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Original Article

Stepping down therapy for well-controlled mild asthma: an experience from University Medical Center at Ho Chi Minh City

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Background: Stepping down treatment for well-controlled mild asthma is challenging to clinicians. The step-down strategy using regularly-intermittent low-dose inhaled corticosteroid has been applied at the University Medical Center (UMC) of Ho Chi Minh City, called as "UMC" approach.
Objective: This study aimed to evaluate the efficiency of UMC step-down strategy in well-controlled mild asthma.
Methods: A real-world retrospective descriptive study was conducted at UMC from 2009 to 2018. All asthmatic patients (age ≥ 12) who received step-down therapy using this UMC approach were evaluated.
Results: Among 2,072 asthma patients to be treated with UMC step-down strategy, only 112 subjects were eligible. The median age was 38.5 years and female was 62.5%. Most patients at their initial presentation were indicated step 4 treatment (87.5%). The controller medications before initiation of UMC treatment included fluticasone propionate 125 μg once-daily, salmeterol/fluticasone propionate 25/125 μg once-daily, and formoterol/budesonide 4.5/160 μg once-daily. After being treated with the UMC approach, the rates of well-controlled asthma ranged from 67.6% to 91.1%. During 1 year with UMC treatment, pulmonary function remained stable and only 7 subjects (6.3%) developed exacerbation.
Conclusion: The UMC step-down treatment for well-controlled mild asthma was relatively efficient in maintaining asthma control, stabilization of pulmonary function, and reducing risk of severe exacerbation.

Keywords: Asthma; Budesonide; Fluticasone propionate; Formoterol; Salmeterol

INTRODUCTION

Global Initiative for Asthma (GINA) recommends stepwise approach for adjusting treatment in asthmatic patients based on their control status [1]. Stepping-up for patients with uncontrolled asthma is obvious but stepping down for patients with well-controlled asthma is more complicated, particularly when their current controller treatment includes once-daily

Author Contributions

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low-dose inhaled corticosteroid (ICS) or once-daily low-dose ICS/long-acting beta-agonist (LABA) combination [2-4]. Moreover, the complete cessation of ICS, which GINA guideline did not recommend clinicians from 2015, could increase the risk of exacerbation [1, 5]. Therefore, "what is the next step for well-controlled asthma with once-daily low-dose ICS or once-daily low-dose ICS/LABA combination" is a question for clinicians worldwide including Viet Nam. Several options of this step-down therapy were suggested [6, 7]:

- Option 1: adherence to once-daily low-dose ICS
- Option 2: switching to once-daily lowest-dose ICS/LABA combination
- Option 3: taking ICS when using short-acting beta-agonist "as needed" or taking budesonide/formoterol "as needed"

Scientific rationales for these options derived from a study by American Lung Association Asthma Clinical Research Centers [8] and the results of SYGMA-1 and SYGMA-2 studies [2, 9]. However, all step-down options have specific limitations, for instances, patients who are indicated option 1 can have poor adherence because the mild asthma patients usually have fewer symptoms, meanwhile, for option 3, the treatment is influenced by the patient's perception.

We have developed the particular step-down strategy for well-controlled mild asthma at the University Medical Center (UMC) of Ho Chi Minh City, called as UMC approach (therapeutic regimen using regularly-intermittent low-dose ICS which was presented in **Fig. 1**). Asthma patients will be treated with one inhalation every other day, subsequently with 2 inhalations a week, followed by reducing further to one inhalation a week if the well-controlled asthma can be maintained at least 3 months after each step (one inhalation was defined as ICS monotherapy or ICS/LABA combination).

From 2003, we have experienced the effective control of asthma with the UMC approach. However, there were no studies accessing the outcome of patients who were administered this approach in our hospital setting. Therefore, this study aimed to retrospectively evaluate the efficiency of the UMC step-down strategy for well-controlled mild asthma.

