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Systemic Corticosteroids in Patients with Bronchial Asthma: A Real-Life Study

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Abstract

Objective: The objective of the present study was to determine the use of systemic corticosteroids (SCs) in patients with bronchial asthma using big data analysis.

Methods: We performed an observational, retrospective, noninterventional study based on secondary data captured from free text in the electronic health records. This study was performed based on data from the regional health service of Castille-La Mancha (SESCAM), Spain. We performed the analysis using big data and artificial intelligence via Savana® Manager version 3.0.

Results: During the study period, 103 667 patients were diagnosed with and treated for asthma at different care levels. The search was restricted to patients aged 10 to 90 years (mean age, 43.5 [95%CI, 43.4-43.7] years). Of these, 59.8% were women. SCs were taken for treatment of asthma by 58 745 patients at some point during the study period. These patients were older, with a higher prevalence of hypertension, dyslipidemia, diabetes, obesity, depression, and hiatus hernia. SCs are used frequently in the general population with asthma (31.4% in 2015 and 39.6% in 2019). SCs were prescribed mainly in primary care (59%), allergy (13%) and pulmonology (20%). The frequency of prescription of SCs had a direct impact on the main associated adverse effects.

Conclusion. In clinical practice, SCs are frequently prescribed to patients with asthma, especially in primary care. Use of SCs is associated with a greater number of adverse events. It is necessary to implement measures to reduce prescription of SCs to patients with asthma, especially in primary care.

Key words: asthma, systemic corticosteroids, big data, artificial intelligence

Resumen

Objetivo: El objetivo del presente estudio fue determinar el uso de corticoides sistémicos (CS) en pacientes con asma bronquial mediante el análisis de big data.

Métodos: Se realizó un estudio observacional, retrospectivo y no intervencionista basado en datos secundarios capturados a partir de texto libre en las historias clínicas electrónicas. Este estudio se realizó a partir de los datos del Servicio Regional de Salud de Castilla-La Mancha (SESCAM), España. Se realizó el análisis mediante big data e inteligencia artificial a través de Savana® Manager versión 3.0.

Resultados: Durante el periodo de estudio, 103 667 pacientes fueron diagnosticados y tratados de asma en los diferentes niveles asistenciales. La búsqueda se restringió a pacientes de entre 10 y 90 años (edad media, 43,5 [IC 95%, 43,4-43,7] años). De ellos, el 59,8% eran mujeres. 58.745 pacientes tomaron SC para el tratamiento del asma en algún momento del periodo de estudio. Estos pacientes eran de mayor edad, con una mayor prevalencia de hipertensión, dislipidemia, diabetes, obesidad, depresión y hernia de hiato. Los SC se utilizan con frecuencia en la población general con asma (31,4% en 2015 y 39,6% en 2019). Los SC se prescribieron principalmente en atención primaria (59%), alergia (13%) y neumología (20%). La frecuencia de prescripción de SCs tuvo un impacto directo en los principales efectos adversos asociados.

Conclusiones: En la práctica clínica, los CS se prescriben con frecuencia a los pacientes con asma, especialmente en atención primaria. El uso de los CS se asocia a un mayor número de efectos adversos. Es necesario implementar medidas para reducir la prescripción de CS a los pacientes con asma, especialmente en atención primaria.

Introduction

Asthma is one of the most common chronic diseases, affecting approximately 339 million people worldwide [1]. In Spain, 14% of children and 8.6% of adults (18-70 years) experience symptoms of asthma [1-5]. The disease remains uncontrolled in a high percentage of patients, although control is not always associated with severity, and poor control may result from incorrect treatment, lack of adherence, and persistence of risk factors [6]. However, the needs of some patients with severe disease are not met using standard therapeutic options. Current data are insufficiently reliable to provide an accurate percentage for patients with severe uncontrolled asthma, since the best information is from specialized asthma units and therefore subject to selection bias. The prevalence of severe asthma in Spain is 3.9% in adults with asthma [7].

