradford multiplier
Core	5	15.15	10	26.32	
Zone 1	28	84.85	28	73.68	9.33
Total	33	100.00	38	100.00	9.33

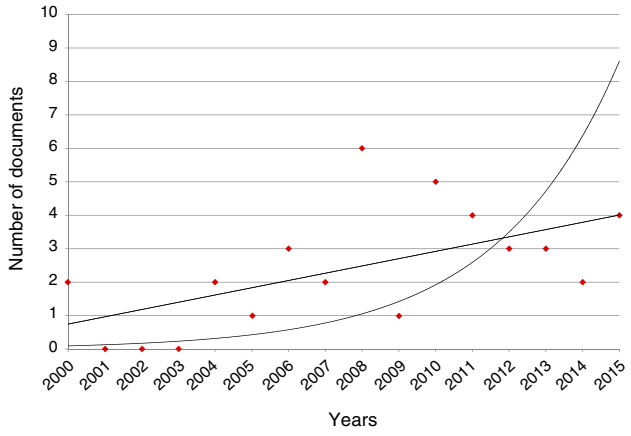

Fig. 5 – Growth of scientific production on statins and miastenia gravis. Data were linearly and exponentially adjusted in accordance with Price law.
Linear adjustment: *and* = 0.2172*x* – 433.58 (*r* = 0.3368).
Exponential adjustment: *and* = 2*E* – 262$e^{0.3001x}$ (*r* = 0.3892).

saturation postulated by Price in his scientific literature expansion theory.[20] This underscores the fact that some issues do not appear to be completely elucidated, for example the causal mechanism or whether the relationship of statins and MG is cause-effect or only an effect over the morbidity and prognosis of the disease.

On the other hand, the present bibliometric data exhibit a close correlation with the prescription data of statins, the use of which has significantly increased worldwide in the past 2 decades,[28] with simvastatin and atorvastatin being the most prescribed statins. This is also apparent in the individual analysis of statins, which shows that simvastatin is the agent that gives rise to the highest number of publications (35.40%), followed by atorvastatin (23.88%). Accordingly, there seems to be a correlation between the consumption of statins and the reporting of adverse effects in the visual domain, although this obviously does not mean that both agents proportionally exhibit higher incidence, prevalence or morbidity of visual myopathies.

In order to analyze the quality of articles, the impact and excellence indicators of the journals for the subject were utilized. The fact that prestigious journals such as *Atherosclerosis* (impact factor [FI] = 3.994), *American Journal of Ophthalmology* (FI = 3.871) or *Investigative Ophthalmology and Visual Science* (FI = 3.404) published articles about the topic is a significant data that underlines the clinic and social relevance that the topic has acquired in recent years. It is worthy of note that the 6 most widely utilized publications for the international diffusion of research on the visual effects of statins feature an impact factor of >2.5.

The fact that Merck & Co. and Pfizer, who are respectively responsible for the development and marketing of simvastatin and atorvastatin, are among the largest scientific producers of the analyzed articles, indicates the involvement of the pharmaceutical industry in the clinic development process of their drugs, both in the research stages prior to approval as well as in the postapproval follow-up. This emphasizes the importance of the work carried out by the medicament departments that make available to the scientific community all data on possible adverse reactions of their products. In this regard, it should be noted that the greatest part of documents included in the sub-analysis on MG are case reports about worsening of symptoms in MG patients being treated with various statins rather than in the appearance of the malady itself.[29–31]

In common with all of bibliometric analyses, this study exhibits a number of limitations.[32–34] Firstly, not all articles about statins and visual function may have been included because of the criteria established by the database (Scopus in this case) determine the subsequent development of analyzed documents. On the other hand, the articles in which authors did not include descriptors about statins in the title or keywords would not appear in the search results. Despite says

limitations, bibliometric studies are useful for assessing the social and scientific relevance of a given discipline or field.[27] These studies constitute an efficient supplement for the opinions and judgments of experts in each field and are a useful and objective means for assessing the results of scientific activity by facilitating a realistic view of the overall situation and trends as well as indicating the way in which the topic being analyzed could evolve.

Taking into account the above mentioned limitations and strong points, the authors believe they were able to provide an image of the representativeness and evolution of research on the ophthalmological effects of statins as well as their relationship with MG in the scientific context, observing the most widely used quality and diffusion parameters in the international field. The present study confirms that research on the relationship between statins and MG has grown in the past 2 decades, in line with other biomedical research fields.

Conflict of interests

No conflict of interests was declared by the authors.

The authors declare that they have no specific commercial interest in relation to the products, equipment or processes mentioned in the present study and that they have not received financial support for the development thereof.

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