

Original Article



Prescription Patterns of Oral Corticosteroids for Asthma Treatment and Related Asthma Phenotypes in University Hospitals in Korea

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ABSTRACT

Purpose: Oral corticosteroids (OCSs) are frequently prescribed for asthma management despite their adverse effects. An understanding of the pattern of OCS treatment is required to optimize asthma treatment and reduce OCS usage. This study evaluated the prescription patterns of OCSs in patients with asthma.

Methods: This is a retrospective multicenter observational study. We enrolled adult (≥ 18 years) patients with asthma who had been followed up by asthma specialists in 13 university hospitals for ≥ 3 years. Lung function tests, the number of asthma exacerbations, and prescription data, including the days of supply and OCS dosage, were collected. The clinical characteristics of OCS-dependent and exacerbation-prone asthmatic patients were evaluated.

Results: Of the 2,386 enrolled patients with asthma, 27.7% ($n = 660$) were OCS users (the median daily dose of OCS was 20 mg/day prednisolone equivalent to a median of 14 days/

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year). OCS users were more likely to be female, to be treated at higher asthma treatment steps, and to show poorer lung function and more frequent exacerbations in the previous year than non-OCS users. A total of 88.0% of OCS users were treated with OCS burst with a mean dose of 21.6 ± 10.2 mg per day prednisolone equivalent to 7.8 ± 3.2 days per event and 2.4 times per year. There were 2.1% (51/2,386) of patients with OCS-dependent asthma and 9.5% (227/2,386) with exacerbation-prone asthma. These asthma phenotypes were consistent over the 3 consecutive years in 47.1% of OCS-dependent asthmatic patients and 34.4% of exacerbation-prone asthmatic patients when assessed annually over the 3-year study period.

Conclusions: We used real-world data from university hospitals in Korea to describe the OCS prescription patterns and relievers in asthma. Novel strategies are required to reduce the burden of OCS use in patients with asthma.

Keywords: Asthma; corticosteroid; phenotype; disease exacerbation; prescription patterns; lung function tests

INTRODUCTION

Inhaled corticosteroids (ICSs) are the mainstay of asthma treatment to achieve symptom control and to reduce the future risk of asthma. However, oral corticosteroids (OCSs) are still important medications for asthma treatment, particularly for severe asthma, and had been the only option for step 5 treatments in the Global Initiative for Asthma (GINA) guidelines for a long time.¹ As steroid-related adverse events are common, the proper dose and duration of OCS treatment are important.^{2,3} Thus, OCSs should only be considered for adults with poor symptom control and/or frequent exacerbations despite good inhaler technique and adherence to GINA steps 4 or 5 treatment after excluding other contributory factors.¹ Short-term OCS use, so-called OCS burst, may also be used as a reliever treatment in patients with an asthma flare-up,⁴ usually for 5–7 days.^{1,5,6} Recent evidence suggests that even short-burst OCS can be associated with adverse effects⁷ and repetitive OCS treatments result in a cumulative burden, regardless of the dose and duration.^{3,8}

Unfortunately, recent studies have reported that many patients do not receive optimal therapy for asthma and are often prescribed maintenance OCS or repeated steroid bursts to control asthma symptoms.³ A considerable proportion of patients treated with GINA step 4-5 treatment still have uncontrolled asthma and require OCS burst.⁹ Actually, over-usage of OCS for asthma treatment has been reported in Korea, which raises the suspicion that OCSs are more commonly prescribed as symptom relievers than rescue inhalers.^{10,11} To optimize asthma treatment and reduce OCS use, understanding the current pattern of OCS use in real practice and the clinical characteristics of OCS-treated patients with asthma is important. As biologics reduce the frequency of asthma exacerbation and OCS usage in patients with a specific phenotype of severe asthma, it is more important to understand the OCS-related asthma phenotypes such as OCS-dependent and exacerbation-prone asthma. However, little is known about the clinical characteristics of patients with OCS-dependent asthma or frequent OCS burst users, and the consistency of such asthma phenotypes.

This study evaluated the patterns of OCS prescriptions for asthma treatment in Korea and investigated the consistency and clinical characteristics of the asthma phenotypes according to OCS usage, including OCS-dependent asthma and exacerbation-prone asthma. We retrospectively collected and analyzed clinical data, including lung function, prescription of

asthma medication, and the frequency of asthma exacerbations from asthmatic patients who were followed up by asthma specialists in 13 referral hospitals for more than 3 years.

MATERIALS AND METHODS

Study design

This is a retrospective multicenter observational study involving 13 university hospitals in Korea. All researchers of this study belong to the Working Group on Severe Asthma of the Korean Academy of Asthma, Allergy, and Clinical Immunology. The study protocol was approved by the Institutional Review Board of each hospital.

Subjects

We retrospectively enrolled patients with asthma who had been followed up by asthma specialists for more than 3 years that included the 3-year study period, and who met the inclusion criteria (**Fig. 1**). The inclusion criteria were (1) adult (≥ 18 years) patients with asthma clinically diagnosed by an asthma specialist, (2) 2 or more visits to the outpatient asthma clinic during the 1-year observation period (from July 1, 2015 to June 30, 2016), and (3) visits to the asthma clinic at least once within the year before and after the observational period (from July 1, 2014 to June 30, 2017). The exclusion criterion was a lack of medical records to evaluate asthma medications. The medical records were reviewed for the days of supply and the dosage of each OCS prescription during the 3-year study period. The OCS dose was calculated as prednisolone equivalents. OCS users were defined as those who were prescribed OCS as an asthma treatment during the 1-year observational period, and the others were defined as non-OCS users. OCS-dependent asthma was defined as the use of OCS for ≥ 6 months per year during the observational period. OCS burst was defined as an OCS prescription with ≤ 14 consecutive days of supply. Exacerbation-prone asthma was defined as 2 or more OCS burst treatments and the use of 2 or more controller medications.^{12,13} The consistency of the asthma phenotypes was evaluated as to whether the phenotype during the 1-year observation period was also observed during the 1-year pre- and post-observational periods.

