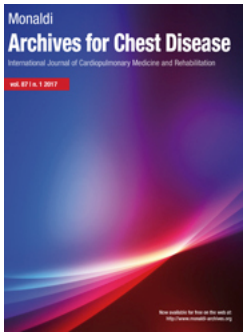

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Global Initiative for Asthma (GINA) guideline: achieving optimal asthma control in children aged 6-11 years

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Abstract

The Global Initiative for Asthma (GINA) 2021 guidelines for asthma have been set forth with some alterations in Step 3, for children from 6-11-year-old age group. The low dose LABA-ICS, very low dose formoterol-ICS, medium dose ICS and ICS-LTRA combination were recommended in the guideline. We organized this study to draw an effective comparison between these three

combinations of controller therapies in pediatric population. A retrospective study was conducted at the Aga Khan University Hospital, Karachi, Pakistan which enrolled 114 children aged 6-11 years old, from July 2021 to December 2022. These children were admitted with asthma exacerbations and were discharged on controller medications as per GINA guidelines on step 3 for control of asthma for 3 months. They were then followed for re-admission within 30 days of discharge, number of ER visits with asthma exacerbations for 1 year, number of admissions with asthma including HDU and PICU admissions, length of stay per admission for all admissions in subsequent one year. The pulmonary function test was done at 1 week follow-up in clinic after discharge and at 3 months visit post discharge. A total of 114 pediatric patients from age 6-11-year-old, were enrolled in the study period out of which 36 (31.57%), 33(28.9%) and 34 (29.82%) patients were categorized into ICS-LABA, ICS and ICS-LTRA groups respectively. ER visits were significantly low in ICS-LABA group followed by ICS-LRTA group and then ICS group (1.75±0.96 *vs* 2.93±1.412 *vs* 3.11±1.21, p<0.001). Similar statistically significant results were observed on average number of admissions per year (1.52±1.02 *vs* 1.96±0.84 *vs* 2.06±1.07, p=0.047) and number of patients needing PICU (13.88% *vs* 26.47% *vs* 39.39%, p=0.034) in these groups respectively. ICS- LABA group patients had the best values of FEV1 and FEV1/FVC ratio after pulmonary function tests at 3 months follow-up followed by ICS-LTRA and ICS group. Amongst the three options regimens for children managed at step 3 on GINA 2021 guidelines, ICS-LABA therapy helps attain optimal patient outcomes and lung functions in children with asthma followed by ICS-LTRA and ICS group respectively.

Key words: asthma exacerbation, pediatric asthma, GINA guideline, long-acting beta agonist, leukotriene receptor inhibitor

Introduction

Asthma is a widely known chronic, heterogeneous airway disease which is prevalent amongst all age groups. According to the latest report by the World Health Organization (WHO) published on May 4th 2023, prevalence of asthma was noted in 262 million people in 2019 and caused 455 000 deaths globally. This is partly due to the key pathophysiology of chronic airway inflammation which over time leads to deterioration of lung function, if poorly controlled. Repeated episodes of airway inflammation manifest as an array of symptoms such as wheezing, shortness of breath,

chest tightness and cough. Interestingly, these symptoms vary over time as well as in intensity together with variable expiratory airflow limitation incurring significant mortality and morbidity [1,2].

To curtail asthma related health burden, multiple efforts have been formulated as a goal to achieve optimal asthma control. In 1993, the Global Initiative for Asthma (GINA) came into play in collaboration with the National Heart, Lung, and Blood Institute, National Institutes of Health, USA, and the WHO [3]. Since then, based on evidence-based strategy for asthma control GINA aims to provide clinicians with an annually updated guidelines, all the while by emphasizing on the role of maintenance and reliever medications such as inhaled corticosteroids (ICS), long-acting beta agonist (LABA), the long-acting muscarinic antagonist (LAMA) tiotropium, and leukotriene receptor antagonists (LTRAs) [4].

Amongst recent advancements, the GINA 2021 guidelines have been set forth with some alterations in the children from 6-11-year-old age group. As shown in Figure 1, the controller medications are subdivided into two groups: preferred and other controller options. Based on symptom severity and asthma control we begin from step 1 and gradually step-up in management plans. Important change of management plans was set-forth in Step 3, as ICS-LABA, medium dose ICS or low dose ICS-formoterol therapies were highlighted. Additionally, in other options, ICS-LTRA combination was also recommended [5].