A particularly relevant group of asthma patients is that requiring regular therapy with systemic corticosteroids (SCs). While these drugs may be effective in some cases of severe asthma [8], they are considerably limited by their adverse effects [9]. Therefore, the risk of adverse effects should be evaluated in patients requiring treatment with maintenance SCs. In addition, patients should be assessed to determine whether they are receiving the most appropriate treatment or whether their clinical profile makes

them candidates for biologics. In practice, asthma is refractory to standard treatment in at least 3%-6% of cases, with the result that biologics may be advisable [10,11]. Consequently, the clinical relevance of using SCs in bronchial asthma necessitates a detailed analysis of the patient's situation to take account of the following: misdiagnosis of asthma, undertreatment, poor adherence to treatment, the coexistence of comorbidities, and continued exposure to asthma-aggravating factors. This evaluation could prove to be of paramount importance for determining real-world use of SCs in bronchial asthma, identifying errors in management, and assessing the potential use of biologics in clinical practice. Current studies are severely limited by the fact that it is impossible to avoid selection bias, since they seldom record the large "occult population", namely, those patients seen by physicians who have received less training in this disease, leading to nonoptimal diagnosis and treatment. The only way to determine the real situation of this disease and the consumption of SCs is by analyzing the whole population of Castille-La Mancha.

The recent advent of nonstructured analysis of information from electronic health records (EHRs) based on big data could provide a solution to this problem [12-14]. The use of big data in the health sector, specifically new technologies for managing and retrieving complex data generated in large volumes from EHRs, is already a reality. Most of the information in computerized medical records is unstructured free text that can be analyzed using big data techniques and artificial intelligence. Savana® has developed *EHRead* technology, which makes it possible to read, process, and order nonstructured free text from EHRs. Once this process is complete, the information from the EHRs is converted into structured data, which can be easily and rapidly stored, consulted, and analyzed for research purposes.

The objective of the present study was to determine the consumption of SCs in all asthmatic patients treated in the Community of Castille-La Mancha, regardless of the severity of the disease, using big data analysis tools and artificial intelligence systems.

Material and Methods

We performed an observational, retrospective, noninterventional study based on secondary data captured in free text from the EHRs. The study was performed based on data from the regional health service of Castille-La Mancha (SESCAM), Spain, which has a catchment population of 2 030 807 inhabitants. The total number of patients seen during the study period was 2 707 587.

We performed our analysis using big data and artificial intelligence tools via the clinical platform Savana Manager, version 3.0 [15,16]. SESCAM has access to the tool Savana Manager 3.0, which can analyze data from the year 2011 onward. The study population comprised all patients diagnosed with bronchial asthma. The supplementary material includes all the terms enumerated in the inclusion criteria (Supplementary material, Table S1).

Savana Manager is a data retrieval system based on artificial intelligence (natural language processing [NLP]) and big data techniques. It enables unstructured clinical information (natural language or free text) to be retrieved from the EHR and converted into reusable and structured information for research purposes, with patient anonymity guaranteed at all times [15]. Furthermore, the complete clinical content can be detected and scientifically validated using computational linguistic techniques (SNOMED CT) [17] based on data from EHRs within the specialized care network of SESCAM (hospitalization, emergency department, and outpatient clinics) and primary care centers. The study period ran from January 1, 2015 to December 31, 2019. The period was evaluated overall, with subsequent annual cut-offs, which enabled us to know not only the situation of the disease during this period, but also how it changed over time. The year 2020 was excluded because of the distortion generated by the COVID-19 pandemic. The study methodology followed has been reported elsewhere [18–20].

Data protection and management: The local information technology departments were responsible for processing and anonymization of data, which were subsequently sent to Savana in such a way that the system did not receive identifying information at any time. In addition, an algorithm was used during data retrieval to enter random confounding data for each patient, while at the same time recovering only part of the individual's information. The result of this approach was the creation of a patient database that was totally dissociated and anonymous, so that all the study reports contained only aggregate data and it was not possible to identify patients or physicians. In line with the European Data Protection Board, once an anonymous clinical registry releases personal data, the General Data Protection Regulation is no longer applicable. The study was approved by the Research Ethics Committee of the Guadalajara Health District.

