

Early achievement and maintenance of stable asthma control using initially higher-dose inhaled corticosteroids as part of combination therapy: an open-label pilot study

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Background: Uncontrolled asthma is characterized by considerable variability. Well controlled asthma is associated with less unplanned use of health care resources and fewer acute exacerbations. In this study, we attempted to increase inhaled corticosteroid (ICS) doses initially in suboptimally controlled asthmatics, hypothesizing that early achievement of asthma control using this strategy would be associated positively with a higher level of stability.

Methods: This was a randomized, open-label, prospective study including patients with uncontrolled asthma who were randomized to receive higher-dose (HD) ICS in combination with a long-acting beta-agonist (LABA) for one month and then shifted to doses suggested in the practice guidelines (GD) or to receive GD therapy alone. Lung function, ie, forced expiratory volume in one second (FEV₁), peak expiratory flow, Asthma Control Test scores, and frequency of acute exacerbations, was followed up for one year.

Results: Seventy-six patients were treated with the HD strategy and 80 with the GD strategy. The increase in FEV₁ from baseline was greater in the HD group than in the GD group, especially during the first month of treatment (304 ± 49 mL versus 148 ± 39 mL, respectively, *P* = 0.01). Numbers of patients with completely or well controlled asthma were higher in the HD group than in the GD group (92.1% versus 81.1%, respectively, *P* = 0.03). Further, there was a significant difference between the groups with regard to frequency of acute exacerbations (9.2% in the HD group versus 21.3% in the GD group, *P* = 0.02); this effect was more pronounced for patients in the HD group with partially controlled or uncontrolled asthma.

Conclusion: Patients receiving HD therapy achieved asthma control more rapidly and maintained greater stability than those receiving GD therapy. This represents a novel strategy for gaining disease control in patients with uncontrolled asthma.

Keywords: asthma, treatment, inhaled corticosteroids, higher doses

Introduction

The aim of treatment for patients with asthma is to achieve and maintain good control of the disease without side effects from treatment.¹⁻³ The GINA (Global INitiative for Asthma) guideline recommends regular assessment, with adjustments made to maintenance therapy based on disease control.¹ Further medications are added if asthma is uncontrolled or only partially controlled, and once control is achieved, the doses are maintained or stepped down to the lowest dose that maintains stability. However, Rabe et al have reported that the level of asthma control worldwide falls short of the treatment aims outlined in the international guideline and that the use of

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anti-inflammatory agents is low, even in patients with severe persistent asthma, ranging from 26% in Western Europe to 9% in Japan.⁴ Daytime symptoms and hospital emergency visits are still high, and guideline-based asthma control was achieved in only 1.3% of participants in the AIRET (Asthma Insights and REality in Turkey) study.⁵ Further, there is a trend towards an increasing incidence of asthma and growing drug costs.⁶ Clearly, more practical and proactive treatment strategies and education programs are needed to meet the goals set out in the guideline for asthma control.

It is now well recognized that adding a long-acting beta-agonist (LABA) to inhaled corticosteroid (ICS) therapy is more effective than ICS alone, even if the ICS dose is doubled, in improving asthma stability and control in symptomatic patients.^{7–9} Combined use of an ICS and LABA is an integral part of the asthma treatment guideline.¹ Theophylline may also be useful as an add-on therapy for patients who do not gain control of their asthma on an ICS alone or on a combination of an ICS and a LABA.^{10,11} Leukotriene modifiers can also help to improve poor asthma control.^{12,13}

Uncontrolled asthma is characterized by wide disease variability. The current asthma guideline focuses on achievement and maintenance of disease control, but few studies have addressed stability and potential duration of control once achieved using composite measures of control. In a post hoc analysis of the results of the GOAL (Gaining Optimal Asthma control) study,¹⁴ Bateman et al identified an association between the level of asthma control achieved during the step-up phase and the stability of control during the maintenance phase. Further, patients achieving the most control are more likely to stabilize at a high level of control, and conversely, patients who were not well controlled initially, and therefore have variable asthma control, are those most likely to consume unscheduled health care resources.¹⁵ Therefore, it is important that physicians achieve asthma control as soon as possible, and then utilize strategies that minimize the risk of further instability and exacerbations.

