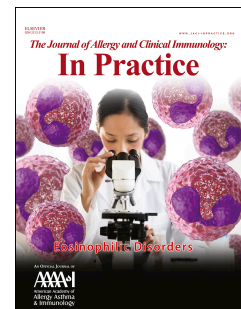


Journal Pre-proof

The clinical course of asthma after withdrawal of inhaled corticosteroids

Dong-Woo Han, MD, Jae Seung Lee, MD, Yeon-Mok Oh, MD, Sang-Do Lee, MD,
Hwa Jung Kim, MD, Sei Won Lee, MD



PII: S2213-2198(20)31106-5

DOI: <https://doi.org/10.1016/j.jaip.2020.09.056>

Reference: JAIP 3171

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 16 February 2020

Revised Date: 23 September 2020

Accepted Date: 25 September 2020

Please cite this article as: Han DW, Lee JS, Oh YM, Lee SD, Kim HJ, Lee SW, The clinical course of asthma after withdrawal of inhaled corticosteroids, *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: <https://doi.org/10.1016/j.jaip.2020.09.056>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

The clinical course of asthma after withdrawal of inhaled corticosteroids

Dong-Woo Han, MD¹; Jae Seung Lee, MD^{1,2}; Yeon-Mok Oh, MD^{1,2}; Sang-Do Lee, MD^{1,2};
Hwa Jung Kim, MD^{3,4*}; Sei Won Lee, MD^{1,2*}

¹Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul, Republic of Korea

²Clinical Research Center for Chronic Obstructive Airway Diseases, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul, Republic of Korea

³Department of Preventive Medicine, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul, Republic of Korea

⁴Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul, Republic of Korea

* These authors contributed equally to this study

Email addresses of all author

Dong-Woo Han: vupix@naver.com

Jae Seung Lee: jsdoc1186@daum.net

Yeon-Mok Oh: ymoh55@amc.seoul.kr

Sang-Do Lee: sdlee@amc.seoul.kr

Hwa Jung Kim: hello.hello.hj@gmail.com

Sei Won Lee: seiwon@amc.seoul.kr

24

25 **Corresponding authors**

26 Sei Won Lee, MD

27 Department of Pulmonary and Critical Care Medicine and Clinical Research Center for
28 Chronic Obstructive Airway Diseases, Asan Medical Center, University of Ulsan College of
29 Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul, Republic of Korea

30 E-mail: seiwon@amc.seoul.kr

31 Phone number: +82-2-3010-3990

32

33 Hwa Jung Kim, MD

34 Department of Preventive Medicine, University of Ulsan College of Medicine, Department of
35 Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College
36 of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul, Republic of Korea

37 E-mail: hello.hello.hj@gmail.com

38 Phone number: +82-2-3010-4638

39

40 **Conflicts of interests**

41 No authors report any conflicts of interest.

42

43 **Funding/support**

44 This study was supported by a grant (2018-0352) from the Asan Institute for Life Sciences,
45 Asan Medical Center, Seoul, Korea.

46

47 **Word count for the text: 3,355**

48 **Word count for the abstract: 266**

49

50

51

Journal Pre-proof

ABSTRACT

Background

Maintenance of inhaled corticosteroids (ICS) is recommended in adult asthmatics. However, adherence rates in patients with mild asthma and side effects of long-term ICS use can lead to withdrawal.

Objective

We analyzed the real-world outcomes of ICS withdrawal by analyzing data from the Korean National Health Insurance (NHI) database.

Methods

Based on claims data from the NHI of Korea between 2011 and 2014, we identified patients diagnosed with asthma without chronic obstructive pulmonary disorder (COPD) or long-term systemic steroid use who had an ICS medication possession rate of > 50% in a year. We compared patients who received ICS consistently (maintenance group) with patients who had no ICS prescription for more than 6 months (withdrawal group). We evaluated exacerbation leading to prescription of systemic steroid and emergency department (ED) visit or hospitalization.

Results

Excluding COPD patients and long-term systemic steroid users, we identified 145,511 patients for the asthma cohort (Mean age 60.0, ever smoker 63.5%): 132,175 maintained ICS and 13,336 withdrew ICS for more than 6 months. Only 71 patients (0.5%) experienced exacerbation leading to an ED visit or hospitalization in the withdrawal group. ICS was restarted within one year for 33.6% of the withdrawal group, and 90% of those patients restarted ICS within 158 days.

