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

Danish Abdul Aziz, Muhammad Aqib Sajjad, Ameema Asad

Department of Pediatrics and Child Health, Aga Khan University Hospital, Karachi, Pakistan

Correspondence: Danish Abdul Aziz, Department of Pediatrics and Child Health, Aga Khan University Hospital, Karachi, Pakistan.
Tel. +92.3332345673.
E-mail: drdanishaziz@gmail.com

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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 the 6-11-year-old age group. The low-dose inhaled corticosteroid (ICS)-long-acting β-agonist (LABA), very low-dose formoterol-ICS, medium-dose ICS, and ICS-leukotriene receptor antagonist (LTRA) combination were recommended in the guideline. We organized this study to draw an effective comparison between these three combinations of controller therapies in the 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 emergency room (ER) visits with asthma exacerbations for 1 year, number of admissions with asthma, including high dependency unit and pediatric intensive care unit (PICU) admissions, and length of stay per admission for all admissions in the subsequent year. The pulmonary function test was done at the 1-week follow-up in the clinic after discharge and at the 3-month visit post-discharge. A total of 114 pediatric patients from 6 to 11 years 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 the ICS-LABA group, followed by the ICS-LRTA group and then the ICS group (1.75±0.96 *versus* 2.93±1.412 *versus* 3.11±1.21, p<0.001). Similar statistically significant results were observed on the average number of admissions per year (1.52±1.02 *versus* 1.96±0.84 *versus* 2.06±1.07, p=0.047) and the number of patients needing PICU (13.88% *versus* 26.47% *versus* 39.39%, p=0.034) in these groups, respectively. ICS-LABA group patients had the best values of the forced expiratory volume in one second (FEV_1) and FEV_1/forced vital capacity ratio after pulmonary function tests at 3 months follow-up, followed by ICS-LTRA and ICS group. Amongst the three options for 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.

Introduction

Asthma is a widely known chronic, heterogeneous airway disease that is prevalent among all age groups. According to the latest report by the World Health Organization (WHO) published on May 4th, 2023, the 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 burdens, 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 an evidence-based strategy for asthma control, GINA aims to provide clinicians with annually updated guidelines, all the while emphasizing the role of maintenance and reliever medications such as inhaled corticosteroids (ICS), long-acting β-agonists (LABA), the long-acting muscarinic antagonist 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 the 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 began from step 1 and gradually stepped up in management plans. An 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, the 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 judgment and the 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 the 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.