Nonetheless, despite the preferred controller medications suggested by the GINA, autonomy is given to healthcare professionals based on clinical judgement and perceived notion of the clinician when prescribing medication. We organized this study to draw an effective comparison between these three combinations of controller therapies in pediatric population, based on clinical outcomes and lung parameters. We hypothesize that a combination of ICS-LABA is superior to ICS alone or ICS-LRTA when given to achieve optimal asthma control.

Methods

A retrospective study was conducted at a tertiary care setting in Karachi, Pakistan as shown in Figure 2. The study duration was from July 2021 to December 2022. This study enrolled children aged 6-11 years who were diagnosed and admitted with asthma exacerbations and were discharged on controller medications as per GINA guidelines on step 3 for control of asthma for 3 months. These patients were then further categorized into three groups as per inhaled controller medication

and other combinations. Patients using combinations of low dose long-acting beta agonist and inhaled corticosteroids ICS-LABA or low dose formoterol- inhaled corticosteroids (formoterol - ICS) combinations were categorized into ICS-LABA group. Patients who were managed on medium dose inhaled corticosteroids (ICS) alone as controller medication were grouped into ICS group. The third category included patients on Inhaled corticosteroids with Leukotriene receptor antagonist (LTRA) labeled as ICS-LTRA group. This contrast management plan in our setting was due to autonomy provided by the GINA guideline as well as the physician's preferences in choosing controller inhaled therapy at step 3 (Table 1). Low and medium dose of steroid were categorized as per GINA guideline reference ranges (Table 2).

These discharged patients were then followed for re-admission within 30 days of discharge, number of ER visit with asthma exacerbations for 1 year, number of admissions with asthma, length of stay per admission, need for HDU and PICU in subsequent one year. All these patients were step down after 3 months on step 2 and followed subsequently. Pulmonary function tests were done at 1 week follow-up in clinic after discharge and at 3 months visit post discharge.

Patients who were managed on Step 1, Step 2, Step 4 and Step 5 for control of asthma as per GINA guideline for first 3 months post discharge were excluded from the study. Patients who were stepped up from Step 3 to higher steps for control of asthma for 3 months post discharge were also excluded from the study. Patients who were lost to follow-up in clinics or didn't have PFTs done at designated time periods or have incomplete medication history were excluded. Similarly, patients admitted with bronchopneumonia, bronchiolitis, upper airway obstruction and previously diagnosed with chronic lung disease, cystic fibrosis, tuberculosis, congenital cardiac diseases, and immune deficiency syndrome were excluded from the study.

Diagnosis of asthma was established according to Global Initiative for Asthma (GINA) guidelines: i) identifying characteristic episodic respiratory symptoms such as wheezing, shortness of breath, chest tightness or cough, and ii) documented variable expiratory airflow limitation. This includes spirometry with bronchodilation, of which an increase of forced expiratory volume in one second (FEV1) >12% after administration of a bronchodilator is indicative of asthma [5].

Asthma exacerbation, as defined by the American Thoracic Society (ATS) and European Respiratory Society (ERS), is a deterioration in symptoms and/or lung function, and/or an increase in rescue bronchodilator use, for at least two days. If no hospital admission or emergency department (ED) visit is required, it will be classified as moderate exacerbation, whereas an

admission or ED visit, along with oral corticosteroid treatment for at least three days, is classified as severe exacerbation [6].

Lung function test were done using easy-On-PC® device and interpretations of FEV_1 readings, ratio of FEV_1 and forced vital capacity (FVC) and other parameters were performed using American thoracic Society Guideline and European Respiratory Society Technical Statement [6]. The study utilized data from the electronic medical records system at the hospital, which contains detailed information on patients' demographic characteristics, medical history, medication use, and clinical outcomes. Assurance of human subjects' protection including Institutional Review Board approval was obtained. Pharmacy records provided data on medication prescriptions, dispensed drugs, and the duration of treatment. This provided the distribution of these patients in three groups according to GINA guidelines 2021 and described their management plan [5].

Statistical analysis

The data were analyzed using IBM Corp. released 2020, IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp. Continuous variables were expressed as mean and standard deviation, while categorical variables were described as frequency and percentages. The ANOVA test and paired *t*-test was used for means and Chi-square test was used for categorical data to assess significant difference the groups. A p-value of ≤ 0.05 was considered significant, with a type I error of 5%.