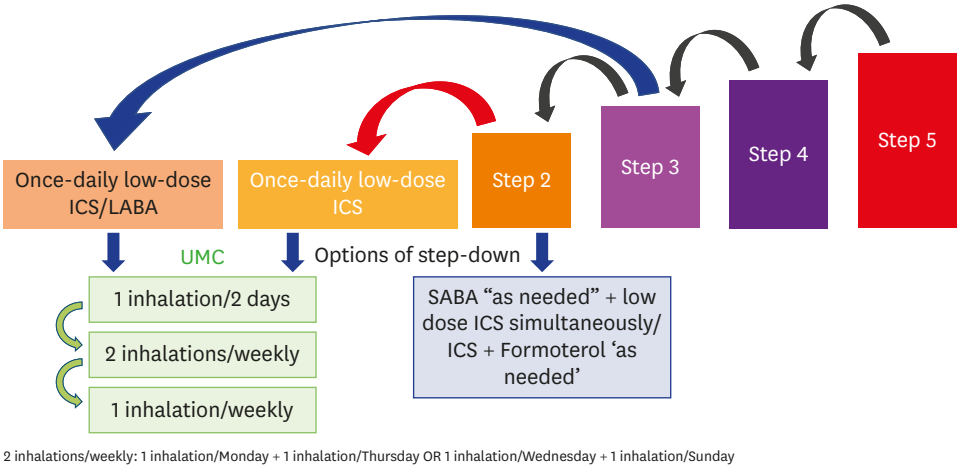

Fig. 1. Flowchart of step-down strategy in UMC. ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; SABA, short-acting beta-agonist; UMC, University Medical Center.

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MATERIALS AND METHODS

Sample recruitment

A real-world retrospective descriptive study was conducted to evaluate patient ≥12 years-old, who visited the Department of Respiratory Functional Exploration, UMC of Ho Chi Minh City from 2009 to 2018. Inclusion criteria were as follows:

- The precise diagnosis of asthma was according to GINA 2015 guideline [1]. More specifically, patients should have (1) one of respiratory symptoms (cough, wheezing, shortness of breath, chest tightness) and (2) a pulmonary functional test indicating a positive response with bronchodilator (post bronchodilator test showed increase over 200 mL and 12% in terms of forced expiratory volume at 1 second [FEV_1], vital capacity, or forced vital capacity).
- Subjects had well-controlled asthma with once-daily low-dose ICS (fluticasone propionate 125 μg once-daily) or once-daily low-dose ICS/LABA combination (salmeterol/fluticasone propionate 25/125 μg once-daily or formoterol/budesonide 4.5/160 μg once-daily) at least 3 months before T_0. We defined T_0 as the time of subject enrollment and initiation of the UMC approach. In detail patients were initiated by fluticasone propionate 125 μg one puff every other day, salmeterol/fluticasone propionate 25/125 μg one puff every other day, or formoterol/budesonide 4.5/160 μg one inhalation every other day. The selected type of controller medication to initiate the UMC approach was the same as the controller medication using. For instance, if the subject was well-controlled with salmeterol/fluticasone propionate 25/125 μg one puff daily, he/she would be initiated by salmeterol/fluticasone propionate 25/125 μg one puff every other day.
- Subjects had enough information to evaluate the efficiency of UMC step-down strategy during one-year after T_0 (at least 3 times of visit during 1-year to check the status of asthma control and pulmonary function test).

Subjects with smoking history more than 10 packs year or those who had pregnancy during the examining period were excluded.

The pulmonary function testing was performed by technicians with more than 5 years of experience with KOKO®PFT machine (nSpire Health Inc., Longmont, CO, USA). Standardization of spirometry and interpretation was compliant with American Thoracic Society/European Respiratory Society guideline 2005 [10].

