

A randomized, double-blind study comparing the efficacy and safety of a combination of formoterol and ciclesonide with ciclesonide alone in asthma subjects with moderate-to-severe airflow limitation

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ABSTRACT

Context: The combination of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA) is widely used in the treatment of moderate-to-severe asthma uncontrolled by ICS alone. **Aims:** To evaluate the efficacy and safety of a new ICS-LABA combination inhaler containing Formoterol (F) and Ciclesonide (C). **Settings and Design:** A double-blind, double-dummy, parallel group fashion, multi-centric study. **Subjects and Methods:** A total of 169 asthma patients received Ciclesonide 80 µg once daily during a 4-week run-in period, after which, they were randomized to receive either C (80 µg) or a combination of F (4.5 µg) and C (80 µg) (FC) both delivered through a hydro-fluro-alkane pressurized-metered-dose inhaler as 1 puff twice daily, for 6 weeks. **Statistical Analysis Used:** Inter-group differences were compared using *t*-test for independent samples at a significance level of 5%. **Results:** From baseline, the improvements in forced expiratory volume in 1 s at 1, 3, and 6 weeks was significantly higher in the FC group compared to Group C (110 ml vs. 40 ml, 140 ml vs. 20 ml, and 110 ml vs. 40 ml, respectively, all *P* < 0.05). From baseline, the improvements in mean morning peak expiratory flow at 1, 3, and 6 weeks was significantly higher in the FC group compared to Group C (17 L/min vs. -3 L/min, 22 L/min vs. 3 L/min, and 30 ml vs. 8 L/min respectively, all *P* < 0.05). The changes in symptom scores were similar in both the groups. The adverse events in the FC group were not significantly different from those in the C group. **Conclusions:** FC provides better improvement than C alone in terms of lung function and symptoms without increased risk of adverse events in asthma patients.

KEY WORDS: Asthma, bronchodilator agents, clinical respiratory medicine, clinical trials

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INTRODUCTION

For asthma patients uncontrolled on low-dose inhaled corticosteroids (ICS) guidelines recommend two options: Either increase the dose of ICS further, or add long-acting beta-agonists (LABA).^[1] The addition of LABA to ICS has several advantages over doubling the dose of ICS. Most of the benefit from ICS is achieved at lower doses and

further increasing the dose provides little therapeutic benefit.^[1] LABA and ICS potentiate each other's effect through synergism. Interestingly, combination of ICS and LABA has the potential to inhibit airway remodeling.^[2,3] In addition, it has recently been shown that bronchoconstriction in asthmatics even in the absence of mucosal inflammation may contribute to airway

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remodeling.^[4] Long-acting bronchodilators such as LABA might prevent airway remodeling by causing sustained bronchodilation.

Combining LABA and ICS in one inhaler has been shown to improve compliance compared to when they are given in two separate inhalers.^[5,6]

Formoterol is a unique LABA because it has both a rapid onset and a sustained duration of action which lasts for at least 12 h. Its lipophilic properties help it to penetrate the cell membrane and be stored in the cytoplasm of smooth muscle cells of the airways leading to sustained bronchodilation, while its hydrophilic properties allow it to access and activate β_2 -receptor rapidly, leading to rapid bronchodilation.^[7]

Ciclesonide is a prodrug which is activated in the lungs by lung-specific esterase to its active metabolite, desisobutyryl-ciclesonide (des-CIC). Since, ciclesonide and des-CIC have almost no oral bio-availability, the systemic absorption of this steroid is minimal and, therefore, has minimal systemic adverse effects.^[8-10] Slow release of des-CIC from the depot of fatty acid esters in the lungs provides longer (24 h) duration to the anti-inflammatory effects of the drug.^[11] In addition, Ciclesonide can be formulated in a hydro-fluro-alkane metered-dose-inhaler (HFA-MDI), providing it a unique advantage of being delivered to the lungs in smaller particle sizes ranging from 1.1 to 2.1 μm , thereby allowing it to exert its anti-inflammatory effects even in the smaller airways.^[12-15]

Because of the unique properties of formoterol and ciclesonide, a combination (FC) may offer distinct advantages in the management of asthma. Recently, the approach of using single ICS + LABA combination inhaler for both maintenance and rescue has gained popularity. However, such approach is associated with exposure to almost 50% increased doses of ICS.^[16] As ciclesonide has lesser systemic bio-availability, it may be a safer alternative to other ICS. In addition, better anti-inflammatory effects of ciclesonide on smaller airways coupled with fast onset and longer duration of action of formoterol make the combination inhaler of formoterol and ciclesonide an attractive alternative over other ICS + LABA combination inhalers.

However, the efficacy and safety of a combination inhaler containing FC have not been adequately studied, although there is evidence for better efficacy and safety profile of other ICS + LABA combination inhalers.^[17] The aim of this study was to compare the efficacy and safety of a combination of ciclesonide 80 μg and formoterol 4.5 μg with ciclesonide 80 μg both given as 1 puff twice daily delivered through an HFA pressurized MDI (pMDI) for 6 weeks in asthma patients having moderate-to-severe airflow limitation.

SUBJECTS AND METHODS

Subjects

Male and female subjects aged 18–70 years with a diagnosis of asthma based on Global Initiative for Asthma guidelines and forced expiratory volume in 1 s (FEV1) between 40% and 80% of predicted were recruited into the study. All subjects demonstrated FEV1 improvement of $\geq 12\%$ and ≥ 200 ml after 200 μg of Salbutamol through a pMDI at screening. All subjects were receiving a stable dose of 500 μg of fluticasone propionate or its equivalent per day for at least 4 weeks before screening. Subjects had smoking history of < 10 pack years and did not have any asthma exacerbation within 12 weeks or any respiratory tract infection within 4 weeks before screening. Subjects who were ever diagnosed to have chronic obstructive pulmonary disease (COPD) or emphysema were excluded.

