

Long-Term Inhaled Corticosteroid Adherence in Asthma Patients with Short-Term Adherence



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What is already known about this topic? Although adherence to inhaled corticosteroids (ICS) is known to be poor in asthma, it is unclear to which extent patients regularly using ICS during consecutive months remain adherent to therapy in the longer-term.

What does this article add to our knowledge? Identifying asthma patients' regular use of ICS during several months does not predict long-term adherence, which suggests quickly waning use in asthma. In our population, markers of asthma severity or lower control, younger age (children and teenagers), and factors contributing to the continuity of care improved drug coverage.

How does this study impact current management guidelines? To allow valid assessment, adherence to asthma therapy should be studied for prolonged periods, because episodes of regular use do not last.

BACKGROUND: Although the use of inhaled corticosteroids (ICS) in asthma is known to be overall erratic, the long-term use of ICS by patients selected during an episode of regular use is poorly documented.

OBJECTIVE: In a cohort of patients with asthma regularly acquiring ICS therapy over several months, we verified whether these patients remained treated in the following 12 months. The correlates of regular ICS use over this period were investigated.

METHODS: A historical cohort of patients with asthma was identified from the *Echantillon généraliste de bénéficiaires* national French health care reimbursement data (2007-2012). Patients (6-40 years) were selected during a regular ICS use

episode, with 3 or more ICS refills within 120 days. Continuous multiple-interval measures of medication availability (CMA) were computed for the 12 months after the third dispensation, and the factors associated with a CMA value of 80% or more (adherent patients) were identified.

RESULTS: Among 5096 patients (42.1% children/teenagers, 48.8% females), only 24.0% had a CMA value of 80% or more (mean CMA = 54.4%) over the 12 months following the ICS selection period. Achieving a CMA value of 80% or more was primarily associated with being a child/teenager ($P = .002$), having more severe or less controlled asthma ($P = .007$), more previous dispensing of short-acting beta agonists ($P < .0001$), and receiving devices with 200 unit doses ($P < .0001$). Adherent patients had more frequent general practitioner visits ($P < .0001$), more distinct prescribers of respiratory therapy ($P = .0002$), and more frequent switches of ICS ($P < .0001$).

CONCLUSIONS: Most patients with asthma selected during an episode of regular ICS use did not maintain therapy over the following months. Adherence should be repeatedly monitored, and the reasons for discontinuation should be investigated, at prescriber and patient levels. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:890-9)

Key words: Asthma; Inhaled corticosteroids; Treatment episodes; Adherence; Claims data

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The regular use of controllers, more particularly inhaled corticosteroids (ICS), is recommended in the management of persistent asthma, even in the absence of symptoms.¹ Irregular use of ICS is however a common issue in persistent asthma.^{2,3} Irregularity has detrimental effects on quality of life and health outcomes, and, at societal level, it brings additional costs because of avoidable medical resource utilization.⁴⁻⁶

Abbreviations used

CMA- continuous multiple-interval measures of medication availability
EGB- Echantillon généraliste de bénéficiaires (permanent sample of beneficiaries, a 1/97th random sample of the French claims database)
FDC- fixed dose combinations
GPs- general practitioners
ICS- inhaled corticosteroids
LTD- long-term disease
SABA- short-acting beta agonist
SNIIR-AM- Système National d'Information Inter-Régimes de l'Assurance Maladie

Although interruptions of chronic therapy can happen at any time, the first weeks following initiation are critical for regular long-term use.^{7,8} A successful initiation requires acceptance of the drug and behavioral changes.⁷ Caregivers should provide at this early stage explanations about the condition and the effects of treatment. The quality of these explanations is pivotal for appropriate use,⁹ because they may impact concerns and perceptions about the drug.¹⁰ Furthermore, tolerability issues, which may impact drug use, generally occur during this early phase.

Patients with asthma getting regular refills in the first months following ICS initiation should have overcome this critical step and the first barriers of adequate use. Nonetheless, maybe from the assumption that regularity is maintained, their longer-term exposure to ICS is poorly documented. More generally, it is unclear whether patients with asthma identified during an episode of regular ICS use remain properly treated over subsequent months, or whether a group of irregularly treated patients eventually appears. In addition, it is of major interest to investigate whether patients with long-term adherence differ from others as to specific personal characteristics or factors related to disease management, namely, ICS treatment or characteristics of follow-up.

Claims data are efficient tools in pharmacoepidemiology because they enable investigation of extensive reimbursed medical resource utilization in large populations of beneficiaries over prolonged periods. Proxies of implementation, such as continuous multiple-interval measures of medication availability (CMA), have been developed to approach drug coverage during specific time windows from dispensation data.¹¹

Using national French claims data, we determined long-term drug coverage by ICS in a cohort of patients with asthma regularly treated by ICS therapy at selection, to verify whether such patients would maintain prolonged use of ICS therapy in the subsequent months. Correlates of an appropriate ICS coverage (CMA $\geq$ 80%) were then identified, according to patient characteristics and factors related to asthma management.