The characteristics of asthma, including lung function tests, complete blood count with differential count, and serum level of total immunoglobulin E, were reviewed at the beginning of the observational period. The number of severe asthma exacerbations, defined as an admission or an emergency department visit for asthma were reviewed.

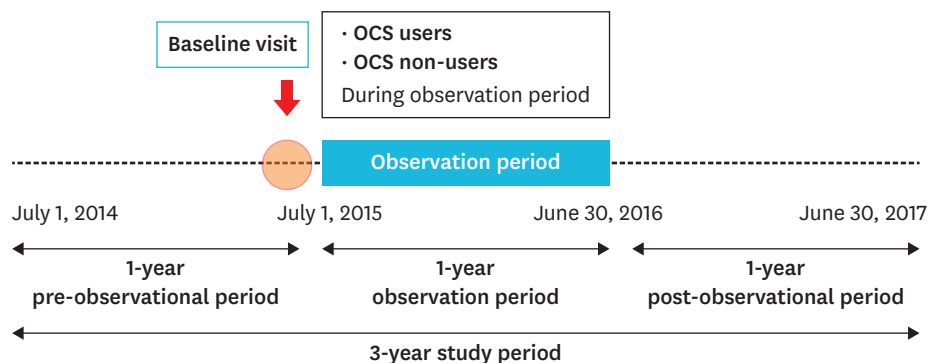


Fig. 1. Study design.

The asthma specialists at each hospital reviewed the asthma medications at the baseline visit, which was defined as a routine visit to the outpatient clinic before and closest to the observational period. The asthma treatment steps were determined according to the GINA 2020 guidelines.¹ Xanthine was included as a controller medication at the same level as leukotriene receptor antagonists (LTRAs). Treatment with a combination of high-dose inhaled ICS and long-acting β_2 -agonist (LABA) was regarded as GINA step 5 treatment. If OCS was prescribed at the baseline visit, the asthma specialist determined whether OCS would be used as a controller or not by reviewing the medical records.

Statistical analysis

The baseline characteristics are presented as mean and standard deviation for continuous variables and relative frequencies for categorical variables. The data were compared using Student's *t* test, the Mann–Whitney *U* test, or the χ^2 test. Multiple logistic regression analysis was used to evaluate the relationships between individual asthma medications and the risk of OCS usage. Analysis for frequency of OCS bursts during each season among 660 OCS users during the 3-year study period were performed using ANOVA among 4 season and *t* test between individual seasons. All statistical analyses were performed using SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). A *P* value of < 0.05 was considered significant.

RESULTS

Characteristics of the OCS users vs. non-users

The characteristics of the study population are presented in **Table 1**. A total of 2,386 patients were enrolled, and 27.7% (660/2,386) were OCS users. There were more female OCS users, but age, body mass index, and peripheral blood eosinophil count were not different between the two groups. OCS users had a lower forced expiratory volume in one second (FEV1 [% pred.]) 74.9% vs. 79.2%, $P = 0.015$), more frequent asthma exacerbations during the previous year (16.7% vs. 9.7%, $P < 0.0001$), and higher GINA asthma treatment steps compared to non-OCS users ($P < 0.0001$). OCS users were treated with more controllers, such as LTRAs and long-acting muscarinic antagonists (LAMAs). The short-acting β_2 -agonist inhaler was used as a reliever drug and more frequently prescribed for OCS users even after adjusting for the GINA treatment steps (odds ratio, 2.023; 95% confidence interval, 1.662–2.462; $P < 0.0001$). According to the GINA asthma treatment steps (**Fig. 2A**), 50.0% of patients who received step 5 treatment and 29.4% of patients who received step 1 treatment required OCS treatment. The patients with asthma and a low FEV1 (% pred.) (< 60%) required an OCS more frequently ($P < 0.0001$; **Fig. 2B**). **Fig. 3** shows the details of the OCS prescriptions according to asthma severity, including the treatment steps, lung function, and history of asthma exacerbations during the previous year among the OCS users. Only 9 asthmatic patients were treated with biologics, which was omalizumab in all cases as it was the only biologic available in Korea at that time.

OCS prescription patterns

The median daily OCS dose for OCS users was estimated to be 20 mg/day (prednisolone equivalents), although a wide dose range was reported (1.25–55 mg) (**Fig. 3**). The median (interquartile range) number of cumulative days of an OCS prescription was 14 (7–41) days; 69.5% (459/660) of OCS users required an OCS treatment for less than 30 cumulative days. OCS burst treatment was observed in 88.5% (584/660) of OCS users with a mean dose (\pm SD) of 21.0 (\pm 8.1) mg per day for 7.8 (\pm 2.9) days per event and 2.4 (\pm 2.8) times per year. **Fig. 4**