The levels of controlled asthma were classified by physicians according to GINA guideline [1]. In this study, subjects with uncontrolled or partly controlled asthma were classified as uncontrolled group and they were evaluated for associated factors of uncontrolled asthma such as inadequate dose of controller medication, adherence, respiratory infection, comorbidities, and technique of using inhalation device. If physicians confirmed uncontrolled asthma associated to inadequate dose, the step-up strategy would be applied with the opposed direction of UMC step-down strategy. If the subjects got worse or asthma exacerbation during UMC step-down strategy, they would be treated according to GINA guideline [3] and stepped up the once-daily dose of existing controller treatment for 2–4 weeks.

This study was approved by the Institutional Review Board (IRB) of University of Medicine and Pharmacy at Ho Chi Minh City with a waiver of informed consent (IRB No. 338/HDDD-DHYD) and performed in accordance with the principles of the Declaration of Helsinki.

Data collection and statistical analysis

Data collection forms were used to record age, sex, comorbidities, symptoms, step of asthma treatment at initial presentation, other variables such as: type of administered ICS with or without LABA, the level of asthma control, spirometry (FEV_1, peak expiratory flow rate [PEFR]), associated factors of uncontrolled asthma respectively at the time of T_0, 3 months after T_0, 6 months after T_0, 9 months after T_0, 12 months after T_0, and the number of severe exacerbations (defined as an episode of worsening asthma symptoms, which require treatment with systemic corticosteroids) during 1 year the patients were treated with UMC step-down strategy. The exacerbation event was collected based on the content of the medical record.

To missing values of FEV_1 and PEFR, the missing value pattern was evaluated with the result consistent to the pattern of missing at random. The multiple imputations were conducted to handle these missing values. Paired samples *t* test was used to evaluate change of pulmonary function during 1-year follow-up. We divided the recruited subjects into 2 groups (uncontrolled vs. well-controlled groups) and chi-square test was applied to find out the significant difference. Data was analyzed by using SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA) and the *p* value < 0.05 was considered as significantly statistical difference.

RESULTS

From 2009 to 2018, there were 2,072 asthma patients to be treated with UMC step-down strategy but only 112 cases were consistent strictly with the selection criteria of this study. The flowchart of enrollment was presented in **Fig. 2**. Among 112 subjects, there were 33.9% living at Ho Chi Minh City and 66.1% from surrounding provinces. Subjects with age < 18 years-

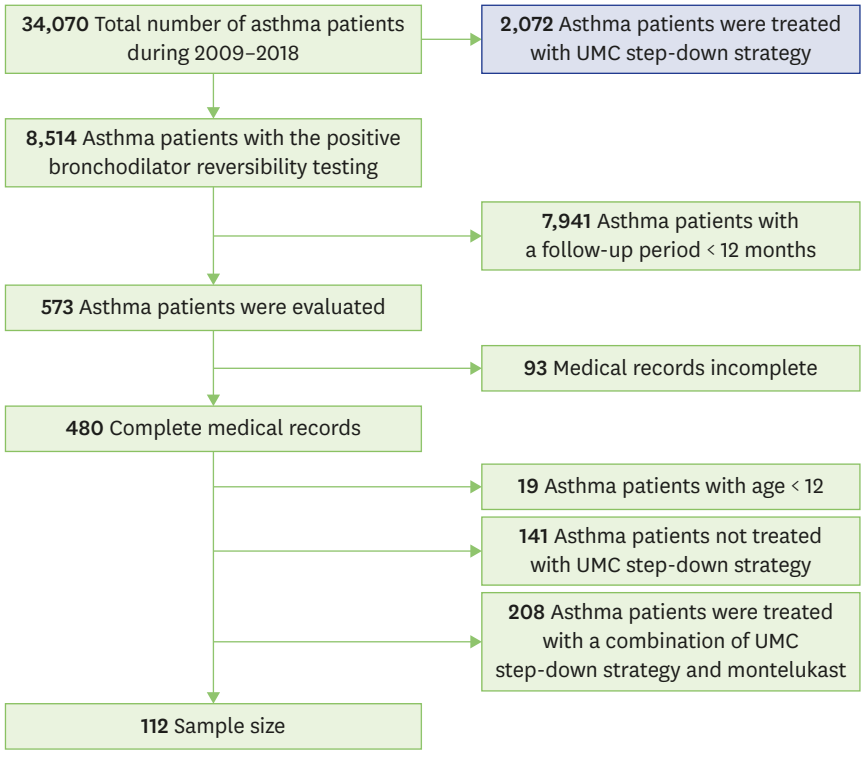

Fig. 2. Flowchart of enrollment. UMC, University Medical Center.