Conclusions

This nationwide study of asthmatics, characterized by a high proportion of elderly and smokers, showed that ICS withdrawal in about 10% of patients appeared to confer relatively minimal harm and exacerbation leading to hospitalization was not common. Further prospective studies are warranted to carefully explore the safety of ICS withdrawal in younger, non-smoking and well controlled asthmatic patients.

Highlights box

What is already known about this topic?

Maintenance of inhaled corticosteroids (ICS) is recommended in most adult asthmatics and GINA revised their recommendation to avoid complete withdrawal of ICS in adults.

What does this article add to our knowledge?

In a group of older asthma patients with a high prevalence of smoking, most patients did not experience exacerbation events leading to hospitalization even after ICS withdrawal in real-life practice.

How does this study impact current management guidelines?

ICS cessation could be considered cautiously in patients who are well-controlled.

Keywords: Asthma, inhaled corticosteroid, acute exacerbation

96 **Abbreviations:** CIs- confidence intervals; COPD- Chronic obstructive pulmonary disorder;
97 GINA- Global Initiative for Asthma guidelines; HRs- Hazard ratios; ICD- International
98 Classification of Diseases; ICS- inhaled corticosteroid; MPR- medication possession ratio;
99 NHI- Korean National Health Insurance;

100

Introduction

Asthma is a global health problem, affecting 235 million people worldwide.¹ Inhaled corticosteroids (ICS) have been emphasized as the major controller to relieve symptoms; improve lung function; and reduce risk of exacerbation, asthma related mortality, and hospitalization.^{2,3} Other asthma therapies without ICS have higher treatment failure rates,⁴ so ICS continues to be recommended as the main treatment at every step for asthma.⁵

Previously, the Global Initiative for Asthma guidelines (GINA) in 2011 suggested that withdrawal of asthma controller therapy could be attempted if asthma is stable for one year of low-dose ICS treatment. However, a recent meta-analysis showed that ICS discontinuation led to higher risk of exacerbation and worse lung function and symptom control.⁶ Based on these findings, the GINA revised their recommendation to avoid complete withdrawal of ICS in adults.

Although maintenance of ICS without discontinuation avoids risks associated with withdrawal, there are some concerns about this in real-life practice. As a steroid, long-term use of ICS has side effects such as adrenal suppression, osteoporosis, cataracts, glaucoma, and skin bruising.^{7,8} There are also realistic challenges with respect to maintaining adherence to inhaler use among patients with well controlled symptoms. In one study, among patients hospitalized for asthma exacerbation, adherence to ICS dropped to almost half within seven days of discharge.⁹ The economic burden of the medication should be also considered as more than half of total medical costs for asthma come from medication.¹⁰ However, the natural course of asthmatics after ICS withdrawal has not been well studied in real-world practice. Therefore, there is a need for the evidence to evaluate the impacts ICS withdrawal and maintenance.

Registration in the National Health Insurance (NHI) system is mandatory in Korea, and data of all prescriptions by clinicians can be collected from this system. This database provides

real-world large-scale epidemiological data that can be used to investigate outcomes associated with changes in ICS prescription. In this study, we investigated the impact of ICS withdrawal in asthma patients by reviewing the nationwide ICS prescriptions for asthma and analyzing exacerbation events following ICS withdrawal.

Materials and Methods

NHI claims database

We retrospectively reviewed the complete NHI claim database of patients with asthma between January 1, 2010 and December 31, 2014 which were provided by the Korean Health Insurance Review and Assessment Service and approved by the Ethics Committee of the National Evidence-Based Healthcare Collaborating Agency. As registration in the NHI is mandatory, the NHI claim database contains the data of approximately 96.7% of all residents in Korea, excluding patients receiving social assistance from the Medical Aid Program.¹¹ This database contains not only information of diagnoses, prescribed drugs, and medical procedures but also information about the healthcare provider, medical costs, and patient income level and medical check-up information including smoking history. Healthcare providers were grouped into primary (clinic, health center, health center branch, Chinese medicine hospital, medical center), secondary (hospital, nursing hospital), and tertiary (advanced general hospital, general hospital) facilities. This study was approved by the institutional review board of Asan Medical Center (2018-0352) and was performed in accordance with the principles of the Declaration of Helsinki.