Materials and 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 exacerba-

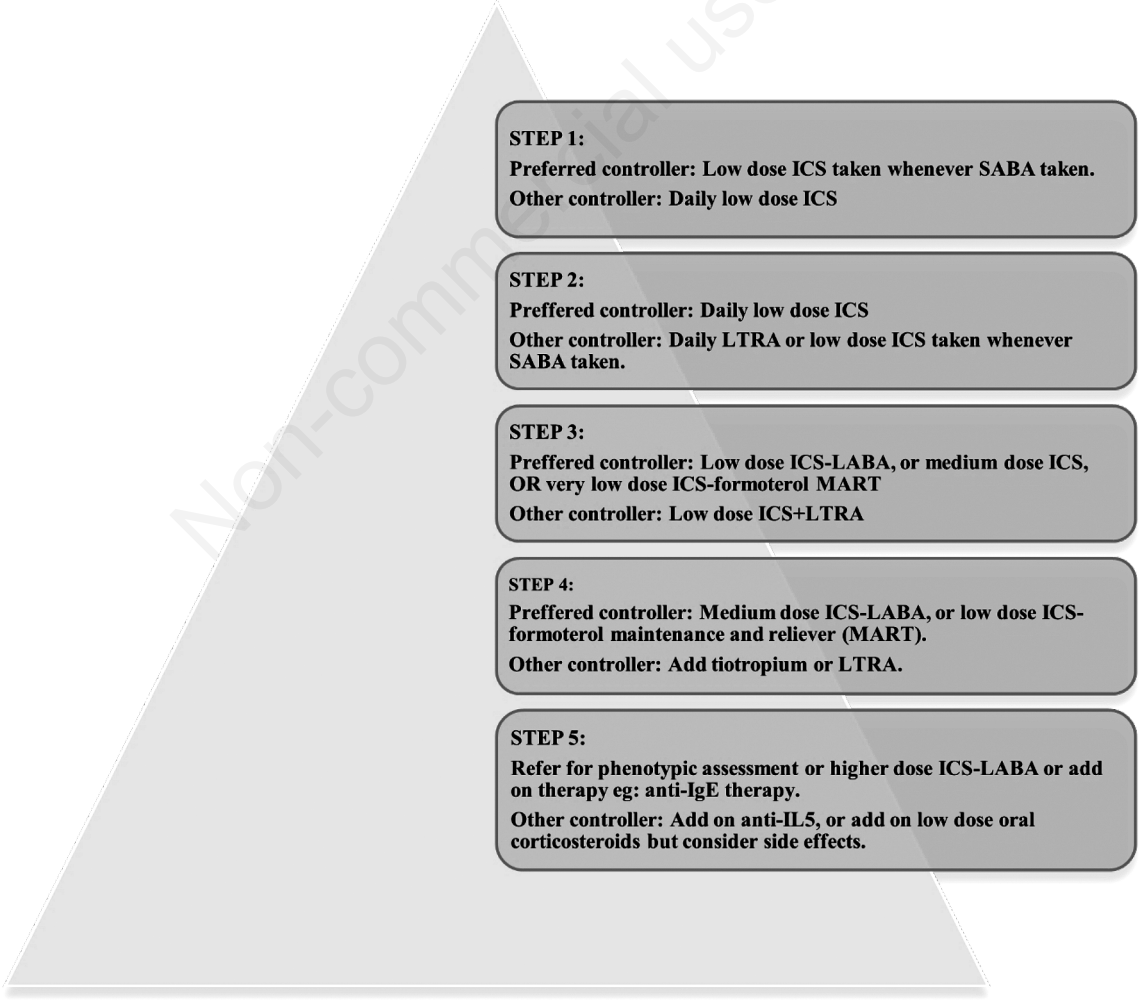

Figure 1. Global Initiative for Asthma guidelines 2021 for 6-11-year-old children. SABA, short-acting β-agonist; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonist; MART, maintenance and reliever therapy; IL, interleukin.

tions 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 LABA and ICS-LABA or low-dose formoterol-ICS combinations were categorized into ICS-LABA group. Patients who were managed on medium-dose ICS alone as controller medication were grouped into the ICS group. The third category included patients on ICS with 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 doses of steroids 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 emergency room (ER) visits with asthma exacerbations for one year, number of admissions with asthma, length of stay per admission, and need for high dependency unit (HDU) and pediatric intensive care unit (PICU) in the subsequent year. All these patients were stepped down after 3 months on step 2 and followed subsequently. Pulmonary function tests (PFT) were done at the 1-week follow-up in the clinic after discharge and at the 3-month visit post-discharge.

Patients who were managed on step 1, step 2, step 4 and step 5 for control of asthma as per GINA guidelines for the 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, did not have PFT done at designated time periods, or had an incomplete medication history were excluded. Similarly, patients admitted with bronchopneumonia, bronchiolitis, and 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 GINA guidelines: i) identifying characteristic episodic respiratory symptoms such as wheezing, shortness of breath, chest tightness, or cough; and

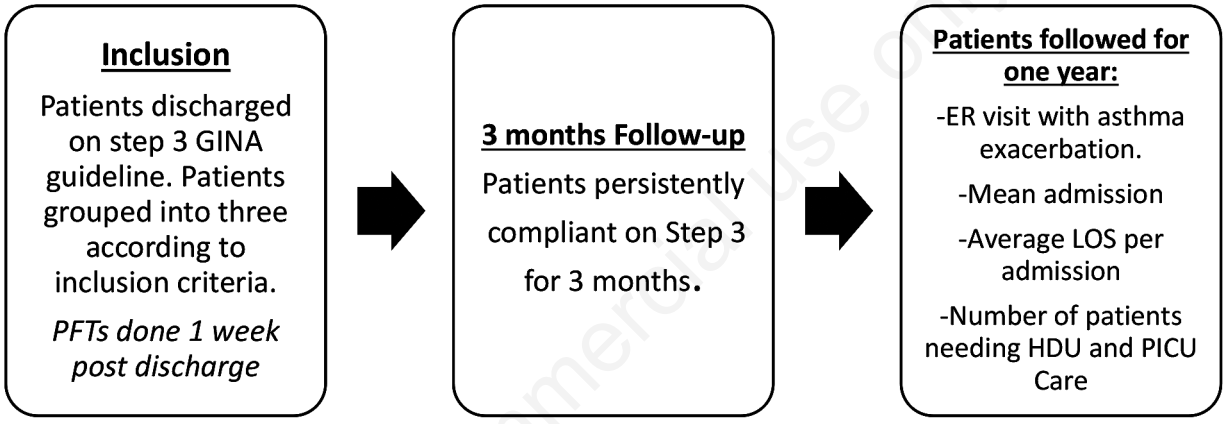

Figure 2. Study design. GINA, Global Initiative for Asthma; PFTs, pulmonary function tests; ER, emergency room; LOS, length of stay; HDU, high dependency unit; PICU, pediatric intensive care unit.