METHODS

Data source

The study was conducted in the permanent sample of beneficiaries (*Echantillon généraliste de bénéficiaires* [EGB]). The EGB database is a 1/97th representative random sample of the Système national d'information inter-régimes de l'Assurance maladie (SNIIR-AM),^{12,13} a French nationwide population-based record of individual and anonymized data on all reimbursements for health care utilization, including therapy and outpatient medical and nursing care. No direct information on the medical indication is linked with

each reimbursement, but the SNIIR-AM includes information on long-term disease (LTD) status coded in *International Classification of Diseases, Tenth Revision*. LTD status allows patients to receive treatment for severe and costly conditions without out-of-pocket payment. SNIIR-AM also contains information on free-access-to-care status, which enables patients of lower socioeconomic status to receive free medical care. Information from the SNIIR-AM database and medical information from the French hospital discharge database (Programme de Médicalisation des Systèmes d'Information) about all patients admitted to hospital in France, including discharge diagnoses coded in *International Classification of Diseases, Tenth Revision* codes, medical procedures, and French diagnosis related groups, are cross-referenced. This observational study was conducted on anonymized data, and the National Informatics and Liberty Committee has delivered an overall authorization to use EGB data for research purposes. This study was performed after approval by the French Institute for Health Data (Institut des Données de Santé, approval no. 86, July 2, 2014).

Study design and study population

ICS-treated patients were identified on the basis of recorded episodes of dispensed ICS therapy.

Inclusion criteria. Treatment episodes were defined from the first occurrence of a cluster of 3 or more refills of the same ICS product consecutively dispensed between January 1, 2007, and December 31, 2012. The 3 consecutive ICS refills could be dispensed at 2 or 3 different dates, but the interval between the first refill and the third refill had to be less than 120 days. Patients were to be aged 6 to 40 years at the date of the first ICS dispensation (cohort entry; Figure 1). Older patients were excluded because of the possible diagnosis of chronic obstructive pulmonary disease. ICS products were those available in France at the time of the study (beclometasone, fluticasone, budesonide, fluticasone/salmeterol, budesonide/formoterol, and beclometasone/formoterol fixed-dose combinations) and the different studied ICS are listed in this article's Online Repository at www.jaci-inpractice.org, based on product, device, strength, and unit doses per device.

Exclusion criteria. Exclusion criteria consisted of any active LTD status for respiratory diseases other than asthma. The patients who received uncommon types of ICS (<10,000 dispensed devices in 2012 in France) were excluded, as were nebulized corticosteroids.

Computation of CMA. Our definition of CMA was the percentage of days covered by dispensed ICS during a defined time window¹¹ (Figure 2). CMA was computed during the 12-month study period following the third dispensation (index date) of the first recorded treatment episode meeting inclusion criteria (Figure 1). The study period corresponded to the 12 months following the index date. Drug coverage provided by the ICS dispensation immediately preceding the index date was counted according to the size of its overlap over the study period. Conversely, drug supply extending beyond the end of the study period was excluded (CMA capped at 100%).

Prescribed daily doses assessed from external data. Given the absence of prescribed daily doses in the EGB, the computation of the number of days supplied by each ICS pack required external data (primary care electronic health records: longitudinal patient data database). General practitioners (GPs) in the longitudinal patient data database are representative of the French