Patients and study design

We identified patients older than 20 years of age and diagnosed with asthma according to the 10th Revision of the International Classification of Diseases (ICD-10) codes J45.x–J46.x who

had been prescribed an ICS (i.e. ICS or ICS in combination with a long-acting beta agonist [LABA]). From these patients, we included patients who used ICS medications for more than one year with medication possession ratio (MPR) > 50%. If patients had several episodes of having an MPR of more than 50%, only the most recent period was used in the study. Patients diagnosed with chronic obstructive pulmonary disease (COPD) by (ICD-10 codes J42.x–J44.x) or patients who used systemic corticosteroids for more than two months with a MPR > 50% were excluded. In order to have sufficient follow-up periods, patients who died after June 31, 2013 were also excluded.

Designation of Groups

The enrolled patients were divided into two groups: the maintenance group and withdrawal group. The maintenance group was defined as patients who had been prescribed ICS medications at least once during the six month period after their MPR for ICS went below 50%. The withdrawal group included patients who had not been prescribed ICS medications for more than 6 months after their MPR for ICS went below 50%. Within the withdrawal group patients, the reinitiation group was classified as the patients who reuse ICS medications within one year after of the end of the six months ICS withdrawal period. Doses of ICS were divided into low, medium, and high according to the GINA guideline.¹²

Definition of Exacerbation and Hospitalization

Moderate exacerbations were defined as patients who received a prescription for systemic steroids of more than the equivalent dose of prednisolone 20 mg for three days associated with an asthma disease code but were not hospitalized. Hospitalization was defined as ‘ICU or ward admission’ or ‘emergency room visit’ associated with an asthma disease code. Hospitalization with steroid was defined as patients who received systemic steroids

regardless of dose and duration during hospitalization. Severe exacerbations were defined when patients were hospitalized with moderate exacerbation. All events of interest including reinitiation of ICS, exacerbation, and hospitalization were analyzed for one year, after six months of the ICS cessation period in the ICS withdrawal group (Figure 1). For the adjustment of hazard ratios multivariate analyses with exacerbation events, age, sex, income, type of healthcare provider, smoking status, and annual MPR, we monitored exacerbation and hospitalization, previous moderate exacerbation within one year, and date of study inclusion.

Statistical Analyses

Differences in categorical variables were compared using the chi-square test, and continuous variables were analyzed using the Student's t-test. Also, the significance of the differences of baseline characteristics between groups were also evaluated with standardized difference because of large sample size and assume that there was no difference between groups if they standardized difference was less than 0.1. Cox proportional hazard regression analyses were used to evaluate factors' associations with exacerbation outcomes and hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. Additionally, we set noninferiority tests with the use of noninferiority limits of 1.2 (one-sided 95% CI). Reinitiation of ICS was shown by Kaplan-Meier analyses using IBM SPSS version 25.0 (IBM, New York, United States). All other statistical analyses were done with Statistical Analysis System ver 9.4 (SAS, North Carolina, United States). We set the significance level at $P = 0.05$.

Sensitivity Analyses

Sensitivity analyses were done with the propensity score matching method. Propensity score matching was done to compare the likelihood of each exacerbation or hospitalization events.

Baseline sex, age, income which is divided by each 5 percentile, smoking history, healthcare provider, annual MPR, and exacerbation events were used to compute the propensity scores.

Results

Patient Characteristics

The flowchart of the patient selection process is shown in Figure 2. There were 5,762,709 patients who had ICD-10 disease codes for asthma in the NHI claim database between January 1, 2011 and December 31, 2014. Excluding COPD patients, ICS were prescribed to 1,472,838 patients, of whom 187,804 (12.8%) patients had a MPR of more than 50% over a one year period. Of all 145,511 remaining patients except long-term steroid user and patients who died or met end of study period within 18 months after the last period of ICS MPR of more than 50%, 132,175 (90.8%) patients were maintenance group, and 13,343 (9.2%) patients were withdrawal group.