Results

A total of 114 pediatric patients from age 6-11 were enrolled in the study period, out of which 36 (31.57%), 33(28.9%) and 34 (29.82%) patients were categorized into LABA-ICS, ICS and ICS-LTRA subgroups respectively. Variables pertaining to demographic information such as age, gender and BMI were insignificant amongst the groups. As shown in Table 3, the ICS-LABA group had the lowest recorded number of ER visits (1.75±0.96) followed by ICS-LTRA group and ICS only group having 2.93±1.412 and 3.11±1.21 visits respectively ($p<0.001$). Secondly, a similar pattern of significant relationship was also observed in the number of yearly admissions due to asthma, with lowest number being recorded in the ICS-LABA group (1.52±1.02), followed by ICS-LRTA and ICS group having 1.96±0.84 and 2.06±1.07 admissions, respectively ($p=0.047$). Amongst the patients who were admitted, only 13.88% of the patients from the ICS-LABA group

required further management in the PICU, followed by 26.47% and 39.39% of the patients in ICS-LRTA and ICS only group respectively ($p<0.001$). Variables like readmission within 30 days of hospital discharge, average length of stay at the hospital and transfers to HDU on admission statistically showed no difference between the groups. Table 4 shows a correlation between pulmonary function tests as a measure of lung improvement post-treatment in each of the three groups. We used FEV_1 and FEV_1/FVC ratio using a hand-held spirometer one week after discharge and on follow up after three months to record lung function parameters and obtain clinical findings. As seen in Table 4, when we compared FEV_1 and FEV_1/FVC ratio within each group, at one week and 3 months' interval, it yielded statistically significant difference ($p<0.001$) in all three groups with improving lung volumes at 3 months. Meanwhile, as we analyzed the differences of both parameters (FEV_1 and FEV_1/FVC ratio) between three groups within a week after discharge, there were no significant differences between the groups (Table 4). However, at three months after discharge, highest reading of FEV_1 was noted in the ICS-LABA group, followed by ICS-LRTA and then ICS only group of 90.19±9.19, 86.51±9.11, and 84.48±10.23 ($p=0.042$), respectively. Similarly, when we compared FEV_1/FVC ratio, significant improvement was observed at three months post-discharge in all three groups, with maximum improvement of 91.16±9.90 was noted in the ICS-LABA group, followed by 86.66±9.37 in the ICS-LRTA and 82.24±9.52 in the ICS only group ($p=0.001$).

Discussion

Our study centered on children with asthma exacerbation who were managed as inpatients and subsequently discharged in alignment with step 3 add-on therapies of the GINA 2021 guideline. We have effectively highlighted the paramount combination of prescribing an inhaled corticosteroid and long-acting beta-agonist (ICS-LABA) as compared to the other two available combinations of an ICS alone or an ICS with an LTRA (leukotriene antagonist) in children aged 6-11. A critical retrospective analysis has yielded significant findings when comparing the difference in outcomes in the three groups. In our study, we noted that the ICS-LABA group had the lowest recorded number of ER visits, followed by ICS-LTRA group and ICS only group. A similar pattern was also observed with the lowest annual number of admissions due to asthma being recorded in the ICS-LABA group, followed by ICS-LRTA and ICS only group.

Alongside these, all three combinations remarkably improved lung function parameters, but the greatest benefit was noted in the ICS-LABA three months post-discharge as reflected in the FEV1 and FEV1/FVC readings with a significant correlation. The second efficacious combination in this age group as shown by this study is ICS-LTRA therapy, making it comparatively more effective than an isolated inhaled steroid therapy. However, we also noted that in our study the length of hospital stays and readmission within 30 days of discharge showed no significant correlation.

Asthma is globally ranked 16th among the leading causes of years lived with disability and 28th among the leading causes of disease burden, as measured by disability-adjusted life years [7]. Owing to this, the management of asthma is regarded as a critical point to reduce the healthcare burden incurred by it. The three most prescribed drugs for asthma are beta-2 adrenergic agonists, corticosteroids, and leukotriene modifiers, usually montelukast; these are more often given as combination therapies for long term asthma control. Literature holds strong scientific rationale for the LABA-ICS combination therapy, as the ICS aids in reducing chronic inflammation due to asthma, while LABA helps in bronchodilation and inhibition of mast cell mediator release, thereby reducing mediators of inflammation in the airway. Thus, these two classes of drug act complementary to each other. To add to this, ICS increases the expression of LABA-receptors which act to combat the loss of these receptors in response to long-term exposure to LABA therapy [8,9]. LTRAs also play an important role as an anti-inflammatory agent thereby helping to relieve tightening of airway muscles and reduced mucus secretion in the airways [10,11].