The dose-response curve for ICS varies widely in different asthma populations. A previous review concluded that commencing ICS at double or quadruple at moderate or low dose has no greater effect than commencing with a high dose.¹⁶ However, our strategy involves prescribing higher doses of controller medications, especially the dose of ICS (fluticasone 500–1000 µg per day) when combined with salmeterol in the initial one-month period, in the hope of achieving asthma control sooner and maintaining future disease stability in patients with uncontrolled asthma.

Materials and methods

Inclusion and exclusion criteria

This prospective, randomized 52-week study was conducted at the Far Eastern Memorial Hospital, a tertiary medical center in Taiwan. Men and women aged >18 years with poorly controlled asthma diagnosed at least 6 months prior to screening were included, and classified as having asthma which was partly controlled, uncontrolled, and uncontrolled with exacerbation.¹ Patients were identified as having uncontrolled asthma with exacerbation if they had a peak expiratory flow <60% of predicted, an Asthma Control Test score <14, and wheezing on auscultation. Subjects were also required to show a reversibility of ≥12% in forced expiratory volume in one second (FEV₁) after inhalation of salbutamol (two actuations, 100 µg per actuation) to be eligible for randomization. Patients also needed to demonstrate correct inhaler technique to be able to participate in the study. Any patient who had been treated with theophylline or leukotriene modifiers before randomization was allowed to continue this medication during the study.

Exclusion criteria included the following: life-threatening asthma within the past year; a hospitalization or emergency department visit for asthma in the 4 weeks before screening; use of systemic corticosteroids in the month before screening; treatment with omalizumab in the previous 6 months; use of a leukotriene receptor antagonist in the week before screening; a history of smoking that was either recent (in the previous 12 months) or equivalent to ≥10 pack years; significant nonreversible active pulmonary disease; and clinically significant respiratory tract infection in the 4 weeks before screening. Current use of medications with an effect on bronchospasm and/or lung function was also an exclusion criterion.

A full medical history, including of asthma and allergic rhinitis, was obtained at baseline. Patients with a history of clinically significant medical illness that, in the opinion of the investigator, could interfere with the study results or require treatment that might interfere with the conduct of the study were not enrolled.

Interventions and randomization

Patients were randomized 1:1 to receive higher doses of ICS (HD group) or to receive the dose suggested by the practice guidelines (GD group). The starting dose of ICS was based on the severity of asthma in each patient. Both study treatments were administered via a hydrofluoroalkane pressurized metered-dose inhaler using a space device (GlaxoSmithKline, Uxbridge, UK). The strategy for HD

was to use medication that was one step higher than that recommended by GINA, specifically a higher ICS dose and prescription of salmeterol for the first 4 weeks, which was then stepped down to the GD dose for the continuous phase lasting 48 weeks. For example, if the patient required step 3 therapy according to the practice guideline, we would step up to a step 4 medication (ie, higher-dose ICS); however, patients in the GD group, therapies for poorly controlled asthma status based on guideline's suggested practice strategy (52 weeks, Figure 1A).

Assessment of efficacy and safety

During the 52 weeks of treatment, the patients underwent clinical evaluation, including lung function tests by spirometry (FEV₁ and forced vital capacity) and peak flow measurements (morning and evening peak expiratory flow), and asthma symptom scoring with the Asthma Control Test.^{17,18} Asthma was defined as totally controlled, well controlled, or not well controlled according to the GOAL criteria.¹⁵ The primary endpoint was asthma control status at weeks 4 and 52. Secondary endpoints included the proportion of asthma-free days (ie, no use of a short-acting beta-agonist, no asthma

symptoms, 24-hour peak expiratory flow variability <20% of baseline, no unscheduled visits to a medical facility, and no nocturnal awakening), time to first acute exacerbation (asthma deterioration resulting in emergency treatment, hospitalization, or treatment with asthma medication other than a short-acting beta-agonist). Spirometry was performed at baseline, at each study visit (at eight-week intervals), and at the end of the study. Adverse events were documented based on spontaneous reporting, patient interview, and diary entries. Daily ICS consumption was also calculated. Ethical approval from the hospital and informed consent from all study subjects were obtained. The study is registered with ClinicalTrials.gov (NCT01647646).