Baseline characteristics of patients are shown in Table 1. The mean age was 57.6 ± 17.9 and 60.2 ± 16.9 , and 51% and 53% of patients were male, respectively in the withdrawal and the maintenance group. Income data were available for 128,701 patients and each five 5 percentiles are combined to quartile, and 40.7% of the withdrawal group and 40.2% of the maintenance group were in the 4th income quartile. In the withdrawal group 61.3% of patients received their first prescription of ICS from a primary healthcare provider, 6.1% received their prescription from a secondary healthcare provider, and 32.6% received their prescription from a tertiary healthcare provider. In contrast, 79.9% of patients in the withdrawal group received their first prescription of ICS in a primary provider, 4.9% from a secondary provider, and 15.3% from a tertiary healthcare provider. Smoking history data were available for 67,011 patients: 59.7% of the withdrawal group were ever smokers, and

63·9% were ever smokers in the maintenance group. The mean MPR was 79·7% in the withdrawal group and 60·3% in the maintenance group.

After propensity score matching, 12,591 pairs were matched in each group. Even though there were significant differences on standardized difference between withdrawal group and maintenance group on age, income, healthcare provider, and MPR, no significance was seen after propensity score matching in standardized difference except minimal difference of healthcare provider (standardized difference = 0·104, Table E1).

Prescription of ICS

Figure 3 shows the monthly and annual prescription totals of ICS medications. Sum of monthly prescriptions showed the highest number in December, 164,150 cases and the lowest in August, 145,336 cases. The annual prescription rate of ICS increased with time from 344,855 prescriptions in 2010 to 379,612 prescriptions in 2013 before decreasing in 2014 to 378,620 prescriptions per year (Figure 3). Low-dose ICS were more frequently prescribed in the withdrawal group (ICS alone agents and ICS/LABA) and higher doses of medium-, and high-dose were more frequent in maintenance group (Table 2).

Exacerbations and hospitalizations

After ICS withdrawal, 3,901 (29·25%) patients experienced moderate exacerbation and 3,461 (25·95%) were hospitalized with the diagnosis of asthma (Table 3). Critical events due to asthma including hospitalizations with steroid administration and severe exacerbations were rare; the proportion of ICS withdrawal patients who experienced hospitalization with steroid administration in one year was 1·99% and who experienced severe exacerbation was only 0·53%. Kaplan-Meier curves showing these events are presented in Figure 4. Similar trends were seen after propensity score matching (Figure E1). Exacerbation and hospitalization

events were significantly higher in the maintenance group than in the withdrawal group ($p < 0.001$, Table 3). Therefore, the withdrawal group was noninferior to the maintenance group and these findings were consistent in multivariate analyses and after propensity score matching (Table 4, Tables E2 and E3). To confirm that these results are not affected by asthma and COPD overlap (ACO), subgroup analysis was performed for never-smoker younger than 50 years old. The withdrawal group did not have more exacerbation events than the maintenance group in this subgroup analysis (Table E4, E5).

In addition, we analyzed main diagnostic codes of hospitalization events. Excluding the codes for asthma (J45 and J46), the J code, except J45 and J 46, for diseases of the respiratory system (20.8%), I code for diseases of the circulatory system (9.5%), and M code for diseases of the musculoskeletal system and connective tissue (9.1%) were also frequent main diagnostic codes.

Restart of ICS in withdrawal group

Among the withdrawal group, 4480 patients (33.6%) restarted ICS within one year after the six months of ICS withdrawal period. Monthly numbers of restarting ICS between 2011 and 2014 is shown in Figure 5A, and ICS re-initiation was more frequent from October to December (598, 553, and 560 instances of ICS re-initiation in October November and December, respectively). A Kaplan-Meier curve of re-initiation is shown in Figure 5B and inflection point was 320 days. Of patients who restarted ICS within one year, 4,032 patients (90%) restarted within 158 days after the end 6 months of ICS withdrawal period (358 days from the beginning of ICS withdrawal).

Discussion

In this real-practice study, about 10% of patients with asthma stopped ICS for more than six months after maintaining ICS for more than one year. Of the patients who stopped ICS, more than 30% of them restarted ICS. Notably, re-initiation of ICS became less common about one year after ICS withdrawal. Another 29.3% of patients had been hospitalized, while less than 1% of hospitalized patients also received a meaningful dose of systemic steroids ($20 \text{ mg} \geq 3$ days). The withdrawal group did not have more exacerbation events when compared to the maintenance group, even after propensity score matching.

