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Persistence with inhaled corticosteroid therapy in daily practice

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Summary *Objective:* To quantify persistence with inhaled corticosteroids (ICS) among new users in daily practice and identify determinants of persistence.

Methods: A retrospective cohort study was performed with data from the Dutch PHARMO system. This system consists of medication and hospital admission records of 325,000 inhabitants of 12 Dutch cities. In patients who were already using other drugs with a labeled indication of obstructive lung diseases (ATC: R03), individuals with a first dispensing of ICS between January 1, 1994 and December 31, 2000 were identified. Persistence with ICS was defined as the number of days on ICS treatment in the first year of use. Determinants of persistence were identified one year before start of the first dispensing of ICS.

Results: Approximately 50% of the patients used inhaled corticosteroids (ICS) for less than 200 days, while 18% continued treatment for one year. One-year persistence rates increased to 40% in patients with a history of multiple respiratory disease related drugs. Persistence rates also increased with lower initial doses, if the initial prescription was instituted by a medical specialist, if a patient was previously hospitalized for obstructive lung diseases, and with increasing age.

Conclusion: The persistence rate of ICS is poor. Preventing early treatment discontinuation may be important to ensure maximal benefit from ICS treatment.

Introduction

Asthma and COPD are among the leading chronic disorders in Western society. In Europe alone, asthma and COPD are ranked as the third most common cause of death,[1] whereas in North America COPD is listed as the fourth,[2] merely exceeded by heart attacks, cancer, and stroke. Mortality figures are still on the rise.

In asthma, there is unambiguous clinical evidence that inhaled corticosteroids (ICS) are not only effective in reducing frequency and severity of exacerbations, and preventing admission to hospital and intensive care units, but also improve lung function, decrease airway hyperresponsiveness, reduce symptoms, and improve quality-of-life.[3,4]

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Although treating COPD-patients with ICS seems to be cost-effective,[5] the exact role of these anti-inflammatory drugs in COPD has yet to be elucidated.[6,7]

However, COPD is still often recognized as poorly responsive asthma. In addition, beneficial clinical effects of ICS were observed in recent randomized controlled trials, be there: amelioration of respiratory symptoms, persistent improvement in airways reactivity, decreased frequency or severity of exacerbations, diminished use of healthcare resources, and improved health-related quality-of-life.[8] One observational study suggested that ICS therapy is associated with reduced COPD-related morbidity and mortality in elderly patients.[8,9]

Lack of persistence of use of ICS—although proven efficacious in clinical studies—is a threat for achieving maximum patient benefit, and even may have serious health consequences.

Persistence studies with other drugs intended for chronic use (e.g. lipid-lowering drugs, antihypertensives, and estrogen replacement therapy) have shown very low 1-year persistence rates—varying from 20% to 40%.[10–15] As far as we know, no studies have yet been performed on persistence with ICS in patients with obstructive lung diseases, and therefore the rationale of the current study is to quantify the persistence with ICS therapy among new users in daily practice, and to identify determinants of persistence with these anti-inflammatory drugs.

Materials and methods

Study subjects

Setting

Data were obtained from 325,000 inhabitants of twelve cities in the Netherlands who take part in the PHARMO medical record linkage scheme. The PHARMO database consists of the complete medication history for all these patients, linked to their existing hospital discharge records. The linkage has a sensitivity and specificity exceeding 95%.[16–18] The computerized drug-dispensing histories contain data concerning the dispensed drug (identified by WHO's Anatomical and Therapeutical Classification (ATC) system), type of prescriber, dispensing date, dispensed amount, and prescribed dose regimens. The hospital records include detailed information concerning the primary and secondary diagnoses, procedures, as well as dates of hospital admissions and discharges. All diagnoses are coded according to the International Classification of Diseases (ICD) system, version 9 (ICD-9-CM).

Cohort definition

From the PHARMO database, we extracted all medical (hospital) and pharmaceutical information pertaining to the 8-year study period from January 1, 1993 through December 31, 2001. From this data set we created a cohort consisting of patients of at least 5 years of age, who had received their first dispensing of ICS somewhere in the 6-year period between January 1, 1994 and December 31, 2000. The types of ICS prescribed included beclometasone, budesonide, or fluticasone. The date of this first ICS dispensing was considered the index date.