Evaluation of data retrieval: The free text in the EHR is analyzed and processed based on NLP techniques using *EHRead*. Medical concepts are detected using computational linguistic techniques and complete clinical content.

Given the novelty of this methodological approach, we evaluated the performance of Savana to ensure the robustness of our clinical findings. The objective of this analysis was to verify the accuracy of the system for identifying registries that contain data on asthma and related variables. The lack of coded data in Spain necessitates the development of an annotated corpus—the gold standard—to carry out the evaluation. The gold standard consists of a set of clinical documents where the appearance of entities/concepts associated with asthma is verified manually by experts. The corpus used in this evaluation comprised a set of 560 documents reviewed by 3 experts to ensure the reliability of the manual review/annotation.

The performance of Savana was assessed automatically using the gold standard created by the experts as a reference. Consequently, the accuracy of Savana for identifying registers in which a study disease and its associated variables are detected was measured with respect to the gold standard. The evaluation of the system was based on standard metrics, namely, precision (P), recall (R), and the F-measure [18], as follows:

Precision (P) = $\frac{tp}{tp + fp}$. An indicator of the reliability of the system for recalling information.

Recall (R) = $\frac{tp}{tp+fn}$. An indicator of the quantity of information the system recalls.

F-measure = $\frac{2xPrecisionxRecall}{Precision+Recall}$. An indicator of the overall performance or information recall.

In all cases, we defined a true positive as a correctly identified register, a false positive as an erroneously identified register, and a false negative as a register that should have been identified but was not.

Statistical analysis: For the purposes of this study, the statistical analysis included a descriptive analysis of all the variables evaluated. Qualitative variables are expressed as absolute frequencies and percentages, whereas quantitative variables are expressed as mean (95%CI) and standard deviation. Numerical variables were analyzed using the independent samples *t* test. In the case of qualitative variables, associations and proportions were assessed using the chi-square test. All differences with a p value (contrast test) lower than 0.05 were considered significant.

Results

During the study period, 103 667 patients were diagnosed with and treated for bronchial asthma at the various care levels of SESCAM. The data analysis was based on 282 875 264 documents. The flow chart for the study population is shown in Figure 1. The search criteria used to identify patients with bronchial asthma and the SCs analyzed are set out in the supplementary material (table S2 and table S3). The linguistic evaluation of the variable “bronchial asthma” has been analyzed and reported on elsewhere [19]. The evaluation yielded a precision, recall, and F-measure of 0.88, 0.75, and 0.81, respectively, indicating that diagnoses of asthma were accurately detected in the study population. For the objectives of the present study, we restricted our search to patients aged between 10 and 90 years (mean age, 43.5 [95%CI, 43.4-43.7] years; 59.8% women).

A total of 58 745 patients had received SCs for their asthma during the study period. These patients were older, with a greater prevalence of hypertension, dyslipidemia, diabetes, obesity, depression, and hiatus hernia. In contrast, rhinitis was less prevalent in this group (Table 1).

SCs are commonly used to treat asthma, with a cumulative frequency that ranged from 31.4% in 2015 to 39.6% in 2019 (Figure 2). This percentage remained relatively stable, with seasonal variations, although the percentage of patients taking SCs was at no time lower than 15% (Figure 3).

By care level, SCs were prescribed mostly in primary care (59%), and much less frequently in allergy (13%) and pulmonology (20%). Although the difference between allergy and pulmonology can be explained by differences in age and patient profile, we were unable to detect any variations with respect to primary care that would account for the widespread use of SCs in this setting (Table 2).

Table 3 shows the impact of SCs on the main associated adverse effects.

Discussion

Current guidelines continue to recommend SCs for the short-term treatment of severe exacerbations or as additional maintenance therapy in patients with severe disease that is refractory to high-dose maintenance inhaled corticosteroids, including novel monoclonal antibodies with specific targets [10]. Consistent with the recommendations in these guidelines, SCs should be restricted to approximately 10% of patients with severe disease. However, worldwide, SCs are used much more frequently than

recommended, suggesting that they may be overprescribed in patients with asthma [20].