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old were 25.0%. Characteristics of all subjects and each group according to the patterns of controller medication were showed in **Table 1**.

Asthma control status

All subjects achieved well-controlled asthma at least 3 months before physicians decided to step down according to UMC approach. Regarding the selected types of controller medication at the initial time (T_0), 33.0% of subjects were administered fluticasone propionate 125 μg monotherapy, 26.8% were administered salmeterol/fluticasone propionate 25/125 μg, and 40.2% used formoterol/budesonide 4.5/160 μg one inhalation every other day. The prevalence of well-controlled asthma which ranged from 67.6% to 91.1% was evaluated every 3 months from the T_0 point (**Fig. 3**). The rate of well-controlled asthma without any uncontrolled time during 1 year was 37.5%. There was no association between the status of uncontrolled asthma with demographic features (age, sex), comorbidities, asthma step, and the result of spirometry at initial presentation (**Table 2**). Associated factors of uncontrolled asthma included inadequate doses (62.7%), uncontrolled allergic rhinitis (26.7%), and respiratory infection (10.6%).

Table 1. Characteristics of 112 subjects

Characteristic	Total (n = 112)	Fluticasone (n = 37)	Salmeterol/fluticasone (n = 30)	Formoterol/budesonid (n = 45)	*p* value
Age (yr), median (IQR)	38.5 (17.7–51.0)	35.0 (16.0–48.0)	39.5 (16.5–56.3)	42.0 (28.0–51.0)	0.526*
Female sex (%)	62.5	73.0	46.7	64.4	0.082
Family history of asthma (%)	20.5	29.7	23.3	11.1	0.105
Comorbidities					
Allergic rhinitis (%)	55.4	59.5	60.0	48.9	0.528
GERD (%)	19.6	16.2	26.7	17.8	0.519
Obesity (%)	4.5	2.7	3.3	6.7	0.647
Symptoms at initial presentation					
Cough (%)	42.9	51.4	26.7	46.7	<0.01
Wheezing (%)	31.3	32.4	46.7	20.0	<0.01
SOB (%)	54.5	54.1	50.0	57.8	<0.01
Chest tightness (%)	1.8	0.0	6.7	0.0	N/A
Asthma step at initial presentation					0.038
Step 4 (%)	87.5	94.6	93.3	77.8	
Step 3 (%)	12.5	5.4	6.7	22.2	
Spirometry at initial presentation					
FEV_1 (%), mean ± SD	79.7 ± 16.9	79.2 ± 14.1	78.9 ± 15.6	81.1 ± 19.1	0.928†
PEFR (%), mean ± SD	74.9 ± 20.8	77.3 ± 23.7	74.7 ± 18.1	73.2 ± 20.5	0.713†
Spirometry at T_0					
FEV_1 (%), mean ± SD	90.9 ± 13.2	90.8 ± 10.6	90.3 ± 15.5	91.4 ± 13.7	0.944†
PEFR (%), mean ± SD	88.6 ± 15.1	87.9 ± 15.3	86.7 ± 16.6	90.4 ± 14.1	0.576†
No. of subjects with 1 inhalation every other day					
After 3 months	65	20	19	26	-
After 6 months	34	13	11	10	-
After 9 months	29	10	9	10	-
No. of subjects with 2 inhalations a week					
After 3 months	37	17	6	14	-
After 6 months	44	22	6	16	-
After 9 months	30	12	5	13	-
No. of subjects with 1 inhalation a week					
After 6 months	6	1	2	3	-
After 9 months	15	6	4	5	-

IQR, interquartile range; GERD, gastroesophageal reflux; SOB: shortness of breath; FEV_1, forced expiratory volume in 1 second; PEFR, peak expiratory flow rate; SD: standard deviation.
p value < 0.05, statistically significant difference.
*Kruskal-Wallis test, †One-way analysis of variance.