Further, to be included in the cohort, patients had to be registered in the PHARMO database for at least 1 year after the index date, and had to be free from past ICS use. Also, to ensure that ICS was being prescribed for obstructive lung diseases, patients who were never dispensed other drugs with a labeled indication of obstructive lung diseases (ATC code R03) in the year before or at the index date were excluded. Patients who did not refill a prescription of ICS within 1 year were also excluded from further analysis, as were patients who started treatment with, or switched to a combination preparation of an ICS and a long-acting beta-agonist, because it is hard to assess whether failure to therapy persistence is attributable to ICS alone or due to the combination.[19,20]

Study design

Outcome definition

The persistence on ICS treatment was defined as the number of days that ICS was used in the period of 1 year after the index date. One-year persistence rates for ICS were defined as the percentage of patients that used ICS for at least 365 days.[14]

Determinants

Determinants of persistence on ICS treatment were amongst others based on persistence studies done with other drugs and included age, gender, year of start of ICS, medical subspecialism of first prescribing physician, and the initial dose of ICS. All these potential determinants were ascertained at the index date.

In the year prior to the index date, proxies for severity of obstructive lung diseases were assessed as possible determinants for persistence with ICS treatment. These markers included hospitalizations for obstructive lung diseases and prior use of drugs

with a labeled indication of obstructive lung diseases, as described by others.[21,22]

Methods

Persistence with ICS

The prescription patterns were ascertained for each patient in the first year after the index dispensing. For each prescription, the legend duration of use was calculated by dividing the number of units dispensed by the number of units to be used per day as defined in the pharmacies. All prescriptions were subsequently converted into episodes of consecutive use of ICS. In case of interruptions between two ensuing prescriptions of less than 30 days, the episode was considered uninterrupted. It should be noted that experiments with smaller and larger permissible lack periods than 30 days, e.g. 15 and 60 days had only minor effect on the episode length. Patients who switched from one type of ICS to another were considered continuing their ICS therapy. The total duration of treatment included the permissible gaps (up to 30 days) between two subsequent dispensings. Using this definition of persistence, the ratio of sum of all legend durations of individual prescriptions/total duration of treatment (including gaps) was more than 80% in 95% of the patients. For patients who remained on treatment at the end of the study period the duration of treatment was censored at that date (1 year).

Determinants of persistence

The dose of ICS was expressed as a fraction of WHO's defined daily dose (DDD equivalents or DDDeq). The defined daily doses for the different ICS were 800 μg for beclomethasone and budesonide and 400 μg for fluticasone. The daily dose for patients aged 5–16 years was defined as half the dose for adults. DDDeq were estimated by dividing the prescribed and defined daily dose. For example, the DDDeq of a prescribed daily dose of 1000 μg beclomethasone with a defined daily dose of 800 μg is 1000/800 = 1.25 DDDeq.

Hospitalization for obstructive lung diseases was defined as a hospitalization with a primary discharge diagnosis of asthma (ICD-9-CM: 493), emphysema (492), chronic bronchitis (491), and chronic airway obstruction (496) or a hospitalization with a secondary diagnosis (493, 492, 491, 496) and a primary discharge diagnosis that was related to obstructive lung diseases such as upper respiratory tract infection or pneumothorax.[19] The use of drugs with a labeled indication of obstructive lung diseases (ATC: R03) included long-acting beta-agonists (ATC-code: R03AC12 and R03AC13), short-acting beta-agonists (R03AC, minus R03AC12 and R03AC13), parasympathicolytics (R03BB), xanthine-derivatives (R03DA), cromoglycates (R03BC), and systemic sympathicomimetics (R03C). Other relating drugs commonly used during treatment of exacerbations included oral corticosteroids (H02AB), antibiotics (J01), antihistamines (R06A), mucolytics (R05CB), cough medications (R05D) and nasal preparations (R01A).

Analyses

Survival functions describing persistence with ICS treatment over time were computed using Kaplan Meier survival analyses. Crude and multivariate analyses to identify independent determinants of persistence on ICS treatment were conducted using Cox's proportional hazard analyses. Variables significantly associated with persistence in the crude analyses were included in the multivariate analysis. The same statistical models were used for subgroup analyses in patients between 15 and 44 years of age—representing mainly asthma-patients, and in patients older than 65 years of age—representing most likely COPD-patients. Statistical significance was defined at an alpha level of 0.05.