Consumption of SCs by asthma patients was very high, especially in primary care, where the frequency of prescription was 59%, compared with 13% in allergy and 20% in pulmonology. The frequency of SCs in patients with asthma was 31.4% in 2015, rising to 39.6 in 2019. This percentage remained relatively stable over time, with seasonal variations, although at no time did the percentage of patients taking SCs fall below 15%. The differences between pulmonology and allergy can be explained by patient age and profile, although we were unable to detect factors that could explain the widespread use of SCs in primary care.

Another multicenter prospective study carried out in Spain analyzed unreached therapeutic objectives and potentially treatable characteristics in a population of patients with uncontrolled severe asthma. The authors reported that 22% of patients had received SCs for at least 3 months during the previous year and that 13% took them regularly [21].

The abovementioned data confirm that SCs continue to be used very frequently. This finding was confirmed in a recent systematic review of 139 studies performed in populations with varying degrees of asthma severity [22]. The authors examined real-life observational studies from Europe, North America, and Asia and found that SCs were widely used in asthma patients and that they are particularly prevalent in patients with more severe disease. Long-term therapy with SCs was generally less frequent than short-term therapy. The review showed that the frequency of SCs in the short term for treatment of any degree of severity ranged from 3.6% [23] to 62.0% [24]. The use of short-term SCs was even greater in patients with severe or refractory asthma, ranging from 23.2% [25] to 92.6% [26]. The studies analyzing long-term therapy with SCs found that they were used less commonly than short-term SCs, ranging from 0% to 1.3% in patients with nonsevere disease compared with those with severe or uncontrolled disease (20%-60%) [21]. These data summarize the excessive use of SCs and indicate that this has not decreased with the inclusion of new targeted therapy for management of severe asthma. The trend differs from that observed in other specialties, such as rheumatology, where prescription of SCs has fallen dramatically thanks to the wide range of targeted options now available for the treatment of rheumatoid arthritis. A potential explanation is that the last year of the review was 2017, and it was late 2015 when the United States Food and Drug Administration approved mepolizumab (2015), reslizumab (2016), benralizumab (2017), and

dupilumab (2018) for patients with severe uncontrolled asthma despite high-dose inhaled corticosteroids combined with long-acting ß-agonists [21]. However, more recent publications show that this trend is now changing, at least in developed countries. A real-world study of patients with severe asthma not controlled with high-dose inhaled corticosteroids combined with additional controller medications (long-acting ß-agonists, long-acting muscarinic agents, leukotriene receptor agonists) showed that use of SCs was infrequent, whereas that of biologics was common, with a similar prevalence for anti-immunoglobulin E and anti-IL-5/IL-5Rα therapy. Nevertheless, differences were found between treatments, and these were associated with the characteristics of the patients and the center, which, according to the authors, should be investigated to ensure fair access to biologics and minimize prescription of SCs [27].

Use of SCs has been associated with a greater risk of adverse events in both the short term and the long term, and this risk increases with exposure to the drugs (cumulative dose) [21, 28]. The risk of an adverse event related to SCs is 3- to 6-fold greater in patients receiving long-term SCs [21, 29]. Short-term rescue therapy for severe exacerbations or loss of control of asthma has also been associated with adverse events, with a 6% increased risk in patients who receive 1-3 short cycles and more than 26% for those who receive ≥4 cycles [28, 30]. Use of SCs, even at doses as low as <5 mg/d has been associated with a greater risk of osteoporosis, diabetes mellitus, and gastrointestinal, cardiovascular, ophthalmological, neurological, and psychiatric problems [31, 32].