The target population of this study was patients who used ICS continuously for at least one year to treat asthma. ICS can be used as a diagnostic tool of asthma to assess variable airflow limitation, or as the therapeutic trial of cough variant asthma. Therefore, short-term transient prescription of ICS may not indicate asthma. Considering this, at least one year of ICS usage with a MPR $\geq 50\%$ was set to ensure that patients with asthma were included in the study. Compliance as indicated by inhaler possession $\geq 50\%$ within a year is not easy to achieve in real-world practice.⁹ Many patients maintain long term ICS adherence because they felt its benefit and patients with asthma who seek ICS more do so because it relieves their symptoms.¹³ In this context, ICS withdrawal for six months after long-term maintenance of ICS is not very common,¹⁴ but patients who do so might be able to continue controlling their symptoms without ICS.

Seasonal conditions may affect asthma symptoms and are closely associated with ICS prescription. Interestingly, ICS prescriptions were more frequent in April and December. Along with the yellow dust blowing from China, the concentration of particulate matter in Korea reaches its peak in April.¹⁵ Particulate matter is associated with higher incidence and prevalence of asthma and asthma-related hospital visits.¹⁶ The diagnosis of asthma is more definitive when symptoms are triggered by cold air and when respiratory symptoms of asthma worsen in cold weather.¹⁷ The trends of ICS prescriptions indicate when we should be

cautious about risk of clinical deterioration. To control symptoms and prevent exacerbation effectively, a shortened follow-up interval or prescription of to be taken as needed may be considered in those seasons. This information may be useful for those with limited access to medical care.

Systemic corticosteroids are the main treatment for acute exacerbation of asthma. If administered within 3–5 days,¹⁸ they have been found to speed resolution of symptoms, improve lung function,^{19,20} and decrease rates of admission and relapse.²¹ Therefore, systemic corticosteroids should be given promptly if patients have already increased their reliever and controller.¹² In our study, 32·4% of all patients had been hospitalized or had visited the emergency room within a year, but less than 1% of those patients received a meaningful dose of systemic corticosteroid during that admission period. This suggests that hospitalization was fairly common in the study population, but hospitalization due to asthma exacerbation was not very common. Patients with asthma could have many comorbidities leading to hospital admission, especially among elderly patients.²² In those cases, asthma medications should be continued irrespective of admission causes, and the registration of asthma diagnosis is necessary for the insurance claim. Considering that patients with relatively mild asthma may not use ICS for periods longer than six months, some of these patients may have been included in the withdrawal group of this study. In addition, patients who did not need ICS may be included in a group who didn't actually have asthma due to the complexity of asthma diagnosis.²³ Relatively high proportion of low-dose ICS prescription in the withdrawal group indicates relatively mild symptoms at withdrawal. Hence, there was no increase in exacerbation or hospitalization events in the withdrawal group in this population, even after propensity score matching. Exacerbation events leading to hospitalization were also relatively rare in other studies on mild asthma, usually less than 1%.^{24,25}

About 33.6% of withdrawal group reinitiated ICS, and most of them (90.0%) restarted ICS within 338 days after withdrawal. This suggested that a considerable number of patients who withdraw ICS eventually restart ICS. This restart of ICS also shows the importance of maintaining ICS in the general population of asthma patients. And, most of the ICS users seek it again within 1 year after withdrawal. Seasonal symptoms may affect influence the re-initiation of ICS. However, some patients can be without ICS for a substantial period after withdrawal. There are several possible explanations for this 'long-term' withdrawal of ICS, such as overdiagnosis of asthma at baseline, non-adherence to inhaler use, and overestimation of asthma control or seasonal asthma. 'Stable, exacerbation-free' asthma patients may have an asthma phenotype that is distinct from patients who experience exacerbation events.^{26,27} Therefore, some asthma patients can continue without ICS for a quite long time after their airway inflammation has resolved. Further studies are necessary to identify patients who can be withdrawn from ICS safely.

How can we apply these data to our clinical practice? The benefit of ICS therapy for treating asthma is enormous. It is the only treatment which reduces asthma mortality,²⁸ and it can also reduce exacerbation⁶ and hospitalization.²⁹ Furthermore, without concomitant ICS, bronchodilation therapy can increase mortality.³⁰ Based on the findings of these studies, it is now recommended that adult asthma patients maintain ICS use indefinitely.¹² However, in real-world practice maintaining ICS adherence in patients, particularly those with mild asthma, can be difficult. Additionally, the economic burden and side effects of ICS are not negligible. Asthma is a heterogeneous disease, and some mild patients can be free from symptoms for quite a long time without treatment. Asthma mortality is usually associated with exacerbation or hospitalization,³¹ so it is not certain that ICS can reduce mortality in mild asthma as it can in severe asthma. Recently, Hong et al reported leukotriene receptor antagonist treatment was not inferior to ICS for reducing exacerbation events in elderly

