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Patterns of oral corticosteroids use in primary care patients with severe asthma

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ABSTRACT

Aim: To assess the pattern of use of oral corticosteroids (OC) in primary care patients with severe asthma.
Methods: Data derived from the Health Search Database (HSD) gathering information on 700 Italian general practitioners. A cohort of severe asthma patients was identified between 2013 and 2017 and followed-up for one year. The association between candidate predictors and the incident escalation to OC was tested through a multivariate Cox regression model.
Results: Among patients with asthma (N = 55,075), 284 were diagnosed with severe asthma. Among them, the proportion of OC users decreased from 82.2% in 2013 to 75.3% in 2017. For what concerns the determinants of OC prescriptions, among 284 patients being defined at baseline (2013–2016) as those suffering from severe asthma, 216 (76.1%) were first-ever prescribed with OC at least once during one year of follow-up. The presence of gastroesophageal reflux disease (HR 1.37; 95% CI 1.02–1.85), osteoarthritis (HR 1.54; 95% CI 1.12–2.12) and moderate asthma exacerbations (HR 1.72; 95% CI 1-02-2.93) was significantly associated with the outcome.
Conclusions: The optimization of asthma treatment and the management of comorbidities may be potential leverages to reduce the inappropriate use of OC in patients with severe asthma.

1. Introduction

Asthma is a chronic condition affecting 300 million people worldwide, which prevalence in the general population has been reported to have increased over the last decades [1,2]. Asthma is a risk factor for the development of other chronic respiratory diseases – including chronic obstructive pulmonary disease (COPD) – and for the occurrence of pneumonia [3,4]. As such, asthma is considered a major cause of disability, which strongly impacts on patients' quality of life and is responsible for high healthcare-related costs [5]. Among asthma patients, those with a severe disease – usually less than 10% of them – explain half of the costs associated with this condition [6].

The progression of asthma severity is characterized by a higher frequency of exacerbations, which usually require the use of oral corticosteroids (OC) for symptoms control. At the same time, escalation to OC may reflect a scarce adherence to the maintenance therapy, which continues to be a major concern among asthmatic patients [7–9]. Despite the proven efficacy, data coming from literature, highlights as an exposure to 4 or more OC prescriptions in the current year was associated with statistically significantly greater odds of having an adverse event in a given year due to: osteoporosis, hypertension, obesity, type 2 diabetes, gastrointestinal ulcers/bleeds, fractures, and cataracts [10]. To note, a dose-response relationship for cumulative exposure of OC with most adverse outcomes began at cumulative exposure of 1.0–2.5 g, and for some of them (e.g., type 2 diabetes) at cumulative exposure of only 0.5–1 g that is equivalent to 4 lifetime OC courses [11].

Given their safety profile and the availability of novel biological therapies targeting directly IgE, IL-5 and IL-5 receptors, the role of OC in the treatment of severe asthma has progressively narrowed. Still, OC remain frequently prescribed in these patients, both as chronic treatments and for exacerbations management [12].

Little is known about which factors trigger OC prescription in

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primary care patients with severe asthma. The aim of the present study was to assess the pattern of use of OC, and the factors associated to their prescription in primary care patients with severe asthma.

2. Methods

2.1. Data source

For the present study, we analyzed data from the Health Search Database (HSD). HSD is an Italian general practice database used for research purposes, that gathers a significant deal of information, including patients' demographics, clinical diagnoses, drug prescriptions, specialist referrals, and date of death. Clinical examinations, drug prescriptions and diseases are coded in accordance with the National Health code system, the Anatomical Therapeutic Chemical (ATC) classification system and the International Classification of Diseases 9th Revision Clinical Modification (ICD-9CM), respectively. Out of a network of about 1000 general practitioners (GPs) – which register patients' data on a voluntary basis – we selected those 700 GPs who fulfill the up-to standard quality criteria for data registration. Such practitioners are homogeneously distributed across Italy and cover a population of more than one million individuals. The representativeness and reliability of HSD data for epidemiological research are supported by a number of studies [13–15].