While short-term therapy with SCs has proven effective for treatment of exacerbations [33], there is some controversy over the risk-benefit ratio of SCs for short-term treatment of asthma [30, 34]. The association between SCs and long-term disease burden has been the subject of research, because the economic cost of treating asthma must be added to management of adverse events and the indirect costs related to lack of productivity while the patient is receiving health care [21]. Also relevant is the fact that while clinical practice guidelines recommend the use of doses <7.5 mg/d, the real situation is very different, with doses reaching up to 22 mg/d [21]. This may be due to resistance to SCs resulting from genetic factors or the widespread belief that SCs are effective for all asthma patients and are prescribed in the absence of markers that could predict an adequate response to them [21,34,35].

The frequency of use of SCs must be minimized. Current guidelines do not provide recommendations for reducing oral SCs in asthma patients. Therefore, the recent

consensus document on prescription of SCs, reduction in frequency of prescription, detection of adverse effects, and shared decision making provides useful information for clinical practice. Nevertheless, the consensus process revealed many areas in which there was disagreement, thus underscoring the need to continue research in this field [34].

The findings of our study, which is based on big data analysis, are robust, since they make it possible to analyze the whole study population and ensure that the number of patients collected and analyzed is very high. Our findings agree with those reported in other observational cohort studies or the results of telephone surveys with much smaller samples [21,34,36]. Also important is the fact that ours was a real-world study, in which the population analyzed comprised all asthma patients seen in our autonomous region and not a selected sample, as is the case in clinical trials and some registry studies.

Our study is limited by the fact that, although it collected information for the whole population, the analysis setting is restricted to a single autonomous region. However, in our opinion, the model of the Spanish health system, which provides universal coverage mainly through primary care in all autonomous regions, enables the general findings of our study to be extrapolated to the whole of the country, with local differences that depend more on the particular interests of some physicians or specific centers.

Another limitation of our study is that with Savana Manager version 3.0 alone, it was not possible to calculate the cumulative dose received or the exact duration of treatment. More advanced computational techniques will make it possible to resolve this technological limitation in the short term.

In conclusion, our study shows that SCs continue to be widely prescribed for treatment of asthma and that this has a major clinical impact in terms of adverse effects. Particularly striking is the highly frequent prescription of SCs by primary care physicians, thus indicating the need for better training and adherence to clinical practice guidelines and for analysis of the potential causes of this overuse. In those cases where all these elements have been evaluated and it is still necessary to prescribe SCs, we should consider prescribing targeted therapy based on the patient's inflammatory endotype, since these have proven able to reduce, or even obviate, prescription of SCs.

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Table 1. Study Population: Demographic characteristics and Main Comorbid Conditions

	Total	Patients taking systemic corticosteroids	Patients not taking systemic corticosteroids	P Value OR (95%CI)
No.	103 667	58 435	45 232	
Mean (SD) age, years	43.8 (22.1	48.2 (22.1)	37.7 (20.6)	< 0.001*
Female sex, %	59.8	64.1	54.3	1.50 (1.46-1.54)
Smoking, %	16.9	20.1	12.8	1.72 (1.66-1.78)
Rhinitis, %	31.8	30.4	33.6	0.86 (0.84-0.89)
Dyslipidemia (%)	21.3	26.9	14.1	2.25 (2.18-2.32)
AHT (%)	28	35.6	18.2	2.49 (2.42-2.56)
Diabetes (%)	14.2	17.7	9.7	2.01 (1.93-2.08)
Obesity (%)	12.5	16.3	7.6	2.37 (2.28-2.47)
Depression (%)	9.6	12.6	5.7	2.38 (2.27-2.49)
Hiatus hernia (%)	8.3	10.77	5.1	2.42 (2.13-2.36)

(*) p value between patients with and without systemic corticosteroids

Table 2. Use of systemic corticosteroids according to care setting

	Primary care	Allergy	Pulmonology
Mean (SD) age, y	44.3 (0.20)	34 (0.20)	57.5 (0.31)
Female sex, %	62.7	56.9	61.9
Systemic corticosteroids, % • Mean (SD) age, y • Sex, %	59 48.2 (0.31) 66.8	13 38.4 (0.56) 63.2	20 62 (0.61) 69.2
No systemic corticosteroids, %	41	87	80

Table 3. Main adverse effects of systemic corticosteroids.