Statistical analysis

Categorical variables were compared using the chi-squared test and continuous variables were compared using the Student's *t*-test. *P* < 0.05 was considered to be statistically significant. Fisher's exact test (qualitative data) or analysis of variance (quantitative data) were used to test homogeneity between the treatment groups. Comparability of the two treatment groups at baseline with respect to FEV₁ and peak expiratory flow was done using analysis of variance. All statistical analyses were performed using the Statistical Package for Social Sciences version 9 for Windows (SPSS Inc, Chicago, IL, USA).

Results

Recruitment and patient disposition

The study was initiated (first patient, first visit) in March 2009. Of the 169 patients randomized (83 patients in the HD group and 86 in the GD group), 156 (92.3%) completed the study and 13 (7.7%) discontinued prematurely (Figure 1B). Of the 13 patients who did not complete the study, six withdrew because of lack of therapeutic effect (three in each group), four were lost to follow-up, and three dropped out for personal reasons.

Baseline demographics and clinical characteristics

The demographics and clinical characteristics of patients in the HD and GD groups are summarized in Table 1. There were no significant differences between the two groups before randomization. Prescriptions for ICS and other medications, including theophylline and leukotriene modifiers, were similar. Most patients (82%–84%) were classified as having partly controlled or uncontrolled asthma at the time of screening, and a minority (15%–17%) were classified as

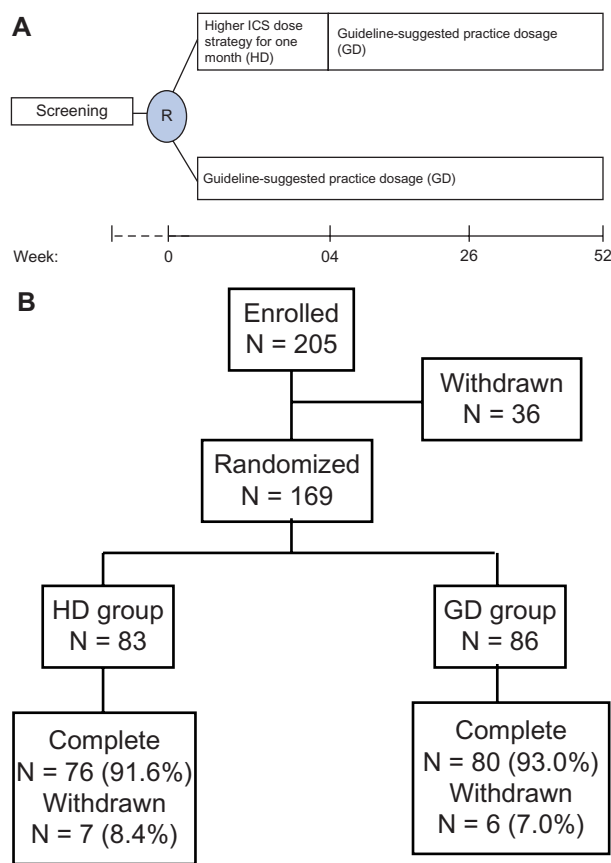


Figure 1 (A) Study design and (B) patient disposition.
Abbreviations: ICS, inhaled corticosteroid; N, number.

Table 1 Demographic characteristics, asthma status, and treatment at screening

Variables	HD group (n = 76)	GD group (n = 80)	P-value
Age	46.4 ± 20.3	48 ± 23.4	0.95
Gender (Male/female)	24/52	26/54	0.88
Atopy status	26 (34.2)	31 (38.6)	0.54
Control status			
Partly controlled (%)	38 (50)	41 (51.3)	0.91
Uncontrolled (%)	25 (32.9)	27 (33.7)	
Uncontrolled + AE (%)	13 (17.1)	12 (15)	
Asthma Control Test	16 ± 4	17 ± 5	0.72
Lung function			
FEV ₁ pre-salbutamol (L)	2.36 ± 0.57	2.34 ± 0.52	0.59
FEV ₁ post-salbutamol (L)	2.71 ± 0.81	2.72 ± 0.92	0.48
FEV ₁ % predicted	66.1 ± 10.3	68.4 ± 9.8	0.27
FEV ₁ reversibility (%)	25.6 ± 11.6	24.9 ± 10.1	0.42
Medications at baseline before R			
Fluticasone/salmeterol, 125/25 (%)	54 (71.1)	52 (65.0)	0.35
Fluticasone, 125 (%)	22 (28.9)	27 (35.0)	
Theophylline (%)	37 (48.9)	39 (48.6)	0.62
Leukotriene modifiers (%)	27 (35.5)	31 (38.7)	0.66
Initial medications after R			
Fluticasone/salmeterol, 250/25 (%)	65 (85.5)	22 (27.5)	<0.01*
Fluticasone/salmeterol, 125/25 (%)	11 (14.5)	53 (66.3)	
Fluticasone, 125 (%)	0 (0)	5 (6.2)	
Theophylline (%)	53 (69.7)	46 (57.5)	0.27
Leukotriene modifiers (%)	41 (53.9)	34 (42.5)	0.36