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Table 2. The association between factors and the status of uncontrolled asthma

Variable	The status of controlled asthma during 1-year follow-up		*p* value
	Well-controlled (n = 42)	Cumulative sum of uncontrolled (n = 70)	
Age (yr), median (IQR)	37.5 (19.3–52.0)	39.5 (17.0–51.0)	0.801*
Female sex (%)	54.8	67.1	0.134
Allergic rhinitis (%)	47.6	60.0	0.140
Gastroesophageal reflux (%)	19.1	20.0	0.554
Obesity (%)	7.1	2.9	0.271
Step 4 at initial presentation (%)	90.5	85.7	0.335
FEV_1 (%), mean ± SD	80.3 ± 18.1	79.3 ± 16.3	0.767
PEFR (%), mean ± SD	78.8 ± 22.7	72.5 ± 19.4	0.147

IQR, interquartile range; FEV_1, forced expiratory volume in 1 second; PEFR, peak expiratory flow rate; SD, standard deviation.
p value < 0.05, statistically significant difference.
*Mann-Whitney *U* test.

Effects of step-down treatment on pulmonary function

Pulmonary function of asthmatic subjects showed significant improvement with controller treatment following GINA guideline ($p < 0.01$), compared to the data on patients' initial presentation. Upon reducing doses with UMC step-down strategy, there was no decrease of pulmonary function compared to the spirometric results at time point of T_0. **Table 3** revealed the FEV_1 and PEFR evaluated every 3 months after the time point of T_0. We only recorded 7 cases (6.3%) occurring severe exacerbation during 1 year applying UMC step-down treatment.