Table 1. Highlighting step 3 from Global Initiative for Asthma 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

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

Table 2. Characterization of inhaled steroid doses as per Global Initiative for Asthma 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.

ii) documenting variable expiratory airflow limitation. This includes spirometry with bronchodilation, of which an increase of forced expiratory volume in one second (FEV_1) >12% after administration of a bronchodilator is indicative of asthma [5].

Asthma exacerbation, as defined by the American Thoracic Society and European Respiratory Society, is a deterioration in symptoms and/or lung function and/or an increase in rescue bronchodilator use for at least 2 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 3 days, is classified as severe exacerbation [6].

PFTs were done using easy-On-PC® (ndd medical, Zurich, Switzerland) device, and interpretations of FEV_1 readings, the ratio of FEV_1 and forced vital capacity (FVC), and other parameters were performed using the 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., IBM Corp, Armonk, NY, USA) Continuous variables were expressed as mean and standard deviation, while categorical variables were described as frequency and percentages. The analysis of variance 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 ≤0.05 was considered significant, with a type I error of 5%.

Results

A total of 114 pediatric patients from ages 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 body mass index 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 the ICS-LTRA group and the ICS 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 the lowest number being recorded in the ICS-LABA group (1.52±1.02), followed by ICS-LRTA and the 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 the ICS-LRTA and ICS groups 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 PFT as a measure of lung

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

	ICS-LABA group	ICS group	ICS-LRTA group	p
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	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

ICS, inhaled corticosteroids; LABA, long-acting β-agonist; LRTA, leukotriene receptor antagonist; 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 1 week after discharge	3-month follow-up	p	Within 1 week after discharge	3-month 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 β-agonist; LRTA, leukotriene receptor antagonist.

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 3 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 1-week and 3-month intervals, it yielded statistically significant differences ($p<0.001$) 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 3 months after discharge, the highest reading of FEV_1 was noted in the ICS-LABA group, followed by ICS-LRTA and then the ICS 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 3 months post-discharge in all three groups, with a maximum improvement of 91.16±9.90 noted in the ICS-LABA group, followed by 86.66±9.37 in the ICS-LRTA and 82.24±9.52 in the ICS groups ($p=0.001$).

Discussion

Our study centered on children with asthma exacerbations 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 ICS and LABA as compared to the other two available combinations of an ICS alone or an ICS with an LTRA 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 the 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 the 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 3 months post-discharge, as reflected in the FEV_1 and FEV_1/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 β-2 adrenergic agonists, corticosteroids, and leukotriene modifiers, usually montelukast; these are more often given as combination therapies for long-term asthma control. The 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 drugs 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 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 that suggests 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 children aged 6-16, the authors concluded that the effect of high-dose ICS *versus* the addition of LABA with a low-dose ICS yielded no significant outcome [14]. In a 1-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 an LABA. The asthma control test (ACT) was used to evaluate asthma control over time. Their results showed that the patients in the ICS group had higher mean ACT scores (16.38±5.5 *versus* 14.25±5.1, $p=0.02$), fewer symptoms of wheezing, nighttime cough, and less school days missed compared to patients in the ICS-LABA group ($p<0.05$ for all). Both the groups had improved percent predicted (pp) FEV_1 and pp forced expiratory flow at 25% and 75% of the pulmonary volume, 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 the 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 *et al.*, the results also concluded in affirmation of ICS-LABA combination therapy. They obtained that the subjects receiving combination therapy experienced fewer exacerbations [relative risk = 0.73; 95% confidence interval (CI) 0.67-0.79] and admissions secondary to asthma, compared with the ICS-only group [16].

A similar activity was conducted by Malone *et al*. to evaluate a total of 203 children aged 4-11 years. The authors 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]. The literature also provides us with an extensive review of clinical trials done in 2009, of which the findings obtained demonstrate the concurrent use of 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 *et al.* 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) [22]. The results showed no statistically significant difference in FEV□, but a significant group difference was observed in the morning and evening peak expiratory flow rates [22].

Limitations of our study include its retrospective design, which resulted 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 guidelines in the pediatric population aged 6-11. By highlighting important comparisons based on patient outcomes between the three different medication strategies, it is imperative to choose the optimal therapy to achieve the 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 guidelines. We recommend more prospective studies and clinical trials in the future to add further weightage to our results.

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