Overuse of Oral Corticosteroids, Underuse of Inhaled Corticosteroids, and Implications for Biologic Therapy in Asthma

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Oral corticosteroid · Severe asthma · Biologic

Abstract
Background: Asthma patients using high cumulative doses of oral corticosteroids (OCSs) are at risk of serious adverse events and are increasingly being treated with steroid-sparing asthma biologics. However, it is unknown whether prescribing these expensive biologics is always justified. Objectives: This study aimed to (1) assess the prevalence of asthma patients using high cumulative doses of OCSs, (2) explore the role of suboptimal inhaler therapy, and (3) estimate the proportion of patients to whom asthma biologics might be prescribed unnecessarily.

Methods: All adults (n = 5,002) with at least 1 prescription of high-dose inhaled corticosteroids (≥500–1,000 mcg/day fluticasone-equivalent) and/or OCSs (GINA step 4–5) in 2010 were selected from a pharmacy database including 500,500 Dutch inhabitants, and sent questionnaires. Of 2,312 patients who returned questionnaires, 929 had asthma. We calculated the annual cumulative OCS dose and prescription fillings and checked inhaler technique in a sample of 60 patients. Patients estimated to have good adherence and inhaler proficiency who still required high doses of OCSs (≥420 mg/year) were considered candidates for initiating biologic treatment.

Results: 29.5% of asthma patients on GINA 4–5 therapy used high doses of OCSs, of which 78.1% were likely to have poor therapy adherence or inadequate inhaler technique. Only 21.9% were considered definitive candidates for biologic therapy.

Conclusion: High OCS use in Dutch GINA 4–5 asthma patients was common. However, in 4 out of 5 patients adherence to inhaled corticosteroid therapy and/or inhalation technique was considered suboptimal. Since optimizing inhaler therapy may reduce the need for OCSs, this should be mandatory before prescribing expensive steroid-sparing drugs.

Introduction

Many patients with severe or uncontrolled asthma use oral corticosteroids (OCSs) in addition to treatment with inhaled corticosteroids (ICS) and long-acting β2-agonists (LABA) [1], either intermittently to treat exacerbations or chronically to maintain acceptable levels of asthma control [2]. Chronic or frequent use of OCS for asthma is known to be associated with a variety of serious and de-

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bilitating acute and chronic adverse effects [3], the incidence, type, and severity of which depend on the cumulative OCS dose used by the patient [4–6]. Even cumulative exposures as low as 0.5–1 g prednisolone equivalent have been reported to be associated with adverse outcomes [1]. Over the past 5 years, new biologics for severe asthma have become increasingly popular after studies had shown that these treatments can significantly reduce OCS courses in patients experiencing frequent asthma exacerbations and lower the OCS maintenance dose in OCS-dependent patients.

A major drawback of these biological treatments however, is the high cost compared to OCS tablets. It is therefore of the utmost importance that these expensive treatments are only prescribed to patients in whom all measures have been taken to reduce or prevent the use of OCS. In particular, it is important to ascertain whether patients have been prescribed sufficiently high doses of inhaled corticosteroids (ICS), whether they demonstrate optimal adherence to ICS and whether their inhalation technique is adequate. There is good reason for uncertainty in this respect, given the large “placebo” effect in the various phase 3 OCS tapering studies [7–9]. Therefore, the aim of the present study was to investigate whether asthma patients with high cumulative OCS use were adherent to ICS therapy and used their inhalers correctly, and to estimate the proportion of patients to whom asthma biologics might be prescribed unnecessarily.