Notes: * is statistically significant and $P < 0.05$.

Abbreviations: AE, acute exacerbations; R, randomization; FEV₁, forced expiratory volume in one second; HD, initially higher-dose inhaled corticosteroids; GD, inhaled corticosteroid dose recommended by practice guidelines; L, liter.

having uncontrolled asthma with exacerbation. The mean baseline Asthma Control Test score was 16 ± 4 in the HD group and 17 ± 5 in the GD group.

Assessment and measurement of outcomes

Efficacy

The majority of patients in each group completed the 52-week treatment period, thereby having sufficient exposure to ICS doses to characterize their response profiles. The proportion of patients using fluticasone 1000 µg/day in the HD group was higher than that in the GD group (85.5% versus 27.5%, respectively, $P < 0.001$) in the initial phase after randomization. No ICS (step 2) was prescribed in the HD group, and only 6.2% patients in GD group used an ICS. The proportion of patients with completely or well controlled asthma at week 4 in the HD group was significantly higher than that in the GD group (64.5% versus 41.3%, respectively, $P = 0.01$) and this advantage was maintained until the end of

the study (92.1% versus 81.1%, $P = 0.03$). Patients in the HD group achieved sustained control of their asthma earlier than those in the GD group. Analysis of pulmonary function tests according to FEV₁ and forced vital capacity showed that lung function improved in both treatment groups during the study. However, greater improvement in FEV₁ was detected by week 4 in more patients in the HD group than in the GD group (141 ± 33 mL versus 66 ± 18 mL, respectively, $P = 0.02$) and this effect was observed at every assessment point throughout the study (HD 304 ± 49 mL versus GD 148 ± 39 mL, $P = 0.01$, Figure 2). Moreover, peak expiratory flow, recorded twice daily by patients before taking their study medication, showed an increase in mean values between baseline and week 52 in both treatment groups, with significantly more improvement in the HD group than in the GD group (248 ± 47 L per minute versus 129 ± 36 L per minute, respectively, $P < 0.01$), with the difference becoming apparent in the first month of the study.

Mean patient-assessed asthma symptom scores on the Asthma Control Test were also higher in the HD group (21 ± 4) than in the GD group (19 ± 5) at the initial week 4 visit. Overall, Asthma Control Test scores improved in both groups during the study, with a statistically significant difference in favor of the HD group compared with the GD group (24 ± 4 versus 20 ± 5, respectively, $P = 0.02$) by the end of the study. The proportion of patients with totally controlled and well controlled asthma was higher in the HD group than in the GD group (92.1% versus 81.1%, respectively, $P = 0.03$). There was a trend towards better quality of life in patients who gained control of their asthma. Absolute mean changes from baseline in mean Asthma Control Test scores were significantly different between the HD and GD groups (8 ± 2 versus 4 ± 2, respectively, $P = 0.04$) at the end of

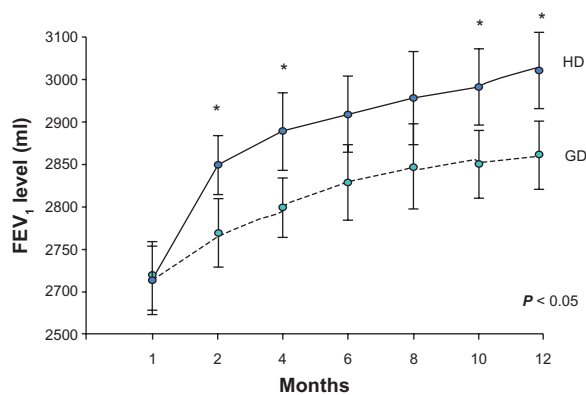


Figure 2 Lung function showing improvement in FEV₁ during the study period.