patients.³² In this context, rather than arguing that ICS should be maintained in all adult asthma patients, further research is needed to identify asthma phenotypes that are amenable to temporary or permanent ICS withdrawal in terms of risk and benefit. In real-world practice, asthma exacerbation leading to hospitalization may not be common in mild asthma patients, which assume temporary withdrawal of ICS to find patients who can withdraw ICS for long time might be not that harmful for patients. There are some protocols for as-needed therapy that have been reported to be comparable to maintenance therapy in terms of exacerbation.²⁴ Our study has its strengths. First, the NHI database was analyzed, which contains information regarding demographics, healthcare utilization, prescriptions, and hospitalization for approximately 96·7% of all residents in Korea.¹¹ This data source and study design could help eliminate follow-up loss and minimize selection bias. Also, a fairly large number of pairs were analyzed by propensity score matching. Second, the study population consisted of patients who used ICS with a MPR over 50% in one year, which excluded uncertain asthma patients or ICS prescription as therapeutic trial. The effect of ICS withdrawal in asthma can be evaluated more clearly in this population of patients with more sustained ICS use. However, this study has limitations due to the data used. First, patients in our database were only Koreans, therefore we need to aware of globalizing the data. In fact, the smoking rate and mean age of asthmatics in South Korea are much higher than that in Europe³³. Further prospective studies are warranted to carefully explore the safety of ICS step down strategy in other global populations. Also, the NHI database does not have the complete medical record of patients; hence, details regarding pulmonary function, blood test, or the exact situation of hospitalization could not be confirmed. To address this limitation, the prescription usage patterns and healthcare utilization were combined to define target patients and exacerbation events.

In conclusion, more than one third of patients who withdrew ICS eventually reinitiated ICS, which emphasizes maintenance of ICS. However, some patients continued without reinitiating ICS use for substantial periods after withdrawal in our study group characterized by a high proportion of elderly and ever-smokers. Most patients with asthma did not experience exacerbation events leading to hospitalization even after ICS withdrawal in real-life practice, although the rates of admission and systemic steroid medication were not rare, therefore temporary withdrawal of ICS for trial of withdrawal may not be harmful for some patients. Our findings provide evidence that ICS cessation could be considered cautiously in patients who are well-controlled and have difficulties in maintaining ICS. Further studies are needed in patients who can tolerate ICS cessation in terms of risk and benefit.

Acknowledgements

This study is supported by Asan Institute for Life Sciences (2018IT03052), Asan Medical Center, Seoul, Korea, and the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. 2020R1A2C1008431, SWL).

References

1. Chronic respiratory diseases, Asthma. Available at: <http://www.who.int/respiratory/asthma/en/>. Accessed September 11, 2018.
2. Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003;361:1071-6.
3. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:332-6.
4. Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF, Jr., Sorkness CA, et al. Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285:2583-93.
5. O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: time for a new approach? *Eur Respir J* 2017;50:1701103.
6. Rank MA, Hagan JB, Park MA, Podjasek JC, Samant SA, Volcheck GW, et al. The risk of asthma exacerbation after stopping low-dose inhaled corticosteroids: a systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol* 2013;131:724-9.
7. Kelly HW, Nelson HS. Potential adverse effects of the inhaled corticosteroids. *The Journal of allergy and clinical immunology* 2003;112:469-78; quiz 79.
8. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med* 1999;159:941-55.
9. Krishnan JA, Riekert KA, McCoy JV, Stewart DY, Schmidt S, Chanmugam A, et al. Corticosteroid use after hospital discharge among high-risk adults with asthma. *Am J Respir Crit Care Med* 2004;170:1281-5.
10. Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. *J Allergy Clin Immunol* 2011;127:145-52.
11. Kim S, Kim J, Kim K, Kim Y, Park Y, Baek S, et al. Healthcare use and prescription patterns associated with adult asthma in Korea: analysis of the NHI claims database. *Allergy* 2013;68:1435-42.
12. 2018 GINA report, global strategy for asthma management and prevention. 2018. Available at: <https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed September 11, 2018.

13. Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. *BMC Pulm Med* 2006;6:13.
14. Boulet LP, Vervloet D, Magar Y, Foster JM. Adherence: the goal to control asthma. *Clin Chest Med* 2012;33:405-17.
15. Yang JY, Kim JY, Jang JY, Lee GW, Kim SH, Shin DC, et al. Exposure and toxicity assessment of ultrafine particles from nearby traffic in urban air in seoul, Korea. *Environ Health Toxicol* 2013;28:e2013007.
16. Gehring U, Wijga AH, Brauer M, Fischer P, de Jongste JC, Kerkhof M, et al. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *Am J Respir Crit Care Med* 2010;181:596-603.
17. Hyrkas H, Ikaheimo TM, Jaakkola JJ, Jaakkola MS. Asthma control and cold weather-related respiratory symptoms. *Respir Med* 2016;113:1-7.
18. Schneider SM, Pipher A, Britton HL, Borok Z, Harcup CH. High-dose methylprednisolone as initial therapy in patients with acute bronchospasm. *J Asthma* 1988;25:189-93.
19. Fanta CH, Rossing TH, McFadden ER, Jr. Glucocorticoids in acute asthma. A critical controlled trial. *Am J Med* 1983;74:845-51.
20. Lin RY, Pesola GR, Bakalchuk L, Heyl GT, Dow AM, Tenenbaum C, et al. Rapid improvement of peak flow in asthmatic patients treated with parenteral methylprednisolone in the emergency department: a randomized controlled study. *Ann Emerg Med* 1999;33:487-94.
21. Littenberg B, Gluck EH. A controlled trial of methylprednisolone in the emergency treatment of acute asthma. *N Engl J Med* 1986;314:150-2.
22. Boulet LP, Boulay ME. Asthma-related comorbidities. *Expert Rev Respir Med* 2011;5:377-93.
23. Lipworth BJ, Jabbal S. Un-diagnosing persistent adult asthma. *Eur Respir J* 2017;50.
24. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med* 2018;378:1877-87.
25. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med* 2018;378:1865-76.
26. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. *Am J Respir Crit Care*

Med 2017;195:302-13.

27. Kimura H, Konno S, Makita H, Taniguchi N, Shimizu K, Suzuki M, et al. Prospective predictors of exacerbation status in severe asthma over a 3-year follow-up. *Clin Exp Allergy* 2018;48:1137-46.
28. Suissa S, Ernst P. Inhaled corticosteroids: impact on asthma morbidity and mortality. *J Allergy Clin Immunol* 2001;107:937-44.
29. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;354:1998-2005.
30. Weatherall M, Wijesinghe M, Perrin K, Harwood M, Beasley R. Meta-analysis of the risk of mortality with salmeterol and the effect of concomitant inhaled corticosteroid therapy. *Thorax* 2010;65:39-43.
31. Kupczyk M, ten Brinke A, Sterk PJ, Bel EH, Papi A, Chanez P, et al. Frequent exacerbators--a distinct phenotype of severe asthma. *Clin Exp Allergy* 2014;44:212-21.
32. Hong SH, Kang HR, Nam JH, Park SK, Kim TB, Lee EK. A comparison of leukotriene receptor antagonists to low-dose inhaled corticosteroids in the elderly with mild asthma. *J Allergy Clin Immunol Pract* 2019;7:2642-52 e3.
33. Kim SY, Sim S, Choi HG. Active and passive smoking impacts on asthma with quantitative and temporal relations: A Korean Community Health Survey. *Sci Rep* 2018;8:8614.

Figure Legends

Figure 1. Study design. Among patients with asthma without the diagnosis of chronic obstructive pulmonary disease, those who used inhaled corticosteroids (ICS) for more than 1 year with a medication possession ratio (MPR) > 50% were enrolled.

Figure 2. Flow diagram of the study population.

Figure 3. The number of ICS prescriptions in study period. The per-month prescriptions of ICS were greatest in December, followed by March (A). The annual prescription rate for ICS increased from 2010 to 2013 (B).

Figure 4. The proportion of patients remaining exacerbation or admission event-free over one year after six months of withdrawal from inhaled corticosteroids. Moderate exacerbation (A) and hospitalization (B) occurred in 29.25% and 25.95% of the withdrawal group, respectively. Meanwhile, hospitalization with steroid administration (C) and severe exacerbation (D) were relatively rare in all groups.