Table 1. Baseline characteristics of the study population

Characteristics	All patients (n = 2,386)	OCS users (n = 660)	Non-OCS users (n = 1,726)	P value
Age (yr)	62.4 ± 14.6	62.7 ± 13.7	62.3 ± 14.9	0.571
Female (%)	1,363 (57.1)	400 (60.6)	963 (55.8)	0.034
BMI (kg/m ²)	24.4 ± 4.1	24.4 ± 4.6	24.3 ± 3.8	0.589
Lung function (No.)	2,244	636	1,605	
FEV1 (L)	1.98 ± 0.78	1.80 ± 0.73	2.05 ± 0.78	< 0.0001
FEV1 (% predicted)	78.0 ± 29.3	74.9 ± 42.2	79.2 ± 22.2	0.015
FVC (L)	2.87 ± 1.02	2.70 ± 0.92	2.92 ± 1.06	< 0.0001
FVC (% predicted)	84.3 ± 18.6	82.6 ± 20.8	85.0 ± 17.7	0.011
FEV1/FVC (%)	69.2 ± 14.9	63.4 ± 17.3	69.5 ± 13.9	0.133
Blood eosinophils (%)	3.7 ± 3.8	3.8 ± 4.5	3.6 ± 3.6	0.581
Blood eosinophils (/ μ L)	271 ± 494	276 ± 353	270 ± 541	0.798
Total IgE (IU/mL)	405.2 ± 784.7	387.3 ± 843.5	412.9 ± 758.6	0.631
History of acute exacerbations in the previous year				
Average No. of OCS bursts	0.87 ± 2.02	1.93 ± 3.16	0.43 ± 1.02	< 0.0001
No. of patients with OCS burst	707 (29.6)	362 (54.8)	345 (20)	< 0.0001
No. of patients with severe AE [†]	277 (11.6)	110 (16.7)	167 (9.7)	< 0.0001
Treatment step at baseline visit				< 0.0001
GINA step 1	202 (8.5)	26 (3.9)	176 (10.2)	
GINA step 2	325 (13.6)	63 (9.5)	262 (15.2)	
GINA step 3	332 (13.9)	68 (10.3)	264 (15.3)	
GINA step 4	1,267 (53.1)	373 (56.5)	894 (51.8)	
GINA step 5	260 (10.9)	130 (19.7)	130 (7.5)	
Frequency of controller medication prescription at baseline visit				
ICS (+/- LABA)	1,916 (80.3)	566 (85.8)	1,350 (78.2)	< 0.0001
LTRA	1,310 (54.9)	453 (68.6)	857 (49.7)	< 0.0001
Methylxanthine	515 (21.6)	176 (26.7)	339 (19.6)	< 0.0001
LAMA	290 (12.2)	110 (16.7)	180 (10.4)	< 0.0001
OCS	76 (3.2)	61 (9.2)	15 (0.9)	< 0.0001
Immunotherapy	65 (2.7)	12 (1.8)	53 (3.1)	< 0.0001
Oral β -agonist	30 (1.3)	10 (1.5)	20 (1.2)	< 0.0001
Biologics	9 (0.4)	1 (0.2)	8 (0.5)	0.266
β -agonist patch	5 (0.2)	2 (0.3)	3 (0.2)	< 0.0001
Reliever prescription [‡]	671 (28.1)	263 (39.8)	408 (23.6)	< 0.0001

Values are numbers (%), means ± SD, or medians with interquartile range.

[†]Emergency room visit and admission for asthma; [‡]Short-acting β_2 -agonist inhaler.

OCS, oral corticosteroid; BMI, body mass index; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; IgE, immunoglobulin E; AE, asthma exacerbation; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist.

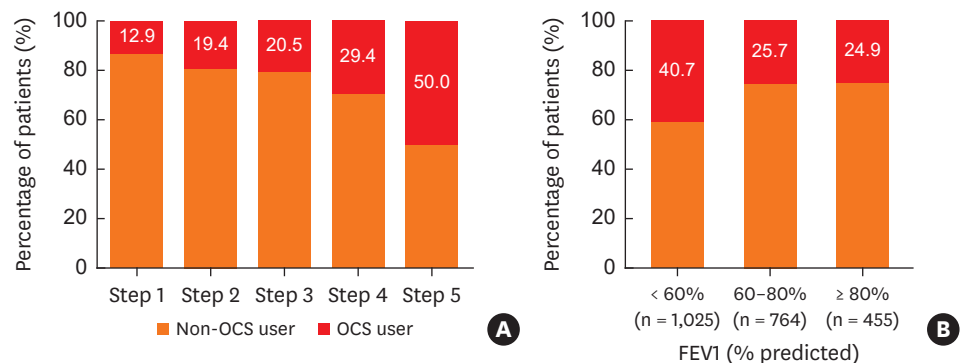


Fig. 2. The proportion of OCS users in the study population according to the GINA asthma treatment steps (A) and FEV1% predicted (B).

OCS, oral corticosteroid; FEV1, forced expiratory volume in one second; GINA, Global Initiative for Asthma.