Notes: * is statistically significant and $P < 0.05$.

Abbreviations: FEV₁, forced expiratory volume in one second; HD, initially higher-dose inhaled corticosteroids; GD, inhaled corticosteroid dose recommended by practice guidelines.

study; further, the mean number of asthma-free days during the study was greater in the HD group than in the GD group (82.4 ± 26.5 days versus 69.2 ± 24.3 days, $P = 0.02$).

There were seven episodes (9.2%) of acute exacerbation in the HD group, comprising emergency department visits by four patients and a need for additional medication in three. However, 17 episodes (21.3%) of acute exacerbation were documented in the GD group, comprising emergency department visits by eleven patients, a need for additional medication in four, and hospitalization in two. There was a significant difference in the rate of acute exacerbations between the HD and GD groups (9.2% versus 21.3%, respectively, $P = 0.02$, Table 2). No episodes of life-threatening asthma occurred during the study. Time to first exacerbation was significantly ($P = 0.01$) longer in the HD group (105 ± 26 days) than in the GD group (67 ± 28 days), indicating more rapid improvement in lung function and control of asthma symptoms using the HD treatment strategy.

In a subgroup analysis, the effect of treatment was more marked in patients with partly or uncontrolled asthma, for whom

Table 2 Efficacy of treatment in patients with asthma using HD versus GD therapy

Variables	HD group (n = 76)	GD group (n = 80)	P-value
Asthma control status at week 4			
Total control (%)	13 (17.1)	7 (8.8)	0.01*
Well controlled (%)	36 (47.4)	26 (32.5)	
Uncontrolled (%)	27 (35.5)	47 (58.7)	
Asthma control at week 52			
Total control (%)	28 (36.9)	19 (23.6)	0.03*
Well controlled (%)	42 (55.3)	46 (57.5)	
Uncontrolled (%)	6 (7.9)	15 (18.9)	
FEV ₁ change at week 4	141 ± 33	66 ± 18	0.02*
FEV ₁ change at week 52	304 ± 49	148 ± 39	0.01*
PEF change at week 52	248 ± 47	129 ± 36	<0.01*
ACT at week 4	21 ± 4	19 ± 5	0.36
ACT at week 52	24 ± 4	20 ± 5	0.02*
Mean ACT change at week 52	8 ± 2	4 ± 2	0.04*
Exacerbation rate (%)	7 (9.2)	17 (21.3)	0.02*
Time to first exacerbation (days)	105 ± 26	67 ± 28	0.01*
Continuous medications			
Fluticasone/salmeterol, 250/25 (%)	33 ± 12	29 ± 13	0.32
Fluticasone/salmeterol, 125/25 (%)	42 ± 17	46 ± 15	0.41
Theophylline (%)	27 ± 11	33 ± 16	0.45
Leukotriene modifiers (%)	21 ± 12	27 ± 14	0.28
ICS consumption (µg/day)	736.6 ± 219.7	663.1 ± 267.2	0.17

Notes: * is statistically significant and $P < 0.05$.

Abbreviations: ACT, Asthma Control Test; ICS, inhaled corticosteroid; HD, initially higher-dose inhaled corticosteroids; GD, inhaled corticosteroid dose recommended by practice guidelines; FEV₁, forced expiratory volume in one second; PEF, peak expiratory flow.

the increase in FEV₁ was significantly higher in the HD group than in the GD group (239 ± 52 mL versus 98 ± 49 mL, respectively, $P < 0.01$) at the initial week 4 visit, and this difference was also significant at each subsequent follow-up visit (Figure 3). Meanwhile, the proportion of patients with uncontrolled asthma was significantly lower in the HD group than in the GD group (9.5% versus 19.1%, respectively, $P = 0.02$). There was also a significantly greater improvement from baseline in mean scores on the Asthma Control Test in the HD group compared with the GD group (9 ± 4 versus 5 ± 3 , respectively, $P = 0.03$) by the end of study, and the rate of acute exacerbations was also lower in the HD group than in the GD group (4.8% versus 13.2%, $P = 0.04$, Table 3).