Results

A total of 8736 patients met the inclusion criteria of our study. The characteristics of new users of ICS are described in Table 1. In 78.4% of the patients was ICS therapy initially instituted by general practitioners. Approximately 50% of the patients filled at least one prescription for another drug with a labeled indication of obstructive lung diseases 1 year before the index date; the most frequently prescribed drugs were the short-acting beta-agonists (46.6%), while 14.4% and 56.2% had been dispensed in the 365 days prior to the index date at least one prescription for short courses of oral corticosteroids, and/or an antibiotic, respectively. One-hundred and ninety-one patients (2.2%) had been hospitalized for obstructive lung diseases at least once in the 1 year period before the index date.

About one percent of the new ICS users had only been using anti-tussive agents in the period before the index date, implying low disease severity, while another 1.0% had been using several drugs with a labeled indication of obstructive lung disease in conjunction with oral corticosteroids and antibiotics, suggesting moderate to high disease severity.

Table 1 Characteristics of new users of inhaled corticosteroids 1994–2000 ($N = 8,736$).

Characteristics		Number	%
At start of ICS			
Gender	Male	3994	45.7
	Female	4742	54.3
Age group (year)	5–14	1376	15.8
	15–44	3005	34.4
	45–64	2306	26.4
	⩾65	2049	23.5
Year of start	1994	1823	20.9
	1995–1996	2759	31.6
	1997–1998	2488	28.5
	1999–2000	1666	19.1
Type of ICS	Beclomethasone	4105	47.0
	Budesonide	2712	31.0
	Fluticasone	1919	22.0
Inhaler type	Metered dose	1484	17.0
	Dry-powder	7252	83.0
Daily dose at start (DDDeq)	0–0.74	2996	34.0
	0.75–1.24	3339	38.2
	⩾1.25	2431	27.8
Prescriber	General practitioner	6853	78.4
	Specialist	1883	21.6
One year prior to start of ICS			
Use of respiratory disease related drugs			
I. asthma/COPD drugs	Long-acting beta-agonists	237	2.7
	Short-acting beta-agonists	4069	46.6
	Cromones/Nedocromil	425	4.9
	Parasympathicolytics	1096	12.5
	Sympathicomimetics	403	4.6
	Xanthine-derivatives	185	2.1
Number of asthma/COPD drugs	1	4477	51.2
	⩾2	891	10.2
II. Other drugs	Antihistamines	1781	20.4
	Coughing agents	1296	14.8
	Mucolytics	1406	16.1
	Nasal preparations	1552	17.8
Number of other drugs	1	2911	33.3
	⩾2	1421	16.3
Use of oral corticosteroids	Yes	1260	14.4
Use of antibiotics	Yes	4906	56.2
Hospitalisation	Yes	191	2.2
*Markers of disease severity**			
Anti-cough medication only, no asthma/COPD drugs, no oral corticosteroids		97	1.1

Table 1 (*continued*)

Characteristics	Number	%
One asthma/COPD drug, no oral corticosteroids	3811	43.6
More than one asthma/COPD drug, no oral corticosteroids	615	7.0
More than one asthma/COPD drug and a combination of oral corticosteroids and antibiotics	88	1.0
Undefined†	4125	47.2

*Groups are mutual exclusive.
†For example patients that received other drugs like antihistamines, and mucolytics, or combinations of different types of drugs.

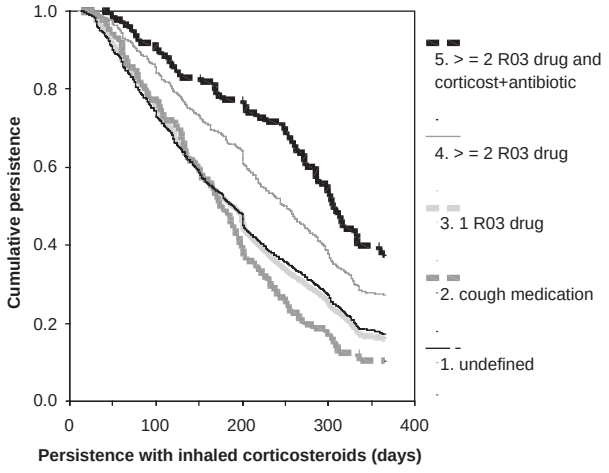

Figure 1 Persistence on ICS treatment in the first year after the index date. Persistence was defined as the total number of days that ICS were used. (1. Undefined, 2. Anti-cough medication only, no respiratory disease related drugs (ATC code = R03), no oral corticosteroids, 3. One respiratory disease related drug, no oral corticosteroids, 4. Multiple respiratory disease related drugs, no oral corticosteroids, 5. Multiple respiratory disease related drugs and combination of oral corticosteroids and antibiotics).