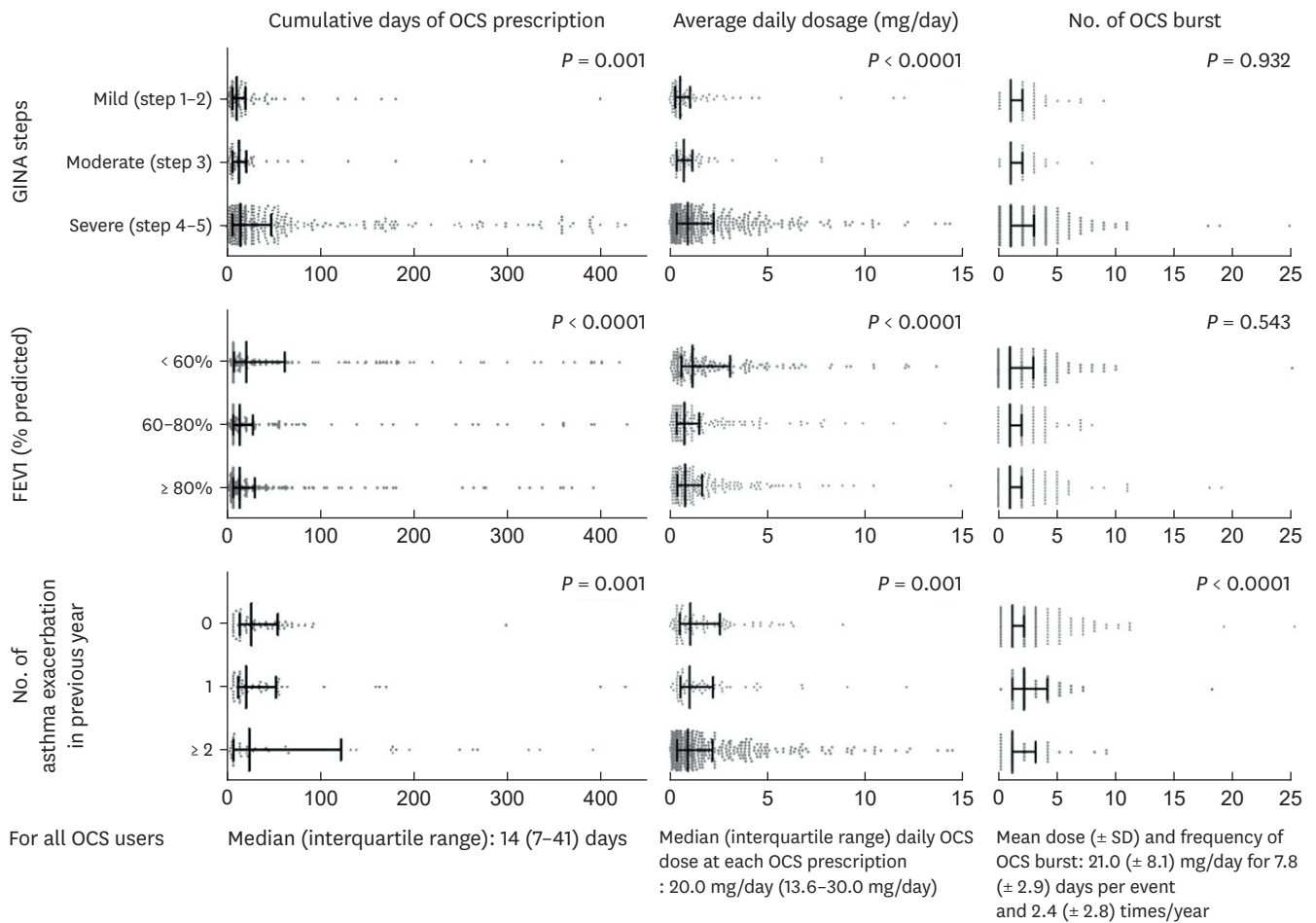


Fig. 3. The pattern of OCS treatment among OCS users. Cumulative days of an OCS prescription, average OCS dose, and number of OCS bursts during the observational period according to severity, including treatment steps, lung function, and the number of asthma exacerbations in the previous year among OCS users. OCS doses were presented as prednisolone equivalents. Error bars indicate median with interquartile range. *P* values were calculated using the Kruskal-Wallis test. OCS, oral corticosteroid.

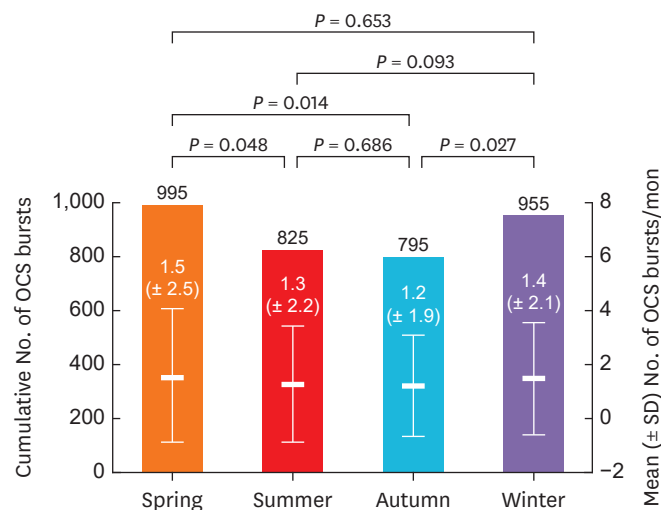


Fig. 4. Frequency of OCS bursts during each season among 660 OCS users during the 3-year study period. Statistical analyses were performed using ANOVA and *t* test. The horizontal lines and error bars represent the mean values and SD, respectively. OCS, oral corticosteroid.

illustrates the seasonal frequency of OCS bursts for the 660 OCS users during the 3-year study period ($P = 0.029$).

OCS-dependent asthma

OCS-dependent asthma accounted for 2.1% (51/2,386) of all patients with asthma, 7.7% (51/660) of OCS users, and 12.3% (32/260) of patients with asthma receiving the GINA step 5 treatment at the baseline visit. The median (interquartile range) daily dose of OCS was 5.8 (4.9–10.7) mg/day for 324 (252–372) days. **Fig. 5A** depicts the controller medications for maintenance in patients with OCS-dependent asthma; 15.7% used a high-dose ICS-LABA inhaler, whereas 11.8% were not prescribed any ICS-contained inhaler. The median number of controller medications besides OCS was two (0–4). **Fig. 5B** depicts the frequency of other controller medications besides ICS and OCS. No differences in the ICS dose or frequency of other controller medications were observed between the OCS burst-treated and untreated patients among those with OCS-dependent asthma.

Table 2 displays the clinical characteristics of the patients with OCS-dependent asthma and the other OCS users. The patients with OCS-dependent asthma were older and had lower FEV1 (L) and forced vital capacity (FVC) (L); 45.1% (23/51) of the patients with OCS-dependent asthma required OCS burst during the observational period with a median of 4 (1–6) times using 20.0 (10.0–22.5) mg per day prednisolone equivalents for 7.2 (6.9–14.0) days. OCS burst users were treated with OCS burst more frequently during the previous year than non-users but the cumulative doses and days of the OCS prescription were not different, although the cumulative days of OCS maintenance tended to be shorter in OCS burst users ($P = 0.058$). When assessed annually over the 3-year study period, the OCS-dependent asthma phenotype persisted during the entire year in 47.1% (25/51) of patients (**Fig. 6A**).