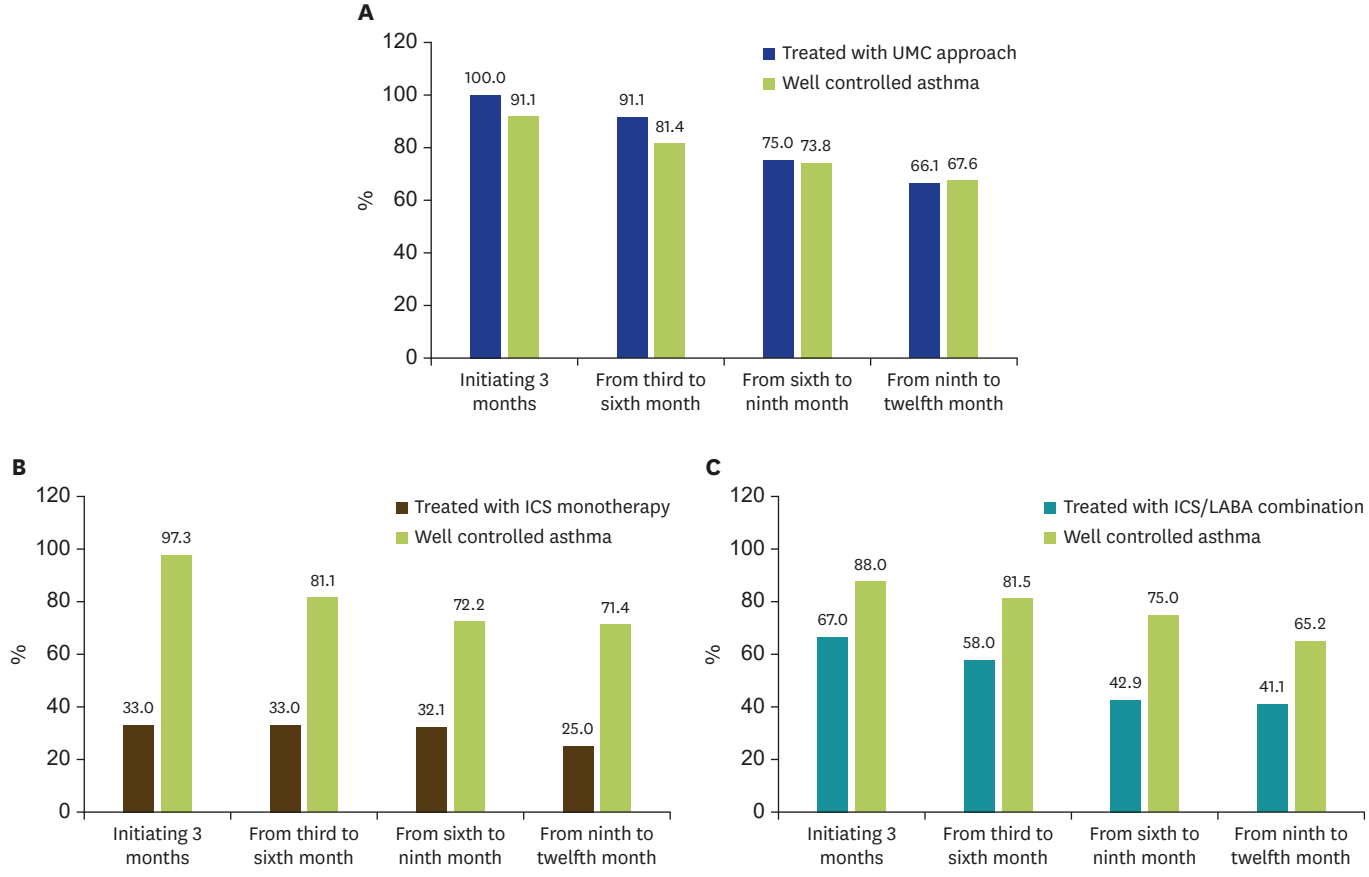

Fig. 3. The rates of 112 subjects were treated and controlled with the UMC step-down approach (ICS monotherapy and ICS/LABA combination). (A) Subjects were treated with the UMC approach. (B) Subjects were treated with ICS monotherapy. (C) Subjects were treated with ICS/LABA combination. UMC, University Medical Center; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist.

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Table 3. Spirometric parameters during one-year period with UMC step-down treatment

Time conducting spirometry	No. of subjects	FEV_1 (%)		PEFR (%)	
		Mean ± SD	*p* value	Mean ± SD	*p* value
Initiation (T_0)	112	90.9 ± 13.2	<0.01†	88.6 ± 15.1	<0.01†
After 3 months	71	91.6 ± 13.4	0.438‡	89.8 ± 15.1	0.283‡
After 6 months	75	89.1 ± 13.2	0.125‡	87.1 ± 15.6	0.073‡
After 9 months	98	88.3 ± 12.9	0.164‡	86.2 ± 13.9	0.337‡
After 12 months	94	87.9 ± 14.0	0.647‡	86.7 ± 18.3	0.507‡

UMC, University Medical Center; FEV_1, forced expiratory volume in 1 second; PEFR, peak expiratory flow rate; SD, standard deviation.
p value < 0.05, statistically significant difference.
†Paired samples test, compared to the spirometry at initial presentation. ‡Paired samples test, compared to the spirometry at T_0.

DISCUSSION

Our study showed that the UMC step-down strategy can help mild asthma patients to achieve well-controlled asthma (67.6%–91.1%), and maintain the stable pulmonary function comparable to those with once-daily low-dose ICS or once-daily low-dose ICS/LABA combination, exceptionally there were 6.3% of cases occurring severe exacerbation during 1-year follow-up. These data indicate the efficiency of UMC step-down strategy in management of asthma. Moreover, this strategy implied the recommendation regarding stepping down of therapeutic dose and frequency of inhalation to address patients' concerns about side effects or tolerance to long-term ICS usage [11, 12].