2.2. Cohort and outcome definition

At first, we formed a cohort of patients diagnosed with asthma (ICD-9 CM: 493*) in the period between January 1, 2013 and December 31, 2017. The date of the diagnosis was considered as the index date. Patients younger than 15 years, and those registered in HSD for less than 1 year were excluded. Information on anti-asthma drugs prescribed within 3 months before and after the index date was collected. The following drugs were considered: inhaled corticosteroids (ICS), short acting β_2 agonists (SABA), long acting β_2 agonists (LABA), fixed combination of ICS + LABA, leukotriene modifier (LTRA), short acting muscarinic antagonist (SAMA), fixed combination of SABA + SAMA, xanthines, OC indicated for the treatment of asthma, and anti-IgE drugs. According to international guidelines, severe asthma was defined as a diagnosis of asthma treated with high dose ICS plus a second controller (i.e. LABA or LTRA or OC). Only patients fulfilling these criteria for a consecutive period of at least 120 days entered the cohort [16]. Among these patients, the incident prescription OC was considered the outcome of the present study. Those diagnosed with severe asthma during the study period were followed up for one year until the occurrence of one of these events, whichever came first: first prescription of OC (namely those with no prescription of OC in the year preceding the index date), end of registration with the GP, death, or the 365th day of follow-up. The cumulative dosage, which is based on prescribed daily dose (PDD) of OC, has been calculated for each participant in the study period.

2.3. Candidate determinants

Demographic, lifestyle and clinical information was collected until the index date. Beyond sex and age, the following conditions were considered: atopy (atopic eczema/dermatitis, allergic rhinitis), chronic rhino-sinusitis, nasal polyposis, COPD, gastro-esophageal reflux disease (GERD), depression and anxiety, overweight and obesity, diabetes mellitus, cardio and cerebrovascular diseases, cancer, osteoarthritis and previous asthma exacerbations. The presence of previous asthma exacerbation was categorized as: moderate, when a diagnosis of asthma was coupled with a prescription of OC and severe, when an admission to emergency department or hospital related to asthma occurred. Given that hospitalizations might be under-registered in HSD, these events have been manually validated by inspecting the related free-text. Namely, whole and truncated words, and synonyms, related to hospital and emergency department admissions, were employed to detect free-text inputs to be manually inspected by the study assessors.

2.4. Analytical approach

Baseline patients' characteristics were reported as mean ± standard deviation (SD) or absolute numbers and percentage (%), as appropriate. The association (hazard ratio [HR] and 95% confidence interval [CI]) between incident OC prescription and patients' characteristics was tested through Cox regression models. All the candidate predictors entered the model simultaneously. HRs can be interpreted as the instantaneous chance to escalate to OC of patients with a given characteristic, divided by the chance to escalate to OC of patients without that characteristic. The proportional hazards assumption was assessed by regressing the scaled Schoenfeld's residuals against the incident outcome. No violation of proportionality was detected. All the analyses were carried out with Stata 13.0 (StataCorp).

3. Results

During the period 2013–2017, out of 55,075 asthma cases identified in HSD, 284 were defined as severe. Patients' mean age was 61.0 (SD 16.2) years and 63% were women. At the index date, 216 (76.1%) patients were prescribed with OC, with annual prevalence figures decreasing from 82.2% in 2013 to 75.3% in 2017 (Fig. 1). In the same period, an increase in the number of OC PDDs has been observed, raising from 7 mg in 2013 to 8.6 mg in 2017 ($P < 0.05$). To note, a less steep increase in OC PDDs has been observed in the overall sample of patients with asthma (from 6.9 in 2013 to 7.1 in 2017; $P > 0.05$).

Table 1 shows the patients' characteristics associated with an incident OC prescription during the first year of follow up. The presence of GERD (HR 1.37; 95% CI 1.02–1.85), osteoarthritis (HR 1.54; 95% CI 1.12–2.12) and moderate exacerbations (HR 1.72; 95% CI 1-02-2.93) – but not severe – was associated with the outcome.

4. Discussion

Our findings show that, in Italy, the 0.5% of primary care patients with asthma suffer from severe asthma. Within them, 76% received at least an OC prescription during the first year since the diagnosis of severe asthma. This figure is in line with data from Italian National Severe Asthma Network (SANI) in which 64% of asthma patients are treated with OC [17]. We documented a decreasing use of OC in the period 2013–2017. The presence of GERD, osteoarthritis and moderate asthma exacerbations resulted associated with the incident prescription of OC.