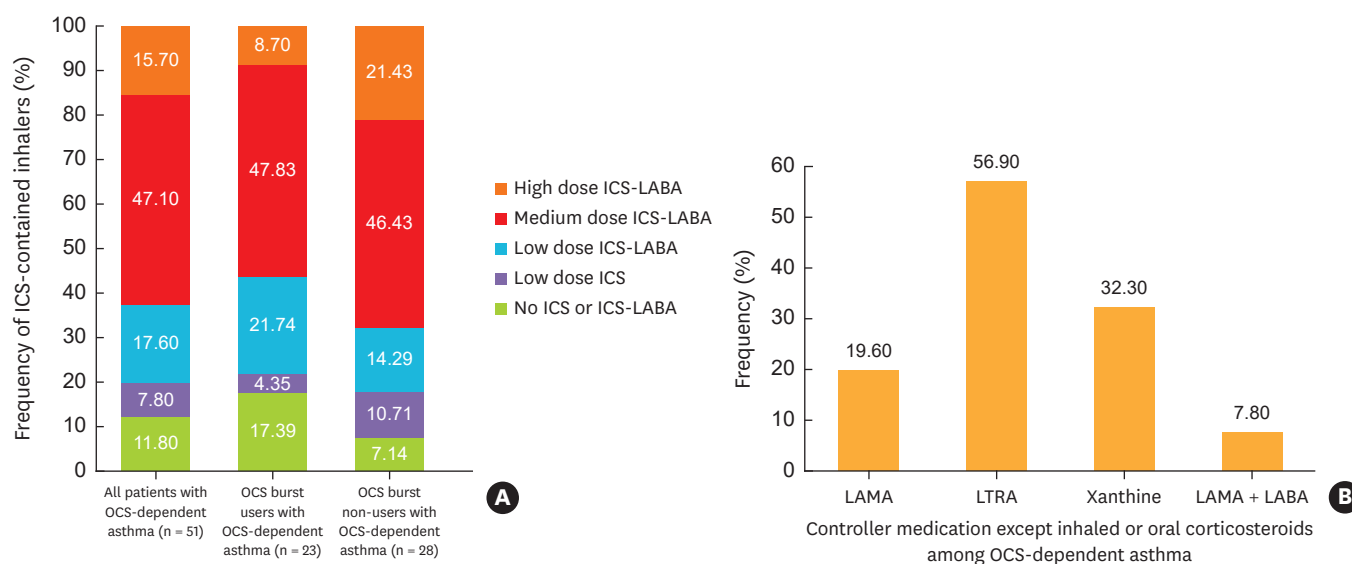


Fig. 5. Frequency of controller medication prescriptions at the baseline visit for patients with OCS-dependent asthma. (A) Frequency of ICS-contained inhalers, (B) frequency of other controllers. ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid.

Table 2. Clinical characteristics of OCS users according to cumulative days of OCS usage during the observational period

Characteristics	Other OCS users (n = 609)	OCS dependent asthma		P value*	P value†	
		Total (n = 51)	With OCS burst (n = 23)			Without OCS burst (n = 28)
Age (yr)	62.3 ± 13.8	66.9 ± 12.1	65.0 ± 9.2	68.5 ± 14.0	0.308	0.022
Female (%)	368 (60.4)	32 (62.7)	15 (65.2)	17 (60.7)	0.741	0.745
BMI (kg/m ²)	24.5 ± 4.7	24.0 ± 3.8	24.3 ± 4.2	23.7 ± 3.5	0.605	0.475
Lung function (No.)	588	48	23	25		
FEV1 (L)	1.83 ± 0.74	1.49 ± 0.60	1.66 ± 0.65	1.33 ± 0.53	0.059	0.002
FEV1 (% predicted)	75.6 ± 43.1	67.5 ± 26.4	73.7 ± 23.8	61.8 ± 27.8	0.121	0.201
FVC (L)	2.74 ± 0.92	2.37 ± 0.78	2.59 ± 0.82	2.16 ± 0.69	0.051	0.006
FVC (% predicted)	82.9 ± 20.7	78.3 ± 21.5	85.2 ± 21.3	71.9 ± 20.0	0.03	0.132
FEV1/FVC (%)	67.0 ± 17.1	62.6 ± 14.4	64.1 ± 14.7	61.4 ± 14.3	0.521	0.086
Blood eosinophil (/ μ L)	269 ± 323	353 ± 612	480 ± 828	236 ± 284	0.19	0.376
Total IgE (IU/mL)	397 ± 868	283 ± 496	392 ± 681	173 ± 153	0.269	0.509
Treatment step					0.305	< 0.0001
GINA step 1	26 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)		
GINA step 2	61 (10.0)	2 (3.9)	2 (8.7)	0 (0.0)		
GINA step 3	64 (10.5)	4 (7.8)	2 (8.7)	2 (7.1)		
GINA step 4	360 (59.1)	13 (25.5)	7 (30.4)	6 (21.4)		
GINA step 5	98 (16.1)	32 (62.7)	12 (52.2)	20 (71.4)		
OCS use in the pre-observational period						
No. of OCS bursts	1 (1-2)	1 (0-4)	2 (0-9)	0 (0-4)	0.002	0.27
Cumulative days of prescription	24 ± 43	216 ± 124	194 ± 115	233 ± 130	0.272	< 0.0001
OCS use in the observation periods						
Cumulative days of prescription	26 ± 33	314 ± 88	309 ± 75	317 ± 99	0.754	< 0.0001
Cumulative dose (mg)	466.4 ± 536.8	2,501.1 ± 2,381.4	2,471.7 ± 1,326.9	2,525.9 ± 3,011.0	0.937	< 0.0001
Days of maintenance use	10 ± 29	292 ± 106	261 ± 109	317 ± 99	0.058	< 0.0001
Dose of maintenance use (mg/day)	2.9 ± 7.3	6.9 ± 4.6	6.4 ± 3.8	7.3 ± 5.2	0.494	< 0.0001
Cumulative dose of maintenance use	128.1 ± 383.6	2,158.0 ± 2,362.3	1,710.2 ± 1,083.7	2,525.9 ± 3,011.0	0.223	< 0.0001
No. of OCS bursts	1 (1-2.5)	0 (0-3)	4 (1-6)	0	< 0.0001	< 0.0001
Daily dose of OCS burst (median)	20.0 (15.0-30.0)	0.0 (0.0-19.0)	20.0 (10.0-22.5)	0	< 0.0001	< 0.0001
Supply days of single OCS burst	7.0 (5.0-9.1)	0.0 (0.0-7.0)	7.2 (6.9-14.0)	0	< 0.0001	< 0.0001
OCS use in the post-observational period						
No. of OCS bursts	1 (0-2)	0 (0-1)	1 (0-2)	0 (0-0)	0.004	0.021
Cumulative days of prescription	26 ± 55	227 ± 136	252 ± 128	208 ± 141	0.247	< 0.0001