Nonetheless, clinicians require a well-established guideline to achieve outcomes when prescribing asthma controller medications; since 1993 the goal of GINA has been to uplift these drugs and adopt a stepwise approach of adding on therapies in scenarios where asthma remains poorly controlled. As such the GINA 2021 guideline has provided the autonomy of three drug combinations: ICS-LABA, ICS, and ICS-LTRA to clinicians dealing with the pediatric asthma population. In our study, patients were already on step 2 of GINA 2021 and were subsequently switched to step 3 and followed for one year.

Several studies in the past have provided evidence which suggest ICS as a superior monotherapy for initial long-term control of asthma in children as suggested by Step 1 of the GINA guideline, and the addition of ICS-LABA or an LTRA is recommended when asthma remains poorly controlled [12]. Moreover, some studies also suggest that combination therapy of LABA with ICSs generates greater improvement in symptom control and lung function when weighed against the

risks of increasing the dose of the ICS [13]. In a pediatric study of 6-16 years old children, the authors concluded that the effect of high dose inhaled ICS versus the addition of LABA with a low dose ICS yielded no significant outcome [14]. In a one-year prospective cohort organized by Turki *et al*., 163 children with a mean age of 5.62±3.61 years were switched from a low-dose inhaled ICS to either a medium-dose ICS only or in combination with a LABA. The asthma control test (ACT) was used to evaluate asthma control over-time. Their results showed that the patients in ICS group had higher mean ACT scores (16.38±5.5 *vs* 14.25±5.1, p=0.02), fewer symptoms of wheezing, nighttime cough, and less school days missed compared to patients in ICS+LABA group ($p<0.05$ for all). Both the groups had improved percent predicted (pp) FEV1, and ppFEF25-75 but the interaction p-value was not significant. Importantly, in conjunction with our findings where patients in the ICS-LABA group had reduced ER visits secondary to asthma exacerbations in comparison to the ICS-only group, the study demonstrated that patients in the ICS group had a treatment failure rate of 77% compared to 23% of the patients in ICS+LABA group who suffered from treatment failure. Thereafter, the authors concluded that as we step up and move towards an add-on therapy in children with uncontrolled asthma on low-dose ICS, switching to ICS+LABA had the additional benefit of less risk of treatment failure when compared to medium-dose ICS [15]. In a meta-analysis by Rodrigo and colleagues, the results also concluded in affirmation of ICS-LABA combination therapy. They obtained that the subjects receiving combination therapy experienced fewer exacerbations (RR=0.73; 95% CI 0.67-0.79) and admissions secondary to asthma, compared with the ICS-only group [16]. A similar activity was inked by Malone *et al*. to evaluate a total of 203 children aged 4-11 years and concluded that 3% of patients in the salmeterol/fluticasone propionate group experienced asthma exacerbations, compared with 8% of patients in the fluticasone-propionate-only group [17]. Literature also provides us with an extensive review of clinical trials done in 2009, of which the findings obtained demonstrate the concurrent use of a LABA with an ICS-positive outcome in terms of reduced ER visits, admissions due to asthma attacks, and improved lung function [18]. However, the review only included three pediatric trials, and hence, the need for critical analysis was highlighted. More recently, in 2015 a review of 28 studies showed that compared with ICS alone, the addition of LABA led to significantly greater improvement in FEV_1 of 2.99%, 95% CI 0.86 to 5.11 [19].

Several studies have also evaluated the role of adding LTRA to an inhaled ICS therapy. As such, the evidence does not support the use of monotherapy with LTRA compared to ICS monotherapy

in children secondary to greater exacerbations, symptom intensity, hospital admissions, and lung function [20]. In a review of 18 clinical trials by Chauhan and Ducharme [20], which included two studies on pediatric age groups from 6-17, similar findings favoring the combination of ICS-LABA versus ICS-LRTA were reiterated. The cumulative results concluded a reduced risk of exacerbations requiring systemic corticosteroids with the combination of ICS-LABA compared with ICS-LRTA - from 13% to 11%. Importantly, in parallel to the previous studies, the authors also put forward the evidence of LABA-ICS combination with improved lung function, quality of life, and patient satisfaction. Nonetheless, due to the comparatively lesser number of pediatric trials enrolled in the review, the need for more conclusive studies was reinforced [21]. Following this, Chauhan [22] conducted another review comprising five pediatric trials to carry out a firm evaluation of the combination of anti-leukotrienes and ICS compared to the same dose of ICS alone (step 3 *versus* step 2 of GINA). The results showed no statistically significant difference in FEV_1, but a significant group difference was observed in the morning and evening peak expiratory flow rates (PEFR) [22].