In accordance with international guidelines on asthma, following a stepwise escalation of controller drugs, OC are usually prescribed in case of scarce symptoms control. Indeed, OC should be prescribed after an appropriate assessment of factors potentially contributing to the exacerbations and treatment optimization. On the other hand, the latest update of the Global Initiative for Asthma (GINA) guidance (2019) states that maintenance OCS are not the preferred treatment in step 5 of GINA, given the high risk of adverse outcomes, suggesting to implement strategies to minimize side-effects [18]. According to a meta-analysis by Engelkes et al., an increase by 25% in the adherence to controller drugs, is associated with about 10% reduction in severe exacerbations in adults with asthma. Interestingly, according to the same study, scarce adherence is also associated with OC utilization [7]. In line with such evidence, in our study the history of asthma exacerbations of moderate intensity was associated with the highest (70%) hazard of being prescribed with OC. On the other hand, severe exacerbation did not result associated with escalation to OC. The limited number of individuals presenting with severe exacerbations (1%) may have not provided enough statistical power to identify the determinants of OC which are likely overused. This may have been driven by the likely underreporting of hospitalization episodes in our data source. Regarding OC dosage and

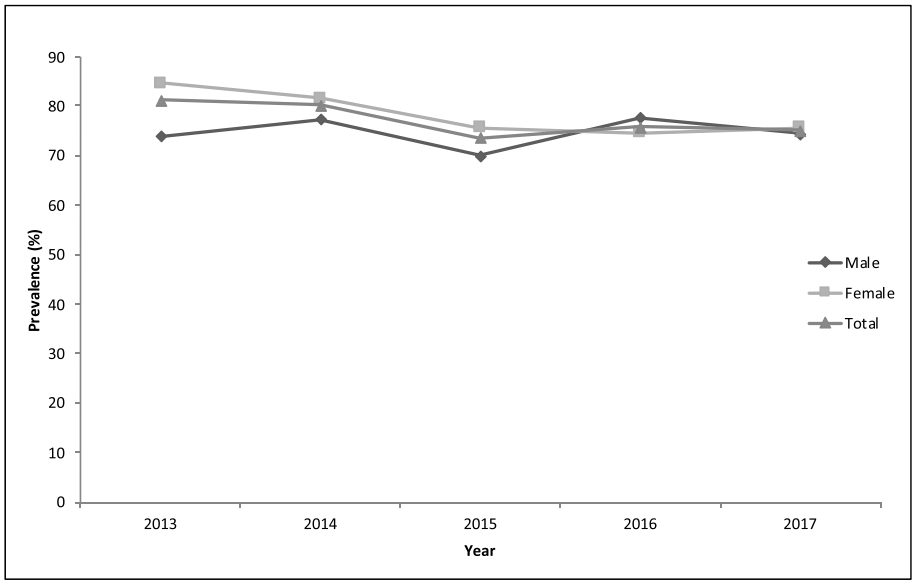

Fig. 1. Annual prevalent use of oral corticosteroids in patients with severe asthma (2013–2017).

Table 1
Association between candidate predictors and incident prescription of oral corticosteroids during 1-year follow-up in primary care patients with severe asthma.

	Severe asthma cases (n = 284)	HR	95% CI
Sex, n (%)			
Female	179 (63.03)	Ref.	–
Male	105 (36.97)	0.97	0.72–1.31
Age (years, mean [SD])	60.95 (16.2)	1	0.99–1.01
Comorbidity, n (%)			
Atopy	48 (16.9)	0.79	0.54–1.17
Chronic rhino-sinusitis	16 (5.63)	1.17	0.65–2.12
Nasal polyposis	17 (5.99)	1.1	0.62–1.94
COPD	76 (26.76)	0.78	0.57–1.09
Gastro-esophageal reflux disease	102 (35.92)	1.37	1.02–1.85
Depression and anxiety	102 (35.92)	1.28	0.95–1.72
Overweight and obesity	122 (42.96)	0.89	0.66–1.19
Diabetes mellitus	31 (10.92)	1.28	0.84–1.94
Cardio and cerebrovascular diseases	32 (11.27)	0.94	0.60–1.46
Cancer	98 (34.51)	1.1	0.82–1.47
Osteoarthritis	111 (39.08)	1.54	1.12–2.12
Moderate Exacerbations	17 (5.99)	1.72	1.02–2.93
Severe Exacerbations	3 (1.06)	0.66	0.15–2.82

CI= Confidence Interval; COPD= Chronic Obstructive Pulmonary Disease; HR= Hazard Ratio.

use duration, the incidence of adverse effects has been previously shown to increase with each year of exposure, particularly when 4 or more OC prescriptions were refilled each year. Data coming from Sullivan et al., show that in patients with severe asthma, OC prescription results in a cumulative burden on current and future health, regardless of dose and duration [10,11]. Arguably, the progressive reduction in OC prescription that we observed between 2013 and 2017 among patients with severe asthma might be due to both a change in the prescribing attitudes of both specialist and GPs, in line with the above mentioned most recent recommendations, and a higher awareness of patients to the consequences of noncompliance. Interestingly, men and women result equally prescribed with OC after 2015. Again, the progressive acquisition of standardized attitudes by the prescribers might explain this finding. Finally, a differential inter-individual response to OC has been described in patients with severe asthma [19]. This may further contribute an element of heterogeneity in the observed prescription patterns.