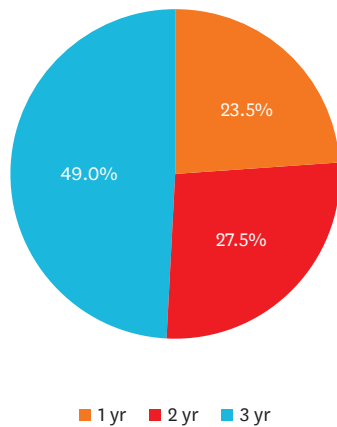
Values are numbers (%), means ± SDs, or medians with interquartile range *OCS-dependent asthma with OCS burst vs. OCS-dependent asthma without OCS burst; †All patients with OCS-dependent asthma vs. other OCS users.

OCS, oral corticosteroid; BMI, body mass index; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; IgE, immunoglobulin E; GINA, Global Initiative for Asthma.

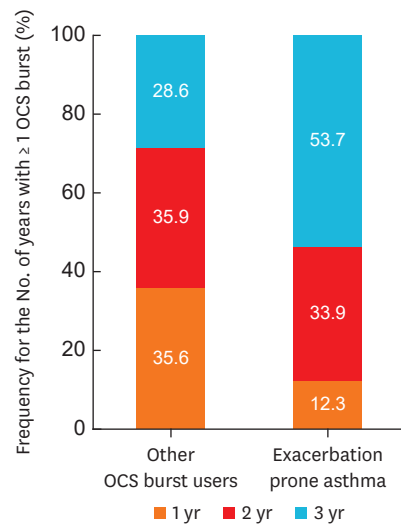
Frequent OCS burst users

Among OCS burst users, 52.9% (309/584) were treated with OCS burst 2 or more times during the observational period, and 38.8% (227/584) had exacerbation-prone asthma (2 or more OCS burst treatments and 2 or more controller medications). **Table 3** gives a comparison of the clinical characteristics between patients with exacerbation-prone asthma and the other OCS burst users. The patients with exacerbation-prone asthma had a lower FEV1 (L), more frequent OCS bursts, and more cumulative days of the OCS prescription than the other OCS burst users despite a higher asthma treatment step. The average duration of OCS prescription at each OCS burst was longer in patients with exacerbation-prone asthma than in the others (mean ± SD, 8.1 ± 2.9 days vs. 7.6 ± 2.9 days, $P = 0.045$), but the daily OCS dose was similar between the 2 groups. Patients with exacerbation-prone asthma had more frequent OCS bursts and more frequent hospital visits during the previous year, although the number of severe asthma exacerbations was not different between the 2 groups. **Fig. 6** summarizes the need for the OCS burst treatment during each year of the 3-year study period. OCS burst treatments were needed more consistently in patients with exacerbation-prone asthma over the 3 years; 53.7% of patients with exacerbation-prone asthma had one or more OCS bursts during each year, and 34.4% (78/227) of patients with exacerbation-prone asthma showed two or more OCS bursts during each year of the 3-year study.

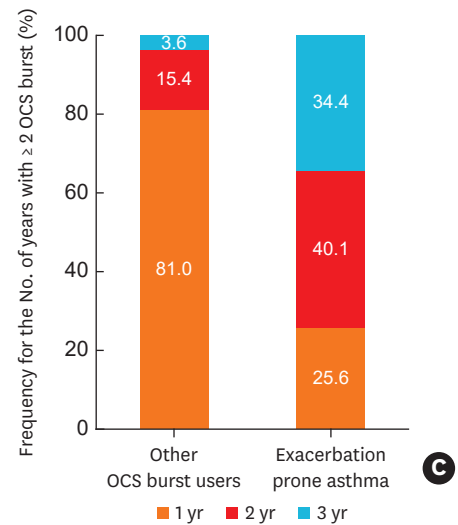
Annual consistency of OCS-dependent asthma during 3-year study period



A



B



C

Fig. 6. Annual consistency of OCS-related asthma phenotypes during the 3-year study period. (A) The annual consistency of OCS-dependent asthma and the annual consistency of the need for OCS burst treatment between exacerbation-prone asthma patients and other OCS burst users. (B) Number of years with 1 or more OCS bursts. (C) Number of years with 2 or more OCS bursts. OCS, oral corticosteroid.

DISCUSSION

Among patients with asthma who had been followed by asthma specialists for more than 3 years in Korea, 27.7% were treated with OCSs during the 1-year observational period. About 24% were treated with OCS burst (mean dose of 21 mg per day prednisolone equivalents for 7.8 days about 2.4 times per year) and 38% of OCS burst users had exacerbation-prone asthma. A total of 2.1% of the study population had OCS-dependent asthma (median 5.8 mg prednisone equivalents per day for 324 days).