Material and Methods

Design and Study Population

This is a cross-sectional study using data from a pharmacy database with prescription data from 65 community pharmacies in the Netherlands, including 500,500 patients from the general population. This database was also used in a previous study on the prevalence of severe asthma by Hekking et al. [10]. First, patients with at least 1 ICS prescription between January 1, 2011, and January 1, 2012 (study period), were identified. From these patients, patients with severe or uncontrolled asthma were identified. This included subjects with at least 1 prescription of high dose ICS (≥1,000 mcg fluticasone-equivalent) or medium-high dose (500–1,000 mcg/day fluticasone-equivalent) combined with maintenance OCS therapy (≥5 mg/day prednisone equivalent for ≥6 months in the previous year). All these patients (n = 5,002) were sent questionnaires, which included questions on demographics, medical history, medication consumption, smoking history, and asthma control. A total of 2,312 patients completed and returned questionnaires (response rate of 46.2%). Table 1 shows characteristics of responders and nonresponders: mean age, ICS, and OCS dose were similar between responders and nonresponders; however, nonresponders were slightly younger and less often adherent to ICS than responders. Based on the data from the questionnaires, we selected adult patients (≥18 years) with a diagnosis of asthma (i.e., self-reported diagnosis of “asthma” or self-reported diagnosis of “COPD” with a smoking history of <10 pack-years). Patients with other self-reported pulmonary diagnoses, such as sarcoidosis, cystic fibrosis, or bronchiectasis, were excluded.

Results

Prevalence of Asthma Patients on High Cumulative Doses of OCSs

Of the patients with severe or uncontrolled asthma in the pharmacies database who returned questionnaires (n = 2,312), asthma was diagnosed in 929 (40.2%). Of these, 274 (29.5%) patients were treated with high cumulative doses of OCS (shown in Fig. 1). These patients were mostly elderly females, with late-onset asthma, allergies, and recurrent exacerbations, taking median prednisone equivalent doses of 750 mg per year (Table 2).

Adherence and Inhaler Technique

Of the 274 asthma patients using high dose OCS, 130 patients (47.4%) were not adherent to ICS (prescription filling <80%). Among a random sample of 60 adherent patients, only 41.6% showed adequate inhaler technique (shown in Fig. 2). Thus, only 21.9% of patients were ad...
herent to ICS therapy and used their inhalers correctly, implying that 78.1% of patients with severe or uncontrolled asthma could be falsely labeled as candidates for biologic therapy.

**Discussion**

This study shows that in 2010–2011 about 30% of asthma patients with severe or uncontrolled asthma (7% of the total asthma population) used high cumulative doses of OCS. Given the median prednisone equivalent dose of 750 mg/year, these patients were at risk of serious adverse effects in the short and long term [5, 11]. However, 78% of these patients were considered to have either poor therapy adherence or inadequate inhaler technique, or both, which may have contributed significantly to OCS overuse. Therefore, only 22% of the patients with high OCS use were regarded definite candidates for initiating therapy with biologics.

In our study, 30% of patients with severe or uncontrolled asthma were exposed to high cumulative doses of OCS. Other studies found slightly different prevalences. A recent systematic review on the use and health-related adverse effects of systemic corticosteroids in asthma elegantly summarized the findings of 129 studies addressing this topic [1]. For patients with severe or difficult-to-treat asthma, short-term OCS was used in 46.3–92.6% of patients over a 1-year period, while chronic OCS use ranged from 33.2 to 65% in 5 studies of patients with moderate-to-severe or severe asthma. A study from Germany in asthma patients treated with high dose ICS/LABA showed that 22% used ≥1 OCS prescription in 1 year [12]. Another study from the United States found that 23% of GINA 4–5 asthma patients could be classified as high OCS users at some point during an average follow-up of 40.8 months), with high OCS use defined as ≥450 mg prednisone equivalent in a 90-day period [13]. An Australian study reported high OCS use defined as ≥1 g prednisone equivalent/year in 10% of asthma patients on high dose ICS/LABA [14]. Such differences in reported prevalences of OCS using asthma patients are not surprising and may relate to differences in population, definitions of OCS use, or management strategies.