Safety

The proportion of patients reporting potentially treatment-related side effects was similar between the groups. Daily ICS consumption in the HD and GD groups was not significantly different (736 ± 219.7 µg versus 663.1 ± 267.2 µg, respectively, $P = 0.17$). Frequently reported side effects were dysphonia (3.2% in the HD group versus 2.8% in the GD group, $P = 0.63$), headache (2.1% versus 2.4%, respectively, $P = 0.59$), tremor (3.4% versus 3.7%, $P = 0.71$), and hoarseness of voice (4.2% versus 3.8%, $P = 0.51$). There were no reports of oral candidiasis or pharyngitis in either treatment group.

Discussion

This study assessed the long-term efficacy of a novel treatment strategy using a higher initial dose of ICS combined with a LABA. We increased the fluticasone dose used in combination therapy for one month, with significant

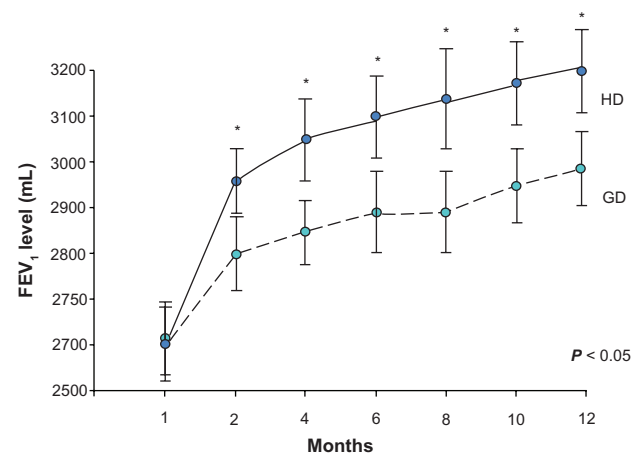


Figure 3 Lung function showing improvement in FEV₁ in patients with partially or uncontrolled asthma during the study period.

Notes: * is statistically significant and $P < 0.05$.

Abbreviations: HD, initially higher-dose inhaled corticosteroids; GD, inhaled corticosteroid dose recommended by practice guidelines; FEV₁, forced expiratory volume in one second.

Table 3 Treatment responses using HD and GD therapy in patients with partially or uncontrolled asthma

Variables	HD group (n = 63)	GD group (n = 68)	P-value
Asthma control status			
Total control (%)	25 (39.7)	13 (19.1)	0.02*
Well controlled (%)	32 (50.8)	42 (61.8)	
Uncontrolled (%)	6 (9.5)	13 (19.1)	
FEV ₁ change in week 4	239 ± 52	98 ± 41	<0.01*
FEV ₁ change in week 52	426 ± 62	286 ± 57	<0.01*
PEF change in week 52	271 ± 51	184 ± 45	<0.01*
ACT in week 4	22 ± 6	20 ± 5	0.05*
ACT in week 52	24 ± 4	22 ± 5	0.05*
Mean ACT change in week 52	9 ± 4	5 ± 3	0.03*
Exacerbation rate (%)	3 (4.8)	9 (13.2)	0.04*

Notes: * is statistically significant and $P < 0.05$.

Abbreviations: ACT, Asthma Control Test; HD, initially higher-dose inhaled corticosteroids; GD, inhaled corticosteroid dose recommended by practice guidelines; FEV₁, forced expiratory volume in one second; PEF, peak expiratory flow.

improvements in lung function and symptom control seen in HD patients compared with GD patients. These effects were sustained throughout the duration of the study, and accompanied by a significant decrease in frequency of acute exacerbations in the HD group. This study indicates that a higher initial ICS dose strategy may result in better asthma control than that achieved following the currently recommended practice guideline.

It is reasonable to assume that patients who do not have controlled asthma have persistent ongoing inflammation and are at high risk of deterioration. If more effective controllers could be prescribed to halt this vicious cycle, control of asthma could be achieved sooner. In this study, we attempted to increase the amount of controller medication, in particular the ICS dose, to suppress the cascade of events initially leading to inflammation and achieve disease stability. Combination of an ICS with a LABA has synergistic anti-inflammatory activity, including inhibition of the acute inflammatory changes that occur during a severe exacerbation, increased fluticasone-induced MKP-1 and modulated airway smooth muscle synthetic function.¹⁹ Several long-term, short-term, and intermittent step-up dosing strategies have been investigated²⁰ for asthma that is not well controlled, given that variability in symptom control is a particularly challenging feature of asthma that necessitates careful monitoring and an individualized therapeutic regimen over time. Our strategy may be as same as the step-up short-term strategy.