Limitations of our study includes retrospective design resulting in difficulty in measuring compliance of the pediatric population. Given the natural history of asthma in children, the effect of climate at the time of subsequent ER visits, and exposure to a trigger factor were also not evaluated which might lead to differing predispositions to the HDU, PICU once admitted or readmissions post-discharge. Nonetheless, the evaluation of the effect of different combination therapies on the need for a high-dependency unit once admitted, transfer to PICU, and length of hospital stays is scarce in the pediatric age group. Hence although our study has shown remarkable improvement in these aspects, more studies must be conducted to further solidify our findings.

Conclusions

Our study has aimed to provide a thorough analysis of GINA Step 3 guideline in pediatric population of 6-11 years of age. By highlighting important comparisons based on patient outcomes between the three different medication strategies, it is imperative to choose the optimal therapy to achieve goals of asthma care. Our study concluded that ICS-LABA therapy provides maximum benefit in terms of lung function, symptom control and hospital admissions in this age group at step 3 as per GINA guideline. We recommend more prospective studies and clinical trials in future to add further weightage to our results.

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Table 1. Highlighting Step 3 from Global Initiative for Asthma (GINA) guideline 2021.

	Step 3
Preferred controllers	Low dose ICS-LABA OR medium dose ICS OR very low dose ICS-formoterol maintenance and reliever (MART)
Other controller options	Low dose ICS + leukotriene receptor antagonist (LTRA)

ICS, inhaled corticosteroids; LABA, long-acting beta agonist.

Table 2: Characterization of inhaled steroid doses as per GINA guideline reference ranges.

Inhalers medications	Low dose	Medium dose	High dose
Beclometasone dipropionate (pMDI, standard particle, HFA)	100-200	>200-400	>400
Beclometasone dipropionate (pMDI, exafine particle, HFA)	50-100	>100-200	>200
Budesonide (DPI)	100-200	>200-400	>400
Budesonide (nebulize)	250-500	>500-1000	>1000
Ciclesonide (pMDI, exafine particle, HFA)	80	>80-160	>160
Fluticasone furoate (DPI)	50		NA
Fluticasone propionate (DPI)	50-100	>100-200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50-100	>100-200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100		200

pMDI, pressurized metered-dose inhalers; HFA, hydrofluoroalkane; DPI, dry powdered inhaler.

Table 3. Demographic and clinical characteristics of patients in each group.

	ICS-LABA group	ICS group	ICS-LRTA group	p-value
Patient n (%)	36	33	34	
Age (years)	7.20 ±2.40	6.8±2.80	6.5±1.98	0.171
Male : female	1.4: 1	1.3:1	1.2:1	
Body mass index (BMI)	15.67±2.36	16.23±1.94	14.98±2.89	0.145
Average duration on diagnosis with asthma (years)	4.84±1.67	4.93±1.40	5.36±1.54	0.187
Re-admission within 30 days of discharge	3 (8.33%)	7 (21.21%)	8 (23.52%)	0.720
ER visit with asthma exacerbation per year	1.75 ±0.96	3.11 ±1.21	2.93 ± 1.412	<0.001
Mean admission with asthma per year	1.52± 1.02	2.06 ±1.07	1.96 ±0.84	0.047
Average LOS per admission	2.55 ± 0.84	3.03± 1.65	2.51±0.81	0.509
Number of patients needing HDU care, n (%)	9 (25%)	15 (45.45%)	12 (35.29%)	0.132
Number of patients needing PICU Care, n (%)	5 (13.88%)	13(39.39%)	9(26.47%)	0.034

ER, emergency room; LOS, length of stay; HDU, High Dependency Unit; PICU: Pediatric Intensive Care Unit.

Table 4. Parameters of lung function improvement in each group.