	Total	Patients taking systemic corticosteroids	Patients not taking systemic corticosteroids	P Value OR (95%CI)
n	103 667	58 435	45 232	
Osteoporosis (%)	6.9	10.3	2.5	4.6 (4.23-4.87)
Glaucoma (%)	2.5	3.5	1.2	3.1 (2.81-3.39)
Cataracts (%)	1.2	1.7	0.4	4.2 (3.62-4.95)
Cushing (%)	0.3	0.5	0.1	7.8 (5.27-11.63)

Figure 1. Flow diagram for the study population

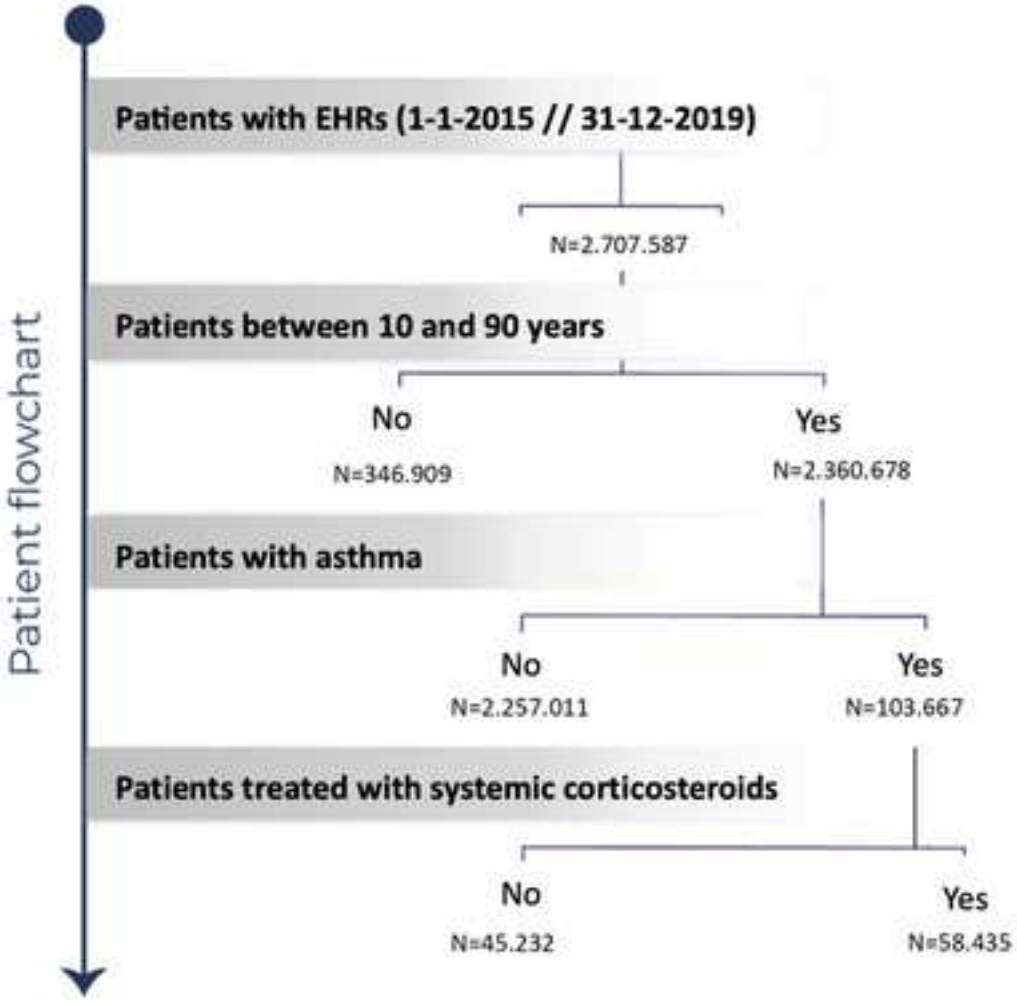


Figure 2. Use of systemic corticosteroids in the general population with asthma between 2015 and 2019.