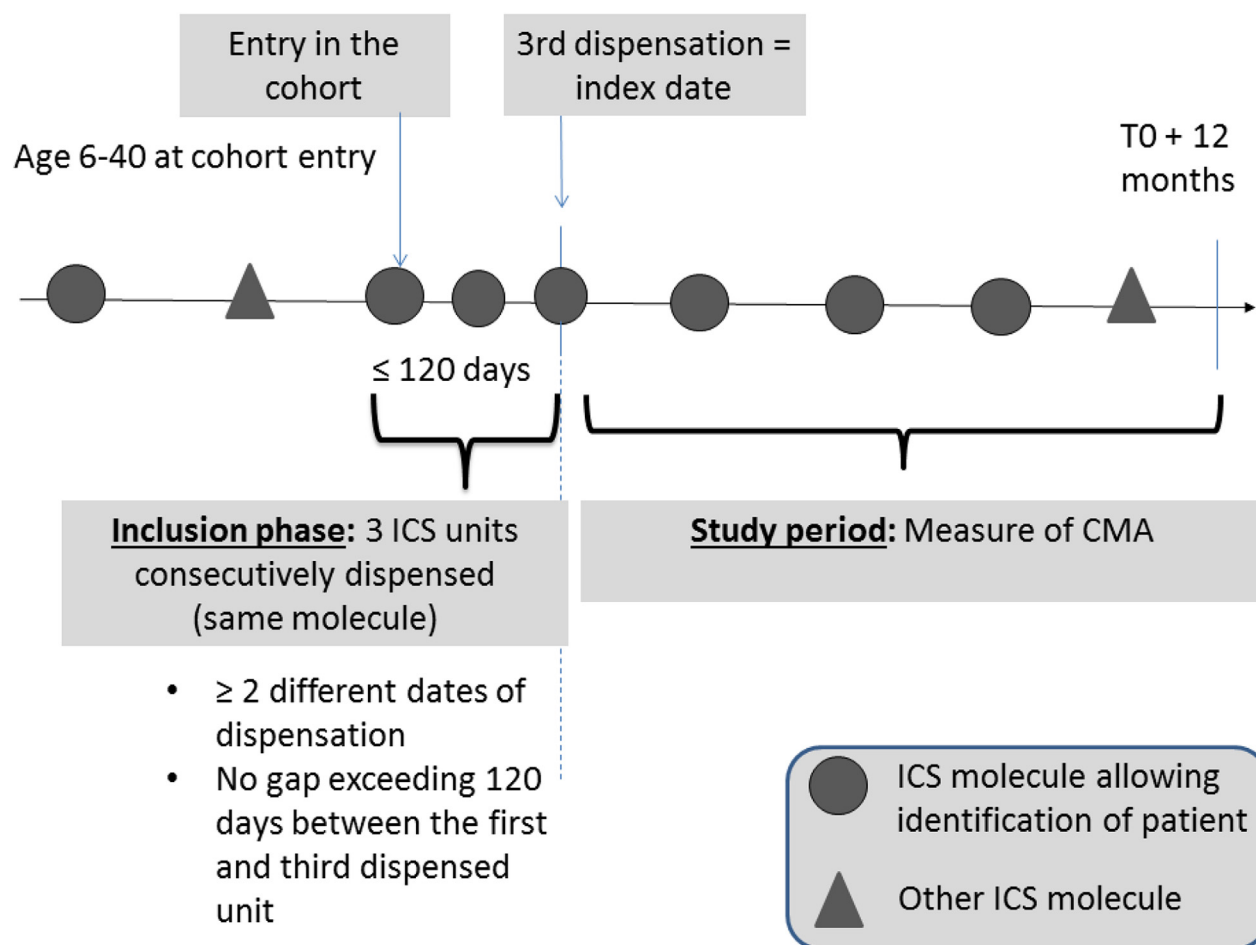


FIGURE 1. Definition of the cohort, inclusion phase, and study period for the computation of CMA. The figure depicts the temporality between the inclusion phase, the index data, and the study period during which CMAs were computed.

population of GPs according to geographical area, age, and sex.¹⁴ A population of longitudinal patient data database patients with asthma aged 6 to 45 years in 2011 and receiving ICS was identified and the prescribed daily doses in 2012 were related to each studied ICS. The corresponding durations of each ICS were computed and applied in this study for CMA computations. More details are provided in this article's Online Repository at www.jaci-inpractice.org.

Data analyses

Patients concomitantly receiving 2 or more different ICS at the index date were not included in the analyses. All ICS dispensed at the index date and 12 months afterward contributed to drug coverage.

The factors associated with CMA values of 80% or more were identified,¹⁵ considering patients' baseline characteristics and factors related to dispensed index ICS or to disease management during the study period. Preliminary univariate analyses (chi-square tests) were followed by multivariate logistic analysis. The probability of achieving the 80% CMA threshold was systematically adjusted for age, sex, marker of asthma severity (asthma-related LTD status and/or hospitalization for asthma during the 12 months before T0), and free-access-to-care status. Other variables were included in the model if there was a statistically significant univariate association ($P < .10$). An additional analysis restricted to patients who remained under the same ICS during the study period (no switch) was also conducted,

using the same cofactors (data not shown). Asthma-related hospitalizations, dispensations of short-acting beta agonists (SABAs), and systemic corticosteroids were compared during the study period between adherent and nonadherent patients. SAS software was used for data management and analyses (SAS Enterprise Guide, version 4.3, Cary, NC).

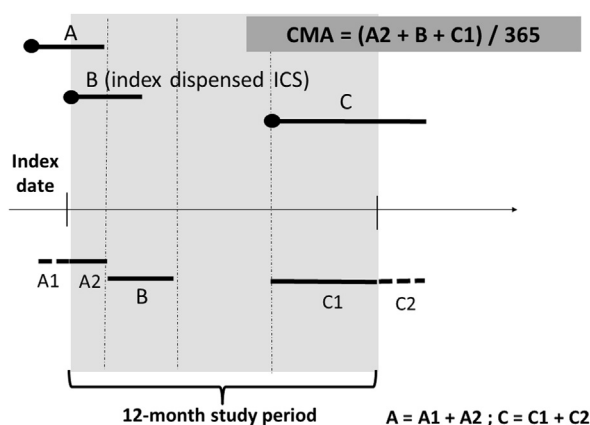
RESULTS

Descriptive results

The successive steps of patient selection are summarized in Table I. A total of 5096 patients were included in the analysis among whom 42.1% were children (6-12 years) or teenagers (13-16 years), and 48.8% were females. Median CMA was 50.7% (interquartile range [31.0%-78.6%]; mean, 54.4%); 24% of patients had a CMA value of 80% or more.

Factors associated with CMA values of 80% or more over 12 months following the index date

Univariate analyses. A greater proportion of children/teenagers than adults had a CMA value of 80% or more: 27.2% of children and 25.5% of teenagers compared with 22.1% of adults. No salient difference appeared between sexes. Patients with more severe asthma (ie, asthma LTD status and/or previous



- Drug coverage provided by the ICS dispensation immediately preceding index date (A1 for dispensation A) was partially counted according to the size of its overlap over the study period.
- Likewise, drug supply extending beyond the end of the study period was excluded (C2 for dispensation C). Consequently, CMA capped at 100%.
- When two dispensations overlapped (A and B), the second one was assumed to start once the preceding one was completed.