	FEV_1 (%)			FEV^1/FVC (%)		
	Within one week after discharge	Three months follow-up	p	Within one week after discharge	Three months follow-up	p
ICS LABA group	74.66±2.99	90.19±9.19	<0.001	75.08±5.92	91.16±9.90	<0.001
ICS group	75.69±4.77	84.48±10.23	<0.001	76.84±7.08	82.24±9.52	<0.001
ICS-LRTA group	76.95±7.64	86.51±9.11	<0.001	78.64±7.51	86.66±9.37	<0.001
p-value	0.201	0.042		0.75	0.001	

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LRTA, leukotriene receptor antagonist).

Figure 1. GINA guidelines 2021 for 6-11-year-old children. SABA, short acting beta agonist; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist; MART, maintenance and reliever therapy.

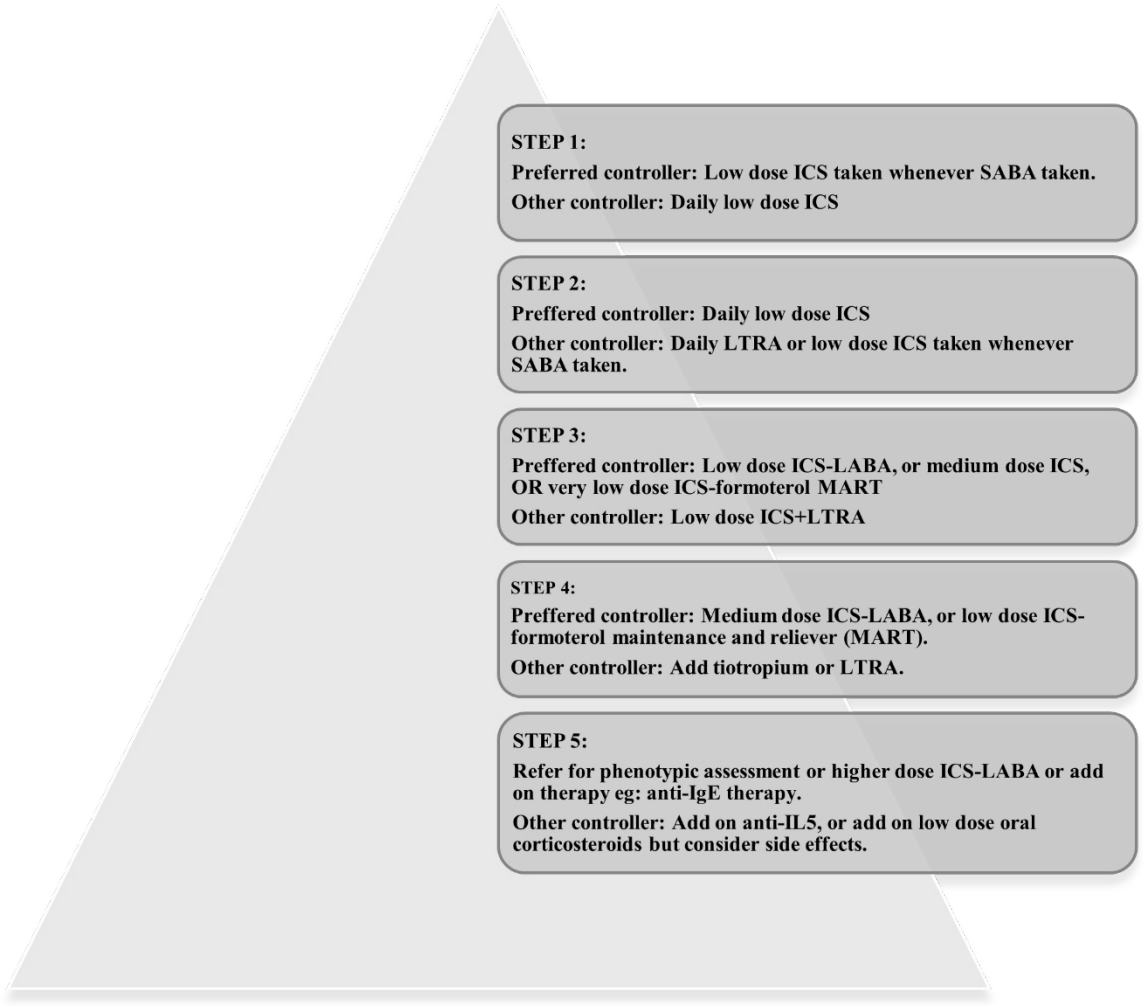

Figure 2. Study design.