Our study shows that 47% of high OCS users were nonadherent to inhaler therapy, which is in line with pre-

**Table 1.** Patient characteristics of responders and nonresponders to the questionnaires

|                      | Responders (n = 2,312) | Nonresponders (n = 2,690) | p value |
|----------------------|------------------------|---------------------------|---------|
| Age, year – med. IQR | 64 (55–74)             | 61 (49–73)*               | 0.000   |
| Male sex – %         | 44                     | 43.5                      | 0.720   |
| Prescribed ICSs per day, mcg† – med. IQR | 1,000 (600–1,000) | 1,000 (600–1,000) | 0.059   |
| Adherence to ICSs, %† – med.IQR | 82 (49–107)    | 67 (39–99)*               | 0.000   |
| Total OCS dose per year, mg‡ – med. IQR | 400 (210–826)    | 360 (210–840)             | 0.329   |

† Inhaled corticosteroid dose is provided as fluticasone-equivalent. ‡ Proportion of prescription that was filled. § OCS dose is provided as prednisone equivalent. * p value <0.05.

**Fig. 1.** Calculation of the prevalence of asthma patients on steps 4–5 who use high doses of OCSs. Results from the clinical questionnaires were combined with data on medication use to calculate prevalences of patients with severe or uncontrolled asthma, and the subset of patients using ≥420 mg prednisone equivalent per year. GINA, Global Initiative for Asthma. OCS, oral corticosteroid.
Table 2. Characteristics of patients with severe or uncontrolled asthma using high cumulative doses of OCSs

| Demographics                                      | N = 274† |
|---------------------------------------------------|----------|
| Age, year – med. IQR                              | 67 59–78 |
| Male sex – n%                                      | 84 30.7  |
| BMI, kg/m² – med. IQR (n = 171)                   | 25 23–30 |
| Current smoker – n% (n = 267)                     | 13 4.9   |
| Pack-years (PY) – med. IQR (n = 271)              | 0 0–1    |
| Asthma features                                    |          |
| Allergy symptoms§ – n% (n = 260)                  | 156 60   |
| Nasal polyps – n% (n = 262)                       | 74 28.2  |
| Treating physician (n = 267)                       |          |
| General practitioner – n%                         | 66 24.7  |
| Pulmonologist – n%                                | 201 75.3 |
| Asthma control                                    |          |
| ACQ-6 score§ – med. IQR                           | 1.67 0.83–2.52 |
| Rescue OCS courses in past year                   |          |
| None – n%                                         | 59 21.5  |
| 1–2 courses – n%                                  | 106 38.7 |
| 3 or more – n%                                    | 109 39.8 |
| Hospital admission for asthma in past year       |          |
| None – n%                                         | 197 71.9 |
| 1–2 admissions – n%                               | 57 20.8  |
| 3 or more – n%                                    | 20 7.3   |
| Medication                                        |          |
| Prescribed ICSs per day, mcg†† – med. IQR         | 750 600–1,000 |
| Total prescribed oral corticosteroid dose per year, mg‡‡ – med. IQR | 750 510–1,650 |

OCS, oral corticosteroid; ICS, inhaled corticosteroid. ACQ-6 is the 6-item Asthma Control Questionnaire. † Unless otherwise stated. ‡ 1 pack year equals smoking of 20 cigarettes per day during 1 year. § Self-reported allergy to common inhaled allergens. †† ICS dose is provided as fluticasone-equivalent. ‡‡ Oral corticosteroid dose is provided as prednisone equivalent.

Fig. 2. Therapy adherence and inhalation technique in GINA 4–5 asthma patients who use high doses of OCSs. From a pharmacy database of 500,000 Dutch patients, 274 were identified with severe or uncontrolled asthma using high doses of OCSs. Of these 78.1% were considered nonadherent or having poor inhalator technique, only 21.9% were truly refractory to inhaled asthma therapy. Adherence rates were derived from prescription refills; inhalation technique was verified by pharmacists in a sample of 60 adherent patients. OCS, oral corticosteroid.

Previous reports showing showed similar disappointing rates, ranging from 42.5 to 65% [14–18]. Still, when checking inhaler proficiency in a representative sample of 60 adherent patients, more than half (60%) were not able to use their inadequate inhaler correctly. Our finding of poor inhaler technique is slightly lower than that from another recent study, in which critical inhaler technique mistakes were made in 70.3–86.6% of patients, depending on the inhaler device [11]. Last, our findings of 21.9% of patients being adherent and showing good inhaler tech-
nique are consistent with the findings of another study showing that after an educational program of adherence and inhaler technique assessment, 27% of patients were truly refractory to therapy [19]. Overall, the observations in this study are important and clinically relevant, since it shows that in the majority of patients with severe asthma and high OCS use, at least 1 major modifiable factor can be identified that is likely to contribute to overuse of OCS which should be addressed before biologic therapy is considered in these patients.