FIGURE 2. Computation of CMA. The study depicts how to compute CMA during a given time interval on the basis of successive dispensations.

hospitalization due to asthma), as well as those with rhinitis, presented more frequently a CMA value of 80% or more. The proportion of patients with a CMA value of 80% or more increased with more frequent dispensations of SABAs and systemic corticosteroids during the 12 months before the index date. Other correlates of CMA values of 80% or more included the number of doses of the ICS at the index date, the frequency of medical visits to GPs, the number of distinct prescribers of respiratory drugs, and receiving index ICS prescription from a hospital physician. Patients who switched to another ICS during the study period more frequently had a CMA value of 80% or more; conversely, those receiving long-acting beta agonist/ICS fixed-dose combinations (FDCs) at the index date less frequently had a CMA value of 80% or more. Other factors had no marked influence on CMA (Table II). CMA during the study period was also related to markers of poor control recorded during the same period: more dispensing of SABAs and systemic corticosteroids, and higher incidence of asthma-related hospitalizations in patients with a CMA value of 80% or more (Table II).

Multivariate analyses. In multivariate analyses, younger age, more severe asthma, more frequent baseline SABA refills, a greater number of doses in the dispensed device, more frequent GP visits, a greater number of distinct prescribers of respiratory drugs, and ICS switch during the study period were all independently associated with a CMA value of 80% or more. Women tended to be less adherent than men, although not significantly so. After adjustment, a marginally higher risk of achieving a CMA value of 80% or more was identified in patients receiving fixed-dose combinations at the index date, although not significantly so (Table III). Our conclusions were not globally affected after restricting the study population to patients who remained under the same ICS (no switch) throughout the study period (data not shown).

TABLE I. Selection of subjects from the EGB database

Successive selection criteria	N
≥1 ICS refill between January 1, 2007, and December 31, 2012	141,746
≥2 ICS refills between January 1, 2007, and December 31, 2012	81,393
≥3 ICS refills between January 1, 2007, and December 31, 2012	58,331
≥3 consecutive ICS refills of the same molecule,* at 2 or 3 different dates	45,993
At most 120 d between first and third ICS refill	29,220
Aged 6-40 y at date of first ICS refill	7,217
Patients alive on October 31, 2013	7,182
Patients without any LTD status for chronic obstructive pulmonary disease nor cystic fibrosis between January 1, 2007, and October 31, 2013	7,109
Continuous presence in the database from the 24th month before cohort entry and up to the 18th month thereafter	6,017
Date of the third ICS refill (index date = T0) between February 1, 2007, and October 31, 2012	5,353
Presence of a studied ICS† at the index date	5,123
No different types of ICS concomitantly dispensed at the index date	5,096

*Beclometasone, budesonide, fluticasone, beclometasone/formoterol, budesonide/formoterol, fluticasone/salmeterol.

†The different types of studied ICS are listed in Table E1.

DISCUSSION

In this population of persistent asthma identified by an episode of regular ICS treatment at selection, less than 1 in 4 patients had a CMA value of 80% or more in the following 12 months. Children and teenagers were better covered by ICS than were adults. CMA values were higher in patients with more severe and/or less well-controlled asthma, as assumed from LTD status, previous asthma-related hospital admissions, or higher prior dispensing levels of SABAs. The presence of regular medical visits in primary care, of several prescribers of respiratory drugs, or change in ICS during the study periods also positively impacted long-term ICS coverage.

Although CMA values noticeably varied between patients, the overall ICS coverage in the 12 months after patient selection was low, with a mean CMA value of close to 50%. Our findings do not differ greatly from those of other studies that reported mean CMA values rarely exceeding 50%, and a minority of patients with a CMA value of 80% or more.¹⁶⁻²⁰ However, the originality of our approach lies in the choice of selective inclusion criteria targeting patients making repeated use of ICS. This was intended to remove patients receiving ICS for acute infections (eg, laryngitis), or subjects who were straightaway irregular users.

The key message is that even in this highly selected population, interruptions in ICS therapy appear within months; that is, the regularity of ICS coverage observed at inclusion does not guarantee sustainable trends. This results in fragmented episodes of ICS use, rarely exceeding a few months, as typically observed in other asthma adherence studies.²¹ This inappropriate use is likely to be in relation to the use of ICS as reliever therapy, according to the common erroneous belief “no symptoms, no asthma.”²²⁻²⁴ Such behavior can be encouraged by the paroxysmic