The results of this study highlight the advantages of early achievement of asthma control that are not mentioned in the current GINA guidelines.¹ First, control can be achieved earlier and greater stability maintained using a higher initial ICS dose. Our patients achieved near-maximal health status

scores and improvement in lung function, and continued to improve using this treatment strategy. Second, rapid achievement of asthma control is associated with a lower risk of acute exacerbations and unscheduled use of health care resources. Therefore, further instability and exacerbations prevented by prescribing higher initial ICS doses are indeed beneficial. Third, there was no significant increase in side effects when using the higher ICS dose in this study.

Stable asthma control means sustained prevention of symptoms with low or no reliever use and few exacerbations over a long period of time, which is the stated goal in the current treatment guideline. Treatment according to this guideline entails a stepwise increase in treatment until control is achieved, and then stepping medication down if control has been maintained for at least 3 months. The first step is always to ensure that standard therapies are optimized when initially treating poorly controlled asthma. However, using a titrated treatment strategy, suboptimal therapy and dose adjustments may hinder drug efficacy and delay achievement of disease control. This might be one of the reasons why surveys continue to report unsatisfactory results in the current management of asthma.^{21–23} In addition to heightening patient awareness^{24,25} and increasing educational asthma programs,^{26–28} we may also need to adjust the therapeutic strategy and treat proactively in different ways. For example, the GOAL study¹⁴ has introduced the novel concept of step-up treatment even in patients with well controlled asthma. Our strategy is different from that used in the GOAL study, which increased doses in a continuous manner. However, both these treatment strategies seem to be beneficial for establishing and maintaining disease control in patients with asthma.

Several meta-analyses^{29–32} have reported no clinical difference in outcome measures, including spirometric lung volumes, symptom control, β -agonist use, and frequency of exacerbations, using daily fluticasone doses of 200–500 μ g. These findings do not support the “start high, step down” approach, and may result in inappropriately high doses of ICS being used in the long term. The initial impressive and sustained response in terms of spirometric lung volumes in our HD group is greater than would be expected from the existing literature. We believe that the major limitation of the meta-analyses published to date is the small number of published studies available using ICS doses higher than 500 μ g/day and did not combine with LABA.²⁹ In this study, we have demonstrated the positive effects of starting with a higher ICS dose in combination with LABA therapy to achieve early asthma control and to decrease the frequency of exacerbations, and our findings are similar to those of

the FACET (Formoterol and Corticosteroids Establishing Therapy) study that used a strategy of high-dose budesonide (800 µg) in combination with formoterol.³³ A larger prospective study should now be performed to investigate the effects of initial higher-dose ICS therapy in more detail.

Our present study should be viewed in light of some limitations. First, this was a single-center study conducted in a teaching hospital and included a relatively small patient population, so there is the possibility of patient selection bias such that our sample may not be representative of the overall population of individuals in the community with asthma. Further, the study was not randomized, double-blind, or prospective in design, so potential bias on the part of the investigators and/or patients cannot be excluded. Second, with regard to the safety of higher-dose ICS therapy, we did not check for adrenal suppression, dermatological effects, effects on bone mineral density, or ocular changes. Third, no inflammatory or molecular parameters, such as eosinophil count, exhaled nitric oxide, or bronchial biopsy, were included as further objective measures of efficacy.

In conclusion, initial step-up ICS therapy in combination with a LABA, as opposed to the current treatment strategy, can increase the chances of achieving disease control, decreasing the frequency of acute exacerbations, and maintaining stability in patients with poorly controlled asthma. This is also a novel way to make advances in asthma therapy in comparison with the conventional “ladder” strategy. Further studies should be performed in larger patient populations, using the present study as a benchmark, to confirm the effectiveness and superiority of initially higher doses of ICS.

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Disclosure

The authors report no conflicts of interest in this work.

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