The step-down treatment for well-controlled asthmatics with once-daily low-dose ICS/LABA combination has been suggested in several published articles, but remains ambiguous [6, 8]. Discontinuation of LABA could result in poor control of asthma symptoms [13]. In addition, in case the indicated LABA does not pose the rapid effect on beta-2 adrenergic receptors such as formoterol, therapeutic recommendation for ICS/LABA “as needed” will become incompatible. Our study suggested that the UMC step-down strategy (low-dose ICS/LABA combination, 1 inhalation every other day or 2 inhalations a week) is able to be considered as an optimal choice.

Using daily low-dose ICS for mild asthma may lead to the lack of patient's adherence because their symptoms are minimal when they are in stable status [14]. The UMC step-down treatment emphasizes the core issue in association between therapeutic dose, severity of asthma, and adherence. The gradual decrease of controller medication, as in the UMC step-down approach, could convince better compliance of asthmatic patients. In term of ICS dosage, in case of daily low-dose ICS (monotherapy or combination) strategy, clinicians have not approached the lowest effective dose of ICS yet, which was suggested in the SYGMA studies (asthmatics could be controlled with daily low-dose budesonide 57 μg and 66 μg, respectively in SYGMA-1 and SYGMA-2) [2]. With the UMC step-down approach, we were successful with the ICS dose lower than in daily low-dose ICS strategy. However, further research needs to be conducted for this issue.

Results from SYGMA-1 and SYGMA-2 studies developed significant change for GINA guideline 2019 in step 1 and step 2 treatment which concentrates using inhaler “as needed” guided by asthma symptoms [4]. However, the “as needed” concept is confusing, depends on patient's perception, influenced by socio-economic factors and family condition. A study evaluated treatment adherence for Asian asthmatics showed many aspects causing the poor compliance such as inconvenience of inhaler using, preference of oral medication, cost of treatment, and options from patient's friends and family [11]. Although asthmatics can

understand their condition well, these barriers would decrease the efficiency of "as needed" treatment when stepping down [15]. They could make patients using over-dose or under-dose ineffectively. Moreover the improvement of pulmonary function in asthmatics using inhaler "as needed" was less than that in one using daily ICS [2, 9]. Meanwhile, the treatment with UMC step-down protocol showed stabilization the pulmonary function similar to the treatment with once-daily low-dose ICS or once-daily low-dose ICS/LABA. Therefore, UMC strategy indicates the step-down process effectively and more obviously which could be more suitable for Asian asthmatics.

The prevalence of severe exacerbation in our study was 6.3% during 1-year follow-up (0.063 per patient-year) which is lower than the estimated prevalence for mild asthma (0.12–0.77 per patient-year) [14]. This implies the efficiency of UMC step-down treatment in reducing exacerbation in the Vietnamese population. Nevertheless, this result should be interpreted carefully in the aspect of factors associated with uncontrolled asthma, given that 62.7% of cases were due to insufficiency of therapeutic dose. Most of uncontrolled asthmatics associated with this factor would be stepped up the therapeutic dose which is out of UMC strategy to obtain well-controlled afterwards. This issue can contribute decrease the rate of exacerbation.

There are several limitations in this study. Data collection every 3, 6, 9, and 12 months after enrollment could be limited comparing to the continuous data collection. Our study has not evaluated the mild and moderate exacerbation which could be important information to conclude the effect of this step-down strategy. Besides, minimal therapeutic dose of ICS is also essential. We documented the median dose of fluticasone propionate 49.1 μg in monotherapy, mean dose of fluticasone propionate 48.0 μg in the combination form, and mean dose of budesonide 63.1 μg in formoterol/budesonide. However, we lack of control group to compare statistical difference. A randomized controlled trial is necessary to strengthen the evidence of this strategy in the near future.