TABLE II. CMA according to patient characteristics—Univariate analyses

Patient characteristics at baseline and during study period	N	Median CMA value	CMA, interquartile range	CMA ≥ 80% (%)	P*
Baseline patient characteristics (12 mo before the index date [†])					
Age group					.0004
Children (6-12 y)	1606	57.3	33.7-83.0	27.2	
Teenagers (13-16 y)	538	53.2	32.9-81.1	25.5	
Adults (17-40 y)	2952	49.3	27.4-75.3	22.1	
Sex					.255
Male	2611	51.5	32.9-79.5	24.7	
Female	2485	49.6	29.3-77.3	23.3	
Free-access-to-care status					<.0001
Yes	901	57.5	32.9-87.1	29.1	
No	4195	49.6	30.4-76.7	23.0	
LTD status for asthma (ICD-10 codes J45 and J46)					<.0001
Yes	227	66.3	41.9-91.0	36.1	
No	4869	49.9	30.1-77.5	23.5	
Previous asthma-related hospitalizations					.028
Yes	145	67.9	46.6-90.4	31.7	
No	4951	50.1	30.4-78.1	23.8	
Rhinitis (≥2 quarters with antihistamines or nasal corticosteroids)					.0009
Yes	3077	53.4	32.9-81.4	25.6	
No	2019	49.3	27.1-75.3	21.6	
Gastroesophageal reflux (≥3 quarters with antacid and/or antireflux therapy)					.2491
Yes	263	53.4	34.0-83.0	27.0	
No	4833	50.4	30.7-78.4	23.9	
Depression, anxiety (≥3 quarters with psychotropic drugs)					.0527
Yes	342	51.1	32.6-83.0	28.4	
No	4754	50.5	31.0-77.8	23.7	
Previous SABAs					<.0001
None	1396	44.2	25.2-73.7	20.1	
1-4 refills	2737	49.6	28.8-76.2	22.1	
≥5 refills	963	66.0	43.0-91.0	35.2	
Previous antibiotics					.7327
None	1676	50.7	31.9-77.9	23.5	
1-3 refills	1563	50.7	29.3-79.2	24.6	
≥4 refills	1857	50.7	31.8-78.4	24.1	
Previous systemic corticosteroids					.0005
None	2316	50.1	30.4-76.8	23.1	
1-2 refills	2012	49.6	29.7-77.0	23.0	
≥3 refills	768	57.5	33.2-84.7	29.6	
ICS dispensed at the index date					
LABA/ICS fixed-dose combinations					<.0001
Yes	3725	49.3	27.4-74.5	20.8	
No	1371	60.8	37.0-91.5	32.8	
Inhaler device					
Pressurized metered-dose inhaler	1361	57.5	34.5-85.2	29.0	<.0001
Dry powder inhaler multidose Diskus	1922	44.7	24.9-70.4	17.7	
Dry powder inhaler Turbuhaler	1333	51.2	31.5-79.5	24.6	
Breath-actuated devices	222	72.3	44.7-100.0	43.2	
Others	258	52.2	33.2-81.9	26.0	
No. of doses in the device					<.0001
<100	2638	46.6	25.2-72.1	18.7	
100-199	1783	53.7	32.9-79.5	24.6	
200	675	72.6	45.5-100.0	43.6	
Specialty of prescriber [‡]					.0007
GP	3671	49.6	29.0-77.8	23.7	

(continued)

TABLE II. (Continued)

Patient characteristics at baseline and during study period	N	Median CMA value	CMA, interquartile range	CMA ≥ 80% (%)	P*
Private practice specialist	893	50.7	32.9-75.6	22.4	
Hospital physician	480	57.9	36.0-87.3	30.6	
Factors related to the study period					
Any switch of ICS during the study period					<.0001
No	3466	45.8	24.9-74.0	20.4	
Yes	1630	62.2	42.5-88.2	31.8	
≥1 visit to a specialist§					.0361
Yes	1343	54.0	32.9-82.2	26.1	
No	3753	49.6	30.1-77.5	23.3	
≥3 different prescribers of respiratory drugs					<.0001
Yes	743	64.7	46.6-88.2	33.2	
No	4353	49.3	27.4-76.2	22.5	
Frequency of GP visits					<.0001
0-2	1326	46.0	24.9-70.4	18.1	
3-6	2054	50.7	32.9-78.1	23.6	
>6	1716	57.5	33.2-84.9	29.1	
Asthma-related hospitalizations					.0573
None	5028	50.4	30.4-78.4	23.9	
At least 1	68	67.5	49.3-88.5	33.8	
Dispensing of SABAs					<.0001
None	1758	42.2	24.4-67.7	16.4	
1-4 refills	2217	49.3	28.8-74.2	20.7	
≥5 refills	1121	73.2	49.6-97.0	42.6	
Dispensing of systemic corticosteroids					<.0001
None	2652	49.3	26.2-74.2	21.1	
1-2 refills	1757	51.8	32.9-80.5	25.3	
≥3 refills	687	61.9	39.2-87.9	32.2	

ICD-10, International Classification of Diseases, Tenth Revision; LABA, long-acting beta agonist.

*CMA ≥ 80% vs CMA < 80%.

†Except for age and sex.

‡Fifty-two missing data.

§Respiratory physician, ear, nose, and throat specialist, pediatrician, hospital physician. The specialty was not documented in the database for hospital physicians.

course of asthma and poor patient understanding of disease and therapy,²⁵ fears about corticotherapy, lack of immediate perceived relief with ICS therapy,^{10,26} and limited explanations provided by caregivers.^{26,27} In addition, patients with asthma are often unaware of the preventability of their symptoms with regular ICS therapy.^{10,28} Erratic prescribing of ICS by physicians, also reported in asthma,²⁹⁻³¹ could partly explain the results, but French claims data do not allow to explore this assumption, because the absence of dispensing could be due to lack of prescribing by health care professionals, or lack of purchase by patients. Likewise, it was not possible to investigate the quality of use with the data available.