Figure 5. The characteristics of inhaled corticosteroids (ICS) reinitiation after withdrawal. ICS restart was most frequent from October to December (A). After 6 months of ICS withdrawal, 90% of patients restarted ICS within 158 days (B).

482 **Table 1. Patient characteristics**

	Withdrawal group (n = 13,336)	Maintenance group (n = 132,175)	Standardized difference
Age	57.6 ± 17.9	60.2 ± 16.9	-0.151
Male sex	6839 (51)	70349 (53)	-0.039
Income			0.131
1st quartile	1806 (14.9)	20594 (17.7)	
2nd quartile	1998 (16.5)	20679 (17.7)	
3rd quartile	2797 (23.1)	28422 (24.4)	
4th quartile	5529 (45.6)	46876 (40.2)	
Healthcare provider			0.104
Primary	10649 (61.3)	81053 (79.9)	
Secondary	648 (6.1)	8025 (4.9)	
Tertiary	2039 (32.6)	43097 (15.3)	
Acute exacerbation within last year	4231 (31.7)	43886 (33.2)	-0.032
Smoking			0.089
Ever-smoker	3529 (59.7)	39041 (63.9)	
Never smoker	2379 (40.3)	22062 (36.1)	
Medication possession ratio	79.7 ± 60.5	60.3 ± 12.8	0.442

483 Continuous variables are expressed as mean ± standard deviation. Categorical variables are
 484 expressed as n (%)

485

486 **Table 2. The ICS dosage initially prescribed during study period**

	Withdrawal group			Maintenance group			P value 487
	ICS	ICS/LABA	Total	ICS	ICS/LABA	Total	488
Low	1,081 (62.8)	7,378 (62.3)	8,459 (62.4)	5,165 (42.2)	46,795 (38.3)	51,960 (38.7)	< 0.001* 489
Medium	216 (12.6)	4,023 (34.0)	4,239 (31.3)	2,864 (23.4)	66,436 (54.4)	69,300 (51.6)	490
High	424 (24.6)	435 (3.7)	859 (6.3)	4,204 (34.4)	8,809 (7.2)	13,013 (9.7)	491
Total	1,721 (12.7)	11,836 (87.3)	13,557	12,233 (9.3)	122,040 (92.3)	134,273	< 0.001* 491

492 ICS, inhaled corticosteroid; ICS/LABA, inhaled corticosteroid / long acting β 2 agonist

493 *Comparison of ICS dose between withdrawal and maintenance groups.

494 **Comparison of ICS or ICS/LABA between withdrawal and maintenance groups

495 Numbers of events are expressed as n (%)

496

497 **Table 3 Comparison of events**

	Withdrawal group (n = 13,336)	Maintenance group (n = 132,175)	p value
Hospitalization	3901 (29.25%)	43266 (32.73%)	< 0.001
Hospitalization with steroid	265 (1.99%)	4084 (3.09%)	< 0.001
Moderate exacerbation	3461 (25.95%)	42604 (32.23%)	< 0.001
Severe exacerbation	71 (0.53%)	1085 (0.82%)	< 0.001

498 Numbers of events are expressed as n (%)

499

500

501 **Table 4 Cox proportional hazard regression analyses of events in the withdrawal group**

	Crude HR	Adjusted HR1	Adjusted HR2
Hospitalization	0·87 (0·84-0·90)	0·92 (0·89-0·95)	0·87 (0·85-0·90)
Hospitalization with steroid	0·64 (0·57-0·72)	0·66(0·58-0·74)	0·66 (0·58-0·75)
Moderate exacerbation	0·77 (0·74 - 0·79)	0·78 (0·75-0·80)	0·80 (0·77-0·83)
Severe exacerbation	0·65 (0·51-0·82)	0·68 (0·54-0·8)	0·65 (0·51-0·83)

502 HR, hazard ratio. HRs are presented as HR (95% confidence interval).

503 Adjusted HR1 hazard ratios were calculated using multivariate analyses adjusting for
 504 exacerbation events, age, and sex. Adjusted HR2 hazard ratios were calculated using
 505 multivariate analyses adjusting exacerbation events, age, sex, income, healthcare provider,
 506 smoking, medication possession ratio, previous exacerbation within one year, and date of
 507 study inclusion. The reference group of analyses was the maintenance group.

508