The majority (43.6%) of the patients had low to moderate disease severity, as illustrated by the use of merely one type of asthma/COPD drug before the index date.

From the total cohort, 1539 patients (17.6%) continued ICS treatment for one year, whereas 50% of the patients used ICS for less than 196 days (95%CI: 192–200) during their first year of follow-up. The 1-year persistence rate with ICS-therapy differed for patients with different medication (Fig. 1 and Table 2). One-year persistence with ICS was low (10%) in patients who had been using merely anti-cough medication, indicating low disease severity or off-label prescribing, and this rate increased to 40% in patients with a moderate disease severity, as indicated by utilization of multiple different respiratory disease related drugs, including a combination of oral corticosteroids and antibiotics. Other determinants of statistically significant higher persistence rates with ICS were, in relative order of highest relative risk, low starting dose of ICS, specialist as the first prescribing physician, one or more hospitalizations in the 1-year period prior to the index date, and older age. Persistence rates were decreased for patients that started ICS therapy in the period of 1999–2000 compared to 1994 (Table 2).

Discussion

The present study indicates that overall, one out of two patients starting on ICS therapy discontinues treatment within 6 months, and that only one out of 5 persists with ICS treatment for one year. Persistence with ICS use is clearly related to severity of obstructive lung disease, as illustrated by the increase of this rate to about 40% in patients using multiple different respiratory disease related medications—albeit it still very poor. That severity plays a role in persistence, is also shown by the finding that the persistence rate in patients who had been hospitalized at least once for an obstructive lung disease was higher compared to patients who had not been admitted in the year before the index date.

Lack of persistence of use of ICS—drugs that have been unambiguously shown to be efficacious in clinical trials in asthma patients in reducing frequency and severity of exacerbations, in preventing admission to hospital and intensive care units, in improving lung function, decreasing airway hyperresponsiveness, and in improving quality-of-life of asthma patients[3,4]—is a threat to achieving maximum patient benefit. Studies have demonstrated that discontinuation of ICS as part of intervention studies, results into deterioration of the clinical condition, an increased need for additional (inhaled) corticosteroids, as well as a

Table 2 One-year persistence rates in patients with relevant determinants of persistence with ICS treatment.

Characteristics of patients	Number	Patients persistent for one year (%)*	RR_{adj}† (95% CI)
All patients	8736	17.6	
Subgroups of patients			
Age (years)			
5–14	1376	14.5	0.87 (0.80–0.95)
15–44	3005	11.9	1.0 (ref)
45–64	2306	20.3	1.33 (1.25–1.41)
>64	2049	25.2	1.57 (1.47–1.68)
Year of start			
1994	1823	18.3	1.0 (ref)
1995–1996	2759	17.8	0.96 (0.90–1.02)
1997–1998	2488	18.9	1.02 (0.95–1.09)
1999–2000	1666	14.6	0.86 (0.80–0.92)
Prescriber			
General practitioner	6853	15.0	1.0 (ref)
Specialist	1883	27.2	1.61 (1.52–1.72)
Dose at start (DDDeq)			
0–0.74	2996	18.7	1.64 (1.52–1.78)
0.75–1.24	4111	17.6	1.24 (1.13–1.28)
⩾1.25	1629	16.3	1.0 (ref)
Hospitalisation in year prior to index date			
No	8545	17.2	1.0 (ref)
Yes	191	37.7	1.54 (1.28–1.86)
Previous medication use as a proxy for asthma severity			
Anti-cough medication only, no asthma/COPD drugs, no oral corticosteroids	97	10.3	1.0 (ref)
One asthma/COPD drug, no oral corticosteroids	3811	16.1	1.24 (1.00–1.53)
More than one asthma/COPD drug, no oral corticosteroids	615	27.3	1.70 (1.35–2.15)
More than one asthma/COPD drug, and a combination of oral corticosteroids and antibiotics	88	37.5	2.16 (1.54–3.03)
Undefined	4125	17.9	1.17 (0.94–1.44)

*Crude persistence rates, not adjusted for other factors.
†All variables were analysed in the same model. $RR>1$ means that the variable increases persistence with ICS therapy.

statistically faster annual FEV_1 decline compared to control subjects.[23]