Children and teenagers more frequently attained a CMA value of 80% or more, possibly in relation to the role of parents and caregivers, yet discordant conclusions have been reported regarding the influence of age on adherence.³² A poorer adherence has been reported among teenagers than among children.³³⁻³⁵ In our data, the probability of achieving a correct CMA did not markedly differ between children and teenagers in multivariate analysis. This could be explained by the selection of our study population based on an episode of regular ICS dispensations, thus excluding teenagers who did not regularly fill their prescriptions. We did not observe lower adherence in

adolescents compared with adults. This is not in line with other findings. Indeed, as a rule, inappropriate adherence has often been observed in teenagers, for example, because of oppositional behavior, reluctance to take treatment in the presence of peers, interest in risk-taking behaviors, and disregard for health concerns.^{33,34}

After adjustment, there was also a trend toward better drug coverage among men; the effect of sex on appropriate use of controllers in persistent asthma remains however disputed.^{16,32} Economic deprivation is a known determinant of poor adherence among patients with asthma,^{36,37} but in our study, the free-access-to-care marker, a low-income marker, was not associated with CMA after adjustment for confounders; the financial facilities provided by this status could counterbalance the effects of economic deprivation. The presence of an LTD status, or previous asthma-related hospitalization, was associated with a CMA value of 80% or more, suggesting a positive effect of asthma severity on adherence. Some studies reported a higher willingness to take asthma therapy when patients were more severe, with more symptoms and/or asthma-related adverse outcomes,³⁸⁻⁴⁰ or when they perceived the severity of their disease.^{27,41} However, the impact of severity on adherence is still debated. For instance, in a recent review, higher severity was associated with a better

TABLE III. Probability of achieving a CMA value of $\geq 80\%$ over 12 mo postindex date, multivariate logistic regression

Patient characteristics at baseline or during study period	N = 5044		
	OR	95% CI	P
Age group			.0021
Adults (17-40 y)	1.00	—	
Teenagers (13-16 y)	1.28	1.01-1.61	
Children (6-12 years)	1.34	1.13-1.59	
Sex			.0555
Male	1.00	—	
Female	0.87	0.76-1.00	
Free-access-to-care status			.5065
No	1.00	—	
Yes	1.06	0.89-1.27	
Previous SABAs (12 mo before the index date)			<.0001
None	1.00	—	
1-4 refills	0.98	0.83-1.16	
≥ 5 refills	1.97	1.61-2.41	
Systemic corticosteroids (12 mo before the index date)			0.1148
None	1.00	—	
1-2 refills	0.87	0.75-1.01	
≥ 3 refills	1.03	0.84-1.26	
Rhinitis (12 mo before the index date)			.1179
No	1.00	—	
Yes	1.12	0.97-1.30	
Depression, anxiety (12 mo before the index date)			.1164
No	1.00	—	
Yes	1.24	0.95-1.63	
LTD status and/or hospitalization for asthma (12 mo before the index date)			.0073
No	1.00	—	
Yes	1.41	1.10-1.81	
No. of doses in the ICS device dispensed at the index date			<.0001
<100	1.00	—	
100-199	1.27	0.98-1.64	
200	3.30	2.33-4.67	
ICS/LABA fixed-dose combination at the index date			.7054
No	1.00	—	
Yes	1.05	0.83-1.32	
Inhaler device at the index date			.0453
Pressurized metered-dose inhaler	1.00	—	
Dry powder inhaler multidose Diskus	0.91	0.67-1.23	
Dry powder inhaler Turbuhaler	1.22	0.98-1.52	
Breath-actuated device	1.26	0.89-1.78	
Others	1.08	0.74-1.57	
Speciality of initial prescriber (index date)			.0025
GP	1.00	—	
Private practice specialist	0.99	0.81-1.20	
Hospital physician	1.48	1.18-1.86	
Any switch of ICS during the study period			<.0001
No	1.00	—	
Yes	1.58	1.36-1.82	
≥ 3 different prescribers of respiratory drugs during the study period			.0002
No	1.00	—	
Yes	1.42	1.18-1.71	
Frequency of GP visits during the study period			<.0001
0-2	1.00	—	
3-6	1.45	1.20-1.74	
>6	1.79	1.47-2.19	

(continued)

TABLE III. (Continued)

Patient characteristics at baseline or during study period	N = 5044		
	OR	95% CI	P
≥1 visit to a specialist* during the study period			.6295
No	1.00	—	
Yes	1.04	0.89-1.22	

LABA, Long-acting beta agonist.

*Respiratory physician, ear, nose, and throat specialist, pediatrician, hospital physician. The specialty was not documented in the database for hospital physicians.

adherence in only 5 of 12 studies.³² Discordant results could be due to heterogeneity in study populations or due to discordant definitions of severity. Previous high dispensation levels of SABAs also predicted a CMA value of 80% or more, possibly as a marker of poor asthma control and patients' need of more intensive controller therapy.²⁹ Patients with a CMA value of 80% or more had more dispensing of SABAs and systemic corticosteroids during the study period than did patients with a CMA value of less than 80%, again supporting the assumption that patients who stopped using ICS were less in need of this therapy than patients who continued using ICS. In line with our findings, other studies have shown better ICS coverage in patients previously using high doses of SABAs.^{16,29,42} More frequent GP visits were also associated with a CMA value of 80% or more, which could be related to poor control, or simply to increased opportunities for prescribing.⁴³

The probability of a CMA value of 80% or more increased with the number of different prescribers of respiratory drugs during the 12-month period. The ability to contact surrogate prescribers and/or referrals when respiratory difficulties arise could improve continuity of care and drug coverage. Furthermore, there was also an association with ICS switches during the study period, possibly reflecting efforts to readjust ICS therapy toward improved effectiveness and/or tolerance, thus contributing to regular therapy.