The pattern of OCS use in the current study was similar to those of previous reports and guidelines.³⁻⁶ As controller treatment using OCS, the GINA guidelines recommend ≤ 7.5 mg/day prednisone equivalents,^{1,2} and various OCS maintenance doses have been reported in many countries: daily 2–50 mg prednisolone equivalents from Australia,¹⁴ 10–15 mg/day from several specialist UK centers,¹⁵ and 5.5–7.5 mg in European countries.¹⁶ Rates of patients treated with OCS burst also vary from study to study: from 3.6% to 62.0% among patients with asthma and any degree of asthma severity;¹⁷ the mean number of OCS bursts ranged at 0.1–2.16 prescriptions per year in patients with any degree of asthma severity¹⁷ and ranged from 1.2 to 2.1 per year for steps 1 to 4, and 5.3 per year for step 5.¹⁸

Our findings do not represent the pattern of asthma medication usage in most Korean hospitals. Several studies using Korean claims data have reported that OCSs are used more frequently than ICSs,^{10,11} suggesting that OCSs are over-used for asthma treatments in most hospitals in Korea. Asthma misdiagnosis, suboptimal management of asthma, and poor adherence to controller medication can increase the risk of exacerbations necessitating OCS use.^{1,3,19-22} Some studies have suggested that more than 50% of patients referred for difficult-to-control asthma do not have refractory disease after a detailed systematic evaluation, but have multiple other mechanisms driving their persistent symptoms.²²⁻²⁴ The Korean government has implemented government-level education and public medicine campaigns to increase the ICS prescription rate and the use of lung function tests. There must be

Table 3. Comparison between exacerbation-prone asthma and other OCS burst users

Characteristics	Other OCS burst users (n = 357)	Exacerbation-prone asthma (n = 227)	P value
Age (yr)	62.2 ± 14.3	63.3 ± 12.6	0.318
Female (%)	230 (64.4)	133 (58.6)	0.156
BMI (kg/m ²)	24.9 ± 5.2	24.0 ± 4.0	0.045
Lung function			
FEV ₁ (L)	1.89 ± 0.76	1.70 ± 0.66	0.002
FEV ₁ (% predicted)	76.6 ± 25.6	74.7 ± 62.6	0.125
FVC (L)	2.78 ± 0.92	2.63 ± 0.92	0.063
FVC (% predicted)	84.0 ± 19.3	81.2 ± 22.1	0.125
FEV ₁ /FVC (%)	68.2 ± 14.6	65.9 ± 20.0	0.153
Blood eosinophils (%)	3.7 ± 4.5	4.0 ± 4.6	0.505
Blood eosinophils (/ μ L)	262 ± 330	303 ± 401	0.206
FeNO [†]	37.4 ± 39.7	42.6 ± 26.4	0.564
PC20 [‡]	13.0 ± 14.1	8.8 ± 13.5	0.228
Total IgE (IU/mL)	397 ± 1,018	385 ± 681	0.912
Atopy	42.2% (62/147)	42.9% (57/133)	0.908
Treatment step at baseline visit			< 0.0001
GINA step 1	24 (6.7)	0 (0.0)	
GINA step 2	53 (14.8)	6 (2.6)	
GINA step 3	53 (14.8)	12 (5.3)	
GINA step 4	186 (52.1)	156 (68.7)	
GINA step 5	41 (11.5)	53 (23.3)	
During observation period			
No. of OCS burst used	1.43 ± 1.04	3.86 ± 3.77	< 0.0001
Average days of single OCS burst	7.6 ± 2.9	8.1 ± 2.9	0.045
Average dose of OCS burst (mg/day)	20.9 ± 8.0	21.2 ± 8.3	0.725
Cumulative days of OCS prescription	23.3 ± 52.4	52.7 ± 76.7	< 0.0001
No. of severe asthma exacerbations [‡]	0.34 ± 0.88	0.29 ± 0.76	0.473
In the previous year			
Cumulative No. of OPD visits	6.8 ± 4.6	8.7 ± 6.0	< 0.0001
No. of OCS bursts	1.13 ± 1.73	2.95 ± 4.35	< 0.0001
No. of severe asthma exacerbations	0.30 ± 0.97	0.35 ± 0.91	0.525

Values are numbers (%) or means ± SD.

[‡]PC20 tests were available for 44 and 26 patients from other OCS burst users and exacerbation-prone asthma patients, respectively; [†]FeNO tests were available for 43 and 24 patients from other OCS burst users and exacerbation-prone asthma patients, respectively; [‡]Emergency room visits and admissions for asthma. OCS, oral corticosteroid; BMI, body mass index; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; PC20, the concentration of methacholine that causes a 20% decrease in FEV₁ in methacholine bronchial provocation test; IgE, immunoglobulin E; GINA, Global Initiative for Asthma; OPD, outpatient department.

an additional institutional approach that enables patients or primary care physicians to activate the services of asthma experts to optimize asthma treatment because identifying comorbidities and risk factors for asthma exacerbations and evaluating differential diagnoses of patients with severe asthma required much expertise and time.^{3,25-27}

It is unclear whether OCS users have received optimal therapy for asthma to justify the OCS treatment, but this study clearly showed that most OCS users were already treated with multiple controller medications but the treatment was not successful. Adding a LAMA and an LTRA was related to an increased risk of OCS use in the multiple logistic regression analysis after adjusting for FEV₁ (% pred.) and other medications. Even in patients with OCS-dependent asthma, 45.1% needed additional OCS bursts for 1 year. A history of asthma exacerbation remained a risk factor for future exacerbations, although OCS users were at higher asthma treatment steps and were all followed by asthma specialists in referral hospitals. Several other studies have suggested that the current strategy to treat asthma may not be sufficient to reduce future risk for asthma exacerbations, particularly in asthmatic patients with a low FEV₁ and a history of

asthma exacerbations during the previous year.^{28,29} These findings suggest that there is a need to reduce the future risk of asthma exacerbations. Fortunately, biologics, such as omalizumab, mepolizumab, benralizumab, reslizumab, and dupilumab, have become available to treat severe asthma; these agents reduce asthma exacerbations and lower OCS exposure.³ Some biologic agents inconsistently improve symptoms, but consistently decrease the number of asthma exacerbations.^{30,31} Although it has been demonstrated that biologics are a good option for reducing OCS use and improving asthma control, only a few asthmatic patients were treated using biologics in this study. Although it was early to adapt biologics for asthma treatment and omalizumab was the only available in Korea during the study period, the low rate of biologics usage was mainly due to their high cost. Therefore, the institutional support, such as insurance coverage and reimbursement, is essential.