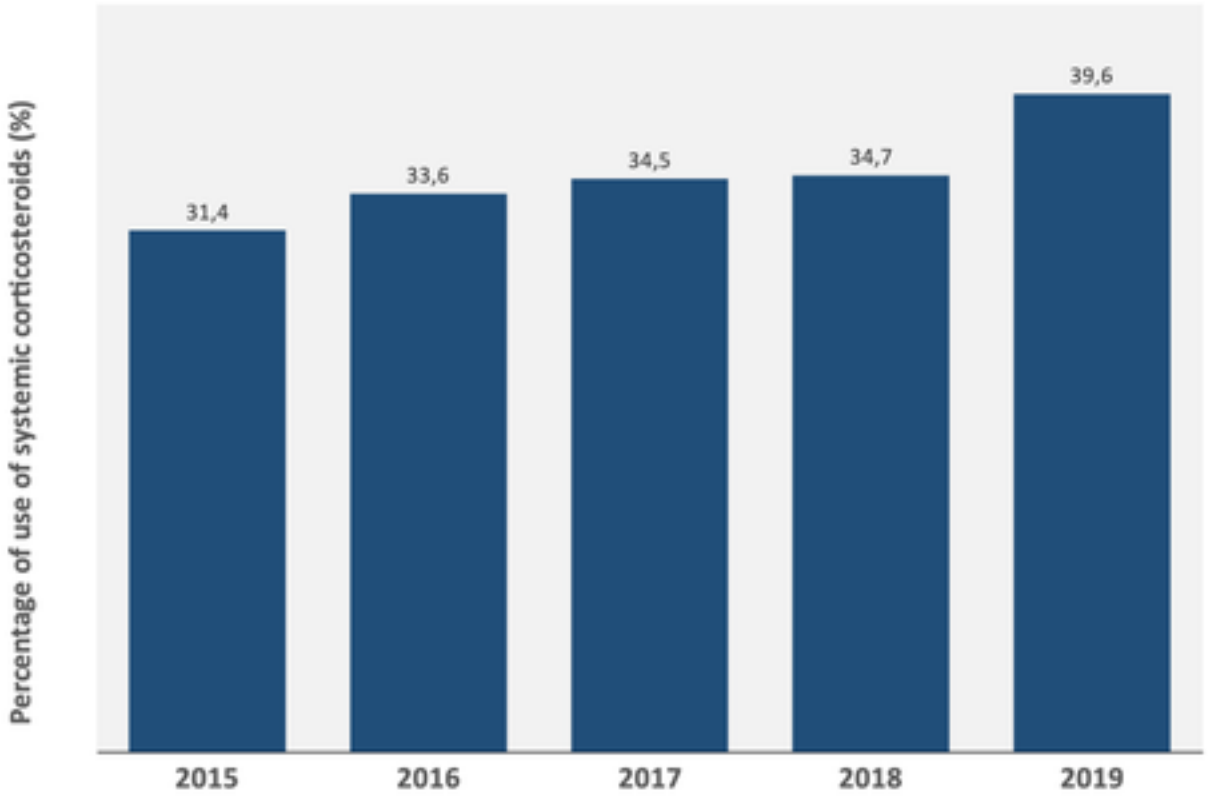
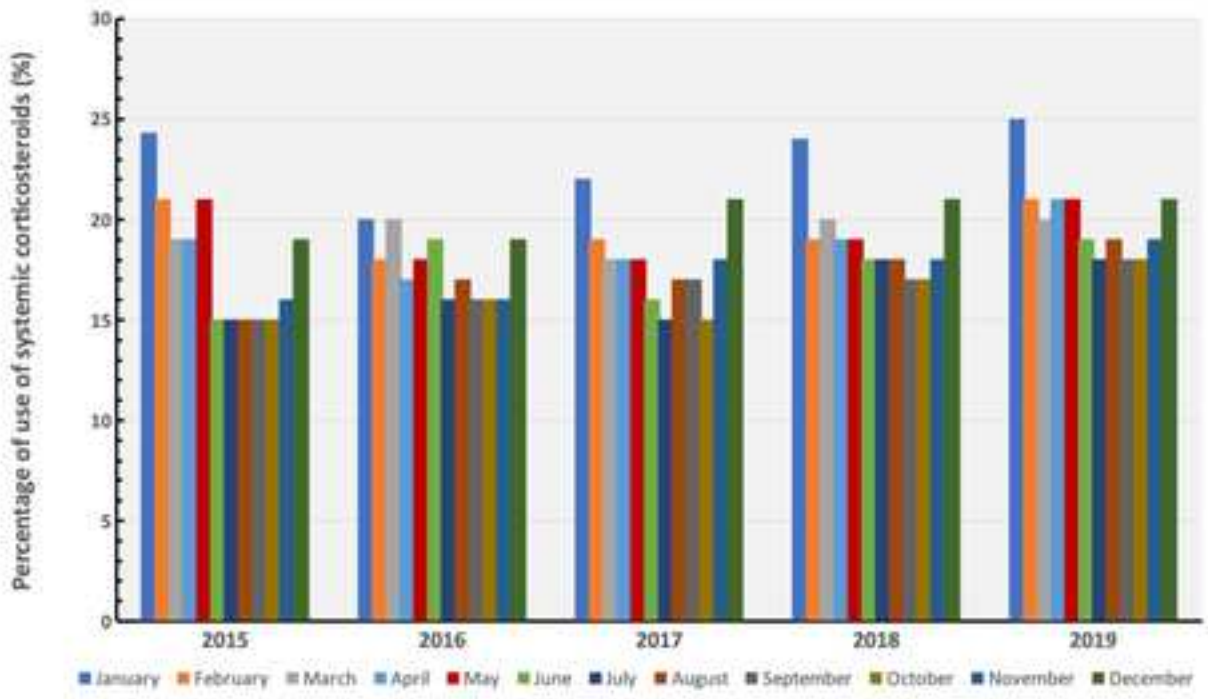