In summary, CMA levels tended to improve with more severe or symptomatic asthma, along with the continuity of care. Patients receiving an ICS pack with 200 unit doses at index date had the longest cover: if 2 doses were prescribed daily, the canister would provide a 100-day supply. Hence, nearly one-third of the 12-month study period (100 of 365) would be covered. This boosted the CMA calculation. Also, the longer duration of drug supplies reduced the necessity of frequent refills, which increase the risk of drug interruption.

No firm conclusions can be drawn regarding the effect of the type of delivery devices on CMA, and inconsistent findings have been reported in the literature regarding this point^{36,37,44}; regularity of use seems primarily affected by choosing the most appropriate device for an individual patient.⁴⁵ Univariate analysis showed lower CMAs in patients receiving FDC at the index date. This could be in part explained by the fact that FDC canisters contained fewer unit doses than did single ICS. Of interest, in multivariate analyses, after adjustment for the number of unit doses, an increased risk of adequate adherence was found (odds ratio = 1.05) for FDC, although not significantly so ($P = .70$). Greater benefits of FDC could have been expected on adherence.^{17,46} However, the potential benefits of FDC could be masked by unmeasured residual confounding, because physicians may preferably prescribe FDC to the patients suspected of non-adherence, who would keep this behavior after switching to FDC.

The study had some limitations. For instance, the population comprised patients with the same ICS dispensed within 120 days of an episode of regular ICS therapy. It was therefore not representative of the general population with asthma. Worse results would nevertheless be expected in a less selected population. CMA was computed as of the third ICS refill identified at inclusion (index date) instead of cohort entry. This choice aimed at limiting the influence of the initial ICS coverage required at inclusion, which would have artificially increased CMA values. Also, it was not possible to compute CMA using the daily doses actually prescribed to each individual patient; this was done using aggregated prescribed daily doses from patients with asthma identified in a primary care electronic health records database. Because the same median prescribed daily dose for all patients receiving a given type of ICS was used, the CMA computation could not take into account variability of prescribed doses between patients, nor potential changes over time. So, using the median dose could inflate estimates of adherence in more severe individuals (ie, the true adherence in individuals with severe disease is actually lower than the adherence computed with the median dose). This artifact could in part explain the positive relationship between adherence and severity observed in this study. However, the adaptation of ICS therapy to patient characteristics and symptoms is infrequent in France.⁴⁷

Our study population included both prevalent and incident patients. Although higher CMA values could in theory be expected in a population with only incident patients, this did probably not markedly affect our findings, given the low persistence to ICS in newly treated patients with asthma.²¹ Also, the inclusion of prevalent patients may result in a selection of more adherent patients who remained longer under therapy, possibly months or years before the study period. Thus, our findings are conservative.

In addition, as always the case for claims data, actual drug use remains unknown and CMA was based on dispensed drug coverage. Also, unfilled prescriptions are not documented in the EGB, and it was not possible to delineate whether interruptions were due to physicians (cessation of prescribing) or due to patients (unfilled prescribed therapy or interrupted medical follow-up), as already mentioned.

A major asset of this study is the use of claims data, which provide a prolonged follow-up with detailed and exhaustive data on reimbursed drugs in large populations, representative of virtually all French beneficiaries, regardless of their literacy, socioeconomic level, medical follow-up, or any other characteristics. These data also enable the investigation of less-accessible populations, such as children, or patients with fragmented care, visiting several health care professionals.

The findings bear implications because the rarity of prolonged exposure to ICS, even after an episode of regular therapy at

inclusion phase, suggests fragmented use of ICS. A better understanding of patients' and prescribers' behaviors is needed, and qualitative studies would be helpful.

In summary, in patients with asthma identified at selection by regular ICS use, this regularity did not last over the following months, with less than 25% of patients continuously using ICS over 12 months. Adherence increased with asthma severity, lower control, and continuity of care. A better understanding of the determinants of this discontinuous use of controller therapy is needed, along with identification of specific patient or health care professional profiles.

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ONLINE REPOSITORY

Prescribed daily doses assessed from external data: Given the absence of prescribed daily doses in the EGB, the computation of the number of days supplied by each ICS pack required external data (primary care electronic health records: Longitudinal patient data database). GPs in the longitudinal patient data database are representative of the French population of GPs according to geographical area, age, and sex.^{E1} A population of longitudinal patient data database asthma patients aged 6 to 45 years in 2011 was identified and the prescribed daily doses related to each

studied ICS in 2012 were considered. Out of 1,167,304 prescriptions, daily dosage regimens were defined for the different ICS, separately in children/teenagers (6-16 years), adult men, and women. Daily dosage regimens without the number of daily doses ("as needed"), null values, and excessive values (>8 daily doses) were excluded. For each studied ICS, the median values of prescribed daily doses were retained. For instance, a pack containing 120 doses with a median value of 4 prescribed daily doses (eg, 2 puffs twice a day) was considered to provide a 30-day supply (Table E1).