Exacerbation-prone asthma is often defined as having two or more OCS bursts per year despite the use of at least 2 controller medications, including a medium or high-dose ICS.^{12,13} Despite great advances in the understanding and treatment of asthma, many patients with severe disease continue to have frequent exacerbations.^{13,32} Exacerbation-prone asthma contributed to 38.6% of OCS burst users in this study, and they showed low FEV1 levels and recurrent exacerbations that required OCS bursts during the previous year, even though they were treated at high asthma treatment steps. Furthermore, the asthma phenotype was relatively stable over the 3 consecutive years. Asthma exacerbations are frequently triggered by acute exposure to environmental stimuli in the presence of incompletely controlled airway inflammation. Seasonal variation in the frequency of OCS bursts were observed in this study, and there could be environmental factors for recurrent exacerbations including seasonal changes in temperature, allergen exposure, and viral infection.^{13,33} Such seasonal variations should be considered in the treatment strategy for patients with exacerbation-prone asthma to prevent future exacerbations. As there have been reports about personal traits in exacerbation-prone asthma, such as uncontrolled inflammation, mucus plugs, airway hypersensitivity, and genetic traits regarding susceptibility to viral infection and inflammation, clinicians should monitor the risk factors for OCS bursts and consider a plan to prevent future exacerbations and future OCS bursts in frequent OCS burst users.

The GINA guidelines suggest that OCSs are used during step 5 as add-on therapy but OCSs are still widely used for the long-term management of severe asthma. Additionally, 40% of patients on the British Thoracic Society Severe Asthma Registry receive regular prednisolone at a daily dose of 10–15 mg¹⁵ and 32% of patients with severe asthma in the Severe Asthma Research Program receive an OCS for more than 50% of the year.^{34,35} This study showed that about half of patients with OCS-dependent asthma required additional OCS bursts despite long-term OCS maintenance treatment. These findings suggest that OCS is a last option for patients with severe asthma, but not a final solution for most of them; thus, other treatments options should be carefully considered, particularly in patients with OCS-dependent asthma and frequent OCS use. Furthermore, the current study showed that eosinophilic inflammation remained an important feature of OCS-related phenotypes. Blood eosinophil counts in OCS-dependent and exacerbation-prone asthma patients did not differ statistically from those of controls even after log-transformation analysis. However, the blood eosinophil counts and fractional exhaled nitric oxide levels of these patients tended to be higher than those of controls, despite frequent or continuous OCS treatment. Since the current biologics for asthma treatments target type-2 inflammation which is characterized as eosinophilia, they are expected to be effective in most patients with OCS-related phenotypes and should be considered for these patients who consistently require systemic steroids.

This study had several limitations. First, the findings cannot be generalized to all patients with asthma in Korea. There may be a selection bias as the enrolled patients were from referral hospitals and were followed up for asthma for more than 3 years. This could explain why the patients enrolled were older than expected based on epidemiological studies on asthma. There are likely more patients with severe asthma. Secondly, COPD patients were not excluded, and no smoking history data were provided. However, the COPD component could be regarded as asthma-COPD overlap, since asthma was diagnosed by asthma specialists with a sufficient observational period. A strength of this study was that it reflects the diversity of asthma phenotypes in the real world. Thirdly, there was no evaluation of comorbidities or side-effects of corticosteroids in the study population due to limitations of the data from a retrospective study. Fourthly, there could be discrepancies between the actual OCS use by the patients and OCS prescriptions. Since OCS prescriptions were investigated retrospectively based on the medical records of each hospital, there could be time differences between OCS prescription and intake, poor adherence to OCS, and missed OCS treatment undertaken at other hospitals. However, the study population and the study period were reasonable for understanding OCS prescription patterns. A 3-year study period may be long enough to examine OCS patterns despite the time difference between prescription and intake, and the chances of OCS treatments for asthma exacerbations at other hospitals would be relatively low for patients who had been regularly visiting a tertiary hospital for asthma treatment. Finally, the current study evaluated only OCS treatment, but not intravenous corticosteroids (IVCSs), so it may not reflect the usage of all systemic steroids for asthma. Although only a different route of administration of systemic steroid is involved, the roles of IVCS and OCS in asthma treatment are totally different. IVCS may be administered to inpatients with asthma or just temporarily for exceptional cases at outpatient asthma clinics, whereas OCS is used as a reliever and maintenance therapy. As regards the frequency of severe asthma exacerbations, including hospitalizations and emergency department visits, which are more closely related with IVCS treatment, there were no differences between OCS-dependent asthma or exacerbation-prone asthma patients and controls.

In conclusion, this study describes the prescription pattern of OCS and other asthma medications using real-world data from university hospitals in Korea. The pattern of OCS prescriptions in patients with asthma seemed appropriate according to the guidelines and was similar to those of previous reports from other countries. Although most of the OCS users had been treated with GINA step 4 or 5 using multiple controllers, exacerbation-prone asthma and OCS-dependent asthma phenotypes were relatively consistent, and about half of the patients with OCS-dependent asthma required additional OCS bursts. These findings suggest that OCSs were not the final solution for patients with severe or exacerbation-prone asthma. Thus, there are still unmet needs to prevent the future risk of asthma exacerbation.

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