Although treating COPD-patients with ICS seems to be cost-effective,[5] the exact role of these anti-inflammatory drugs in COPD is less clear.[6,7] However, COPD is still often recognized as poorly responsive asthma. In addition, a study by Jackevicius et al.[24] has shown that ICS was more commonly prescribed for COPD (43%) than for asthma (37%) and that there was little difference in the use of ICS for asthma and COPD patients.[25] Aforementioned is in contradiction with COPD management guidelines. These recommend a trial period of ICS, and advise to discontinue ICS therapy if no objective or perceived clinical improvement can be discerned. Thus, including COPD-patients in

the current study might underestimate the actual persistence rate of ICS therapy. Regrettably, we lacked data on diagnoses, and were therefore not able to objectively distinguish between asthma and COPD. However, stratified analysis in patients between 15 and 44 years of age (predominantly asthma-patients), and patient of 65 year and older (majority likely to be COPD-patients), yielded no substantial difference in persistence rate, nor in determinants of persistence (data not shown). In fact, as discussed above, persistence rates were higher in older aged patients.

In order to include patients that used ICS for chronic diseases only, we excluded patients that did not refill their ICS prescription within one year. Our data still contained a considerable number of patients (50%) that had not used respiratory drugs before the start of ICS. This is a remarkable finding for asthma/COPD patients, but consistent with recently published data on the use of ICS in the United Kingdom.[26] On the other hand, 81% of the patients used short-acting β-agonists or parasympathicolytics during follow-up (results not shown).

Another factor that might have underestimated the actual persistence rate is that we excluded combination compounds of inhaled corticosteroids and long-acting beta-agonists. However, we hypothesized that patients on these combinations products would be more persistent because of the direct noticeable bronchodilating effect of long-acting beta-agonists, and not because of the effect of ICS, which are not directly apparent. During the study period only 1.3% of the patients in the source population started on the fixed combination and only 1.9% of the patients starting with ICS had a dispensing for a fixed combination preparation in the follow-up period of 1 year. Hence, the actual persistence rate would not be much influenced by excluding patients on these combinations and exclusion of these patients can not explain the low persistence rates of ICS observed in this study.

The low persistence rates observed in the current study are corroborated by studies that have shown low compliance rates for ICS (30–60%).[27–30] These and other compliance studies revealed that many patients do not understand the role of their medications, have problems with the inhalation devices or have misconceptions and fears with regard to ICS, reducing their willingness to use them.[29,31,32]

Low persistence rates (20–40%) have also been described for many other drugs intended for long-term use, like lipid-lowering drugs, anti-hypertensives, estrogen replacement therapy, osteoarthrosis and antidiabetics.[13,14] These studies and the current study—as discussed above—have shown a relationship between persistence and severity of the disease intended to treat, suggesting that more severe patients are more likely to take medications as directed because of the perceived need to treat their condition effectively[11,14,29].

Persistence was also been found to be lower in patients who started on higher daily doses of ICS, implying that persistence might be facilitated by prescription of the lowest possible doses. An explanation for the latter could be that patients experienced side effect on higher doses.[33] Although systemic side effects are seen less often by the inhaled than the oral route, there is growing awareness of unwanted systemic effects of inhaled steroid use given the availability of high-concentration formulations.[34]

Also, in patients in whom ICS therapy was initially instituted by a specialist showed higher persistence rates—something that is also observed in other studies on persistence.[12,13] This could be due to a difference in disease severity between patients treated by a medical specialist as compared to patients treated by generalists. Alternatively, as has been suggested in persistence studies for other pharmacotherapeutic areas, it might be indicative of greater persuasiveness of specialists, being more aware of the need for continued supervision and support.[30] Although there are no studies in patients with obstructive lung diseases, as far as we know, that supports the latter in our patients.

In analogy to others,[21,22] short courses of corticosteroids and antibiotics, as well as the use of different types of drugs with a labeled indication of obstructive lung diseases were used as markers of disease severity. This is also in agreement with an add-on-step-down approach as recommended in different obstructive lung disease management guidelines. We do realize that not every physician will diminish the number of different drugs once a patient's disease is under control. For sure, a better marker for severity would be clinical measurement. However, we had no data on lung function tests to our disposal.

In conclusion, the current study has shown that new users of ICS had worrying low persistence with ICS-therapy in the first year of follow-up. Preventing this early treatment discontinuation is of crucial importance to ensure maximal benefit from ICS treatment.

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