In conclusion, the UMC step-down strategy should be considered for well-controlled mild asthma, especially among asthmatic patients who feel difficulties to apply the "as needed" strategy or who have been well-controlled with once-daily low-dose ICS/LABA with the slow onset of bronchodilating action. Further studies are mandatory to provide more evidence for this strategy.

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REFERENCES

1. The Global Initiative for Asthma. Global Strategy for asthma management and prevention - update 2015 [Internet]. The Global Initiative for Asthma; [cited 2015 Aug 11]. Available from: www.ginasthma.org

2. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, Jorup C, Lamarca R, Siwek-Posluszna A, FitzGerald JM. As needed budesonide-formoterol versus maintenance budesonide in mild asthma. N Engl J Med 2018;378:1877-87.
PUBMED | CROSSREF
3. The Global Initiative for Asthma. Global strategy for asthma management and prevention - updated 2020 [Internet]. The Global Initiative for Asthma; [cited 2020 Jun 4]. Available from: https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf
4. Muneswarao J, Hassali MA, Ibrahim B, Saini B, Ali IAH, Verma AK. It is time to change the way we manage mild asthma: an update in GINA 2019. Respir Res 2019;20:183.
PUBMED | CROSSREF
5. Rank MA, Hagan JB, Park MA, Podjasek JC, Samant SA, Volcheck GW, Erwin PJ, West CP. 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.
PUBMED | CROSSREF
6. Chipps BE, Bacharier LB, Murphy KR, Lang D, Farrar JR, Rank M, Oppenheimer J, Zeiger RS. The asthma controller step-down yardstick. Ann Allergy Asthma Immunol 2019;122:241-62.
PUBMED | CROSSREF
7. Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E, Crimi N, Vignola AM, Morelli P, Nicolini G, Fabbri LMBEST Study Group. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med 2007;356:2040-52.
PUBMED | CROSSREF
8. American Lung Association Asthma Clinical Research Centers. Peters SP, Anthonisen N, Castro M, Holbrook JT, Irvin CG, Smith LJ, Wise RA. Randomized comparison of strategies for reducing treatment in mild persistent asthma. N Engl J Med 2007;356:2027-39.
CROSSREF
9. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, Jorup C, Lamarca R, Ivanov S, Reddel HK. Inhaled combined budesonide–formoterol as needed in mild asthma. N Engl J Med 2018;378:1865-76.
PUBMED | CROSSREF
10. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger JATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005;26:319-38.
PUBMED | CROSSREF
11. Chiu KC, Boonsawat W, Cho SH, Cho YJ, Hsu JY, Liam CK, Muttalif AR, Nguyen HD, Nguyen VN, Wang C, Kwon N. Patients' beliefs and behaviors related to treatment adherence in patients with asthma requiring maintenance treatment in Asia. J Asthma 2014;51:652-9.
PUBMED | CROSSREF
12. Boulet LP. Perception of the role and potential side effects of inhaled corticosteroids among asthmatic patients. Chest 1998;113:587-92.
PUBMED | CROSSREF
13. Fowler SJ, Currie GP, Lipworth BJ. Step-down therapy with low-dose fluticasone-salmeterol combination or medium-dose hydrofluoroalkane 134a-beclomethasone alone. J Allergy Clin Immunol 2002;109:929-35.
PUBMED | CROSSREF
14. Dusser D, Montani D, Chanez P, de Blic J, Delacourt C, Deschildre A, Devillier P, Didier A, Leroyer C, Marguet C, Martinat Y, Piquet J, Raherison C, Serrier P, Tillie-Leblond I, Tonnel AB, Tunon de Lara M, Humbert M. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. Allergy 2007;62:591-604.
PUBMED | CROSSREF
15. Lam NH. Barriers and solutions to stepping down asthma treatment. Open J Asthma 2020;4:013-5.