The present study may have some limitations. First, the prevalence of high OCS users may have been underestimated for several reasons such as differences between responders and nonresponders to the questionnaires in adherence rates (lower in nonresponders) or other factors such as ongoing allergen exposure or uncontrolled comorbidities that were not taken into account. Second, our study was confined to the Dutch population, which may limit generalizability to other countries. And lastly, it is likely that OCS overuse is not restricted to patients with severe or uncontrolled asthma and also occurs in patients with less severe disease (e.g., GINA step 2–3) [1].

The strengths of this study are the large number of representative patients in the pharmacy database, the availability of clinical data derived from questionnaires, the availability of therapy adherence data, as well as the assessment of inhaler technique in a representative sample. Further, we were able to compute the cumulative dose of OCS therapy, which increased the accuracy of assessing the prevalence of patients excessively exposed to OCS and thus the population at risk for adverse side effects.

The possible reasons for OCS overuse in asthma patients are numerous. However, the most obvious and common reason is that many patients are under-treated with ICS/LABA, due to nonadherence to treatment or inadequate inhaler technique [18, 20]. These patients are likely to require much less OCS if these factors were addressed. This is also illustrated by the large placebo effect observed in many controlled trials with oral steroid-sparing biologics [7–9], Another reason of OCS overuse may be that these drugs are prescribed inappropriately for nonsteroid responsive conditions, including nontype 2 asthma, remodeled airways without active inflammation, or symptoms of comorbidities such as obesity, dysfunctional breathing, or bronchiectasis [21, 22]. Finally, some asthma patients may still use high cumulative doses of OCS because they are not recognized as high OCS users and are not referred to an asthma specialist. This is illustrated by the present study in which 1 in 4 patients with high OCS use was not monitored by a pulmonologist.

This study has important clinical implications. Patients who require high doses of OCS, either recurrent short courses or maintenance treatment, should always undergo a thorough clinical assessment, including an evaluation of adherence, inhaler technique, exposures to asthma triggers, and comorbidities [23–25]. If not done before, they should also undergo trial therapy with long-acting muscarinic antagonist or macrolides. Patients that are still refractory to therapy despite all these measures and who show clear signs of type 2 airway inflammation should be eligible for biologic therapy. This also includes chronically poor adherent patients who carry a very large burden of the disease (e.g., patients admitted in ICU, frequently admitted in the ward, or already suffering from very severe OCS-induced side effects) to whom all efforts available have been provided.

In summary, our study shows that almost one-third of GINA step 4–5 asthma patients in the Netherlands were exposed to high and potentially harmful cumulative doses of OCS in the prebiologic era. Eighty percent of these patients were considered to be nonadherent to inhaled asthma treatment or to have inadequate inhaler proficiency, 2 major factors that are known to contribute to poor asthma control and could be improved. OCS use could probably have been reduced in a proportion of patients if these issues had been addressed. Physicians should therefore not prescribe expensive biologics to patients with high OCS use until they have thoroughly verified that inhaled ICS therapy is being used in an adequate and appropriate manner.

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Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Approval for this study was obtained from the Medical Ethics Committee (MEC W11-064; NTR No. 3546). The analysis was performed with anonymized data. Written informed consent was obtained from patients undergoing a check of their inhalation technique.
Conflict of Interest Statement

K.E., M.A., S.H., P.W.H., and C.L. have no conflicts of interest to declare. E.H.B. reports grants and personal fees from AstraZeneca, G.S.K., Novartis, Sanofi/Regeneron, Teva, Chiesi, and Sterna outside the submitted work.

Author Contributions

M.A., P.W.H., and E.H.B. participated in the collection of data. E.H.B., K.E., M.A., S.H., P.W.H., and C.L. were involved in the designing of the study, analysis of data, writing, and reviewing the manuscript.

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Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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