Apart from poor adherence to maintenance therapy, a few other factors may be responsible for inadequate symptom control among which: refractory nature of the disease, limited access to health care professionals and patient's poor health literacy [20]. To the best of our knowledge, this is the first study exploring the determinants of escalation to OC treatment in primary care patients with severe asthma. Previous studies had described the association between OC use and comorbidities, but mostly looking at OC as a predictor of adverse drug-related events [10,11,21]. In our study, a concurrent diagnosis of GERD was associated with a 40% higher hazard of being prescribed with OC within the first year from the diagnosis of severe asthma. In the literature, up to 65% of patients with asthma have been reported to suffer from GERD, which is among the most frequent contextual causes of asthma and chronic cough [22]. The relationship between these two conditions is indeed bidirectional and the scarce pharmacological control of both, encompassing the use of proton pump inhibitors and chronic asthma controllers, often triggers a vicious circle where negative intrathoracic pressure on one side and aspiration on the other side exacerbate symptomatology each other [22]. To note, the presence of nasal polyps, a common complication of severe asthma, usually treated with OC, in our study did not appear a significant predictor. In spite of nasal polyps being diagnosed in 5% of our study population, the low number of cases probably did not provide enough statistical power [23].

In our cohort, osteoarthritis resulted associated with a 50% higher hazard of receiving OC. The association between respiratory diseases – including asthma – and degenerative diseases of bone and joints has extensively reported in the literature, and can be explained by the presence of a number of common risk factors [24,25]. Osteoarthritis is a prevalent cause of disability, leading to diminished tolerance to exercise and chronic pain. The reduced tolerance to exertion may lower the threshold of exacerbations in patients with asthma, also affecting the subjective perception of the symptomatology. In this respect, a suboptimal maintenance asthma therapy may worsen the overall clinical picture. This is indirectly corroborated by the evidence in our study of a 70% higher hazard to escalate to OC for patients experiencing moderate asthma exacerbations. On the other hand, OC are sometimes prescribed to treat symptomatic osteoarthritis [26]. This may partially explain the association found in our study.

A few limitations of the present study are worthy to be mentioned. First, because of the nature of the database, we were able to include

among the potential predictors only a limited number of variables. We cannot exclude residual confounding derived from uncollected data. However, the measures we used are those commonly available in primary care databases, which practitioners base their decisions upon. Second, for the present study we did not have enough analysis power to include adherence to respiratory maintenance drugs as candidate predictor. This analysis would have been sensitive to reverse causation bias (i.e. higher adherers result at greater risk of OC use), and ad-hoc design and analyses should be planned. Finally, the low proportion of asthma exacerbation cases, might be due to the difficulty to fully retrieve such information in our database.

In conclusion, among primary care patients with severe asthma, almost eight in ten receive at least one OC prescription during the first year since the diagnosis. Both disease severity (i.e. presence of exacerbations) and concomitant conditions as GERD and osteoarthritis trigger the use of OC during the follow-up. Such risk factors might be easily monitored in primary care. The optimization of asthma treatment on one side – primarily the improvement of the adherence to inhaler drugs – and of comorbidities, on the other side, may be considered potential leverages to reduce the inappropriate use of OC in patients with severe asthma. The availability of new-generation treatments, as the biological drugs, might contribute to reduce the inadequate prescription of OC in patients with asthma. This would require however an improvement of the diagnostic workflow, promoted by general practitioners in collaboration with the specialists.

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Declaration of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: FL and EM provided consultancies in protocol preparation for epidemiological studies and data analyses for Chiesi, Novartis and GSK; CC provided clinical consultancies for Chiesi, Novartis and GSK. DLV, AZ, EB and FPL have no conflict of interests to disclose.

CRediT authorship contribution statement

Davide L. Vetrano: Writing - original draft, Writing - review & editing, Methodology. **Alberto Zucchelli:** Writing - original draft, Writing - review & editing, Methodology. **Elisa Bianchini:** Formal analysis. **Ettore Marconi:** Visualization, Writing - review & editing. **Francesco P. Lombardo:** Supervision, Conceptualization. **Claudio Cricelli:** Supervision, Conceptualization. **Francesco Lapi:** Conceptualization, Methodology, Project administration, Supervision.

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