TABLE E1. List of studied ICS with median daily prescribed doses obtained from LPD data and computed average duration in days

Studied ICS	Median daily dose				Average duration (d)		
	Children/ teenagers	Females	Males	No. of doses/pack	Children/ teenagers	Females	Males
Fluticasone/salmeterol fixed-dose combination							
Seretide Diskus 100 µg/50 µg/actuation oral inhalation 1 Diskus device, 60 recipients unidoses	2	2	2	60	30	30	30
Seretide Diskus 250 µg/50 µg/actuation oral inhalation 1 Diskus device, 60 recipients unidoses	2	2	2	60	30	30	30
Seretide Diskus 500 µg/50 µg/actuation oral inhalation 1 Diskus device, 60 recipients unidoses	2	2	2	60	30	30	30
Seretide 50 µg/25 µg/actuation oral inhalation 1 pressurized dispensed device, 120 doses	4	4	4	120	30	30	30
Seretide 125 µg/25 µg/actuation oral inhalation 1 pressurized dispensed device, 120 doses	2	3	3.5	120	60	40	34
Seretide 250 µg/25 µg/actuation oral inhalation 1 pressurized dispensed device, 120 doses	2	4	4	120	60	30	30
Beclometasone/formoterol fixed-dose combination							
Innovair 100/6 µg/dose oral inhalation pressurized dispensed device, 120 doses	3	3	3	120	40	40	40
Budesonide/formoterol fixed-dose combination							
Symbicort Turbuhaler 100/6 µg/actuation oral inhalation 1 inhaler, 120 doses	2	2	2	120	60	60	60
Symbicort Turbuhaler 200/6 µg/actuation oral inhalation 1 inhaler, 120 doses	2	3	3	120	60	40	40
Symbicort Turbuhaler 400/12 µg/actuation oral inhalation 1 inhaler, 60 doses	2	2	2	60	30	30	30
Beclometasone							
Becotide 250 µg/actuation oral inhalation pressurized dispensed device, 200 doses	2	3	3	200	100	67	67
Beclojet 250 µg/actuation oral inhalation pressurized dispensed device, 200 doses	3.5	2	3.5	200	57	100	57
Ecobec 250 µg/actuation oral inhalation pressurized dispensed device, 200 doses	2	4	4	200	100	50	50
Qvarspray 100 µg/actuation oral inhalation pressurized dispensed device, 100 doses	2	3	3	100	50	33	33
Qvar autohaler 100 µg/actuation oral inhalation pressurized dispensed device, 200 doses	2	3	3	200	100	67	67
Miflasone 200 µg oral inhalation 60 capsules (+ 1 inhaler)	2	2	2	60	30	30	30
Miflasone 400 µg oral inhalation 60 capsules (+ 1 inhaler)	2	2	2	60	30	30	30
Beclospray 250 µg/actuation oral inhalation pressurized dispensed device, 200 doses*	NA	3	3	200	NA	80	67
Beclometasone teva 50 µg/actuation oral inhalation pressurized dispensed device, 200 doses	5	6	4	200	40	33	50
Beclometasone teva 250 µg/actuation oral inhalation pressurized dispensed device, 200 doses	2	3	3	200	100	67	67

(continued)

TABLE E1. (Continued)

Studied ICS	Median daily dose				Average duration (d)		
	Children/ teenagers	Females	Males	No. of doses/pack	Children/ teenagers	Females	Males
Budesonide							
Pulmicort Turbuhaler 200 µg/actuation oral inhalation 1 inhaler, 200 doses	2	2	2	200	100	100	100
Pulmicort Turbuhaler 400 µg/actuation oral inhalation 1 inhaler, 100 doses	2	2	2	100	50	50	50
Miflonil 200 µg oral inhalation 60 capsules (+ 1 inhaler)	2	2	2	60	30	30	30
Miflonil 400 µg oral inhalation 60 capsules (+ 1 inhaler)	2	2	2	60	30	30	30
Novopulmon novolizer 200 µg/actuation oral inhalation 1 dispensed device, 200 doses (+ 1 inhaler)	2	2	2	200	100	100	100
Novopulmon novolizer 400 µg/actuation oral inhalation 1 dispensed device, 100 doses (+ 1 inhaler)	2	2	2	100	50	50	50
Novopulmon novolizer 400 µg/actuation oral inhalation 1 dispensed device, 100 doses	2	2	2	100	50	50	50
Flixotide							
Flixotide 50 µg/actuation oral inhalation pressurized dispensed device, 120 doses	3	2	4	120	40	60	30
Flixotide 125 µg/actuation oral inhalation pressurized dispensed device, 120 doses	2	2	2	120	60	60	60
Flixotide 250 µg/actuation oral inhalation pressurized dispensed device, 120 doses	2	3	3	120	60	40	40
Flixotide Diskus 100 µg/actuation oral inhalation 1 Diskus inhaler, 60 doses	2	4	4	60	30	15	15
Flixotide Diskus 250 µg/actuation oral inhalation 1 Diskus inhaler, 60 doses	2	2	2	60	30	30	30
Flixotide Diskus 500 µg/actuation oral inhalation 1 Diskus inhaler, 60 doses	2	2	2	60	30	30	30

LPD, Longitudinal patient data.

*Given the absence of documented prescribed daily dose of Beclospray for children and teenagers in the database, men and women prescribed daily dose were used for boys and girls, respectively.

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