Figure 3. Seasonal variations in the use of systemic corticosteroids during the 5-year study period



Supplementary material (tables)

Table S1

Inclusion criteria

Patients with a clinical diagnosis of bronchial asthma. This criterion also includes the following: Unstable asthma, Adult-onset asthma, Intrinsic asthma, Asthma attack, Asthma exacerbations, Exercise-induced asthma, Asthma without status asthmaticus, Mixed asthma–COPD phenotype, Asthma in children ≥3 years, Asthmatic bronchitis, Cough variant asthma, Allergic asthma, Mild asthma, Moderate asthma, Occasional asthma, Severe asthma, Chemical-induced asthma, Substance-induced asthma, Intermittent asthma, Seasonal asthma, Occupational asthma, Chronic obstructive airway disease with asthma, Asthma in children aged <3 years, Untreated asthma, Treated asthma, Persistent asthma, Recent-onset asthma, Induced asthma.

Exclusion criteria

Patients with a specific diagnosis other than bronchial asthma, including COPD, pulmonary edema, pneumonia, pulmonary embolism, pneumothorax, rib fracture, aspiration, pleural effusion, or any other associated respiratory or nonrespiratory infection.

Table S2. Systemic corticosteroids analyzed

Triamcinolone

Dexamethasone

Prednisone

Prednisolone

Hydrocortisone

Paramethasone acetate

Methylprednisolone

Betamethasone

Fludrocortisone

Deflazacort

Table S3. Search criteria used to identify patients with bronchial asthma.

Asthma in children <3 years
Untreated asthma
Treated asthma
Persistent asthma
Recent-onset asthma
Induced asthma
Asthma without status asthmaticus
Occupational asthma
Exercise-induced asthma
Chemical-induced asthma
Mixed asthma
Unstable asthma
Nonallergic asthma
Asthma attack
Asthma in children ≥3 years
Adult-onset asthma
Asthma exacerbation
Acute asthma
Bronchial asthma
Cough variant asthma
Mild asthma
Moderate asthma
Occasional asthma
Substance-induced asthma
Allergic asthma