The study was conducted across 9 centers in India and approvals were obtained from all local Ethics Committees before the start of the study. The study was conducted in accordance with the declaration of Helsinki (1964 and subsequent revisions) and Good Clinical Practice guidelines. Written informed consent was obtained from all study participants. The study was sponsored by Cipla Pharmaceuticals Ltd. and their representatives were involved in developing the study protocol, statistical analysis, and preparation of the manuscript. The study was registered with clinical trials registry of India (www.ctri.nic.in; Reg No: CTRI/2009/091/000547).

Study design

This was 6 weeks, randomized, double-blind, double-dummy, parallel-group, prospective study. Patients who met the selection criteria entered into a run-in period of 4 weeks, during which they received ciclesonide 80 μg (Cipla Ltd., India) via a pMDI one puff once daily after the previous medications were stopped. Levo-salbutamol 50 μg (Cipla Ltd., India) pMDI was allowed as rescue medication [Figure 1]. Symptoms, use of rescue medications and adverse events were recorded by all study participants on a paper diary. Daytime symptoms were recorded on a 5-point scale ranging from 0 to 4, and night-time symptoms were recorded on a 4-point scale ranging from 0 to 3 [Table 1]. Subjects measured their peak expiratory flow (PEF) in the morning (8 am before study drug) and in the evening (8 pm before study drug) using a validated EU scale peak flow meter (Breathometer, Cipla Ltd., India) and the best of the three readings was recorded in the subject diary.

Subjects who satisfied any two of the following criteria at the end of the run-in period were randomized: Total day-time symptom score of more than 2 on at least 3 of the last 7 days of the run-in period [Table 1], nocturnal awakenings due to asthma on any 2 of the last 7 days, use of rescue medication more than twice daily on at least 2

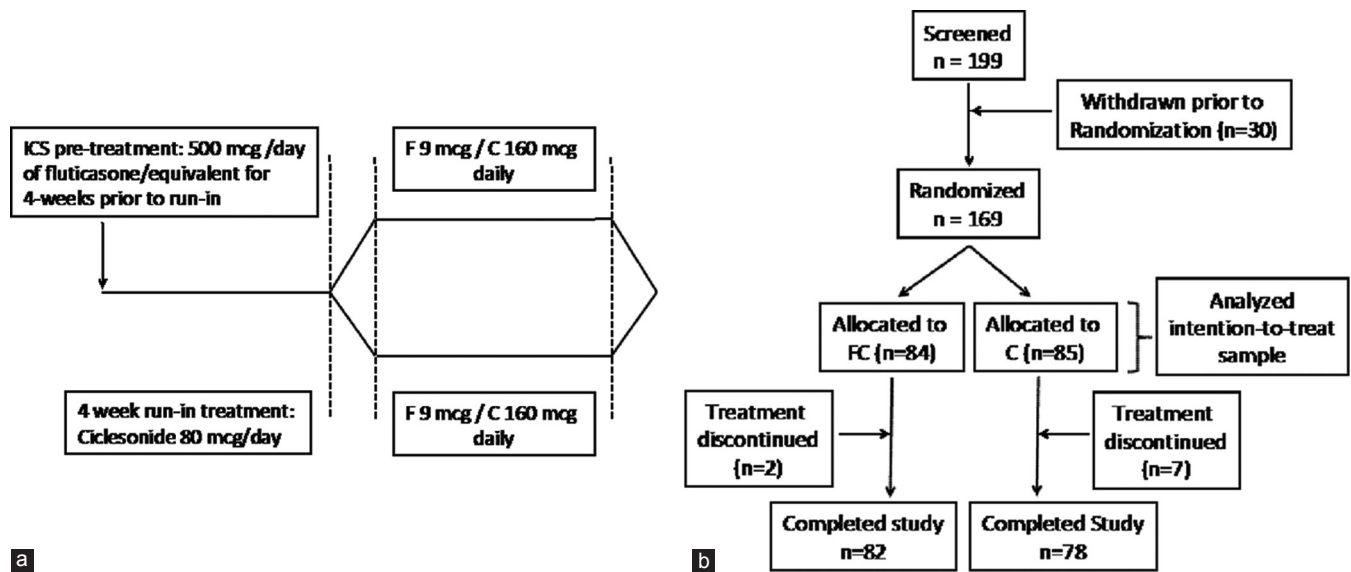


Figure 1: (a) Study design, (b) flow of patients (CONSORT diagram)

Table 1: Day-time and night-time symptom scores

Day-time symptom scores	
0	No symptoms
1	One episode of wheezing, cough, or breathlessness
2	More than one episode of wheezing, cough, or breathlessness without interference with normal activities
3	Wheezing, cough, or shortness of breath for most of the day which interfered to some extent with normal activities
4	Asthma very bad, unable to carry out daytime activities as usual
Night-time symptom scores	
0	No symptoms, slept through the night
1	Woke up once because of asthma (including early wakening)
2	Woke up several times because of asthma (including early wakening)
3	Bad night, awake most of the night because of asthma

of the last 7 days; diurnal PEF variation >20% on at least 2 of the last 7 days. Randomization was done through www.randomization.com in blocks of 4 by the statistician.

Subjects were randomized to receive either formoterol-ciclesonide combination (FC) 80/4.5 µg HFA pMDI or Ciclesonide (C) 80 µg HFA pMDI for 6 weeks (ratio 1:1). Since the FC and C inhalers looked different and had different sizes, we used a double-dummy design to ensure double-blinding. Placebo and drug inhalers for FC and C were provided by Cipla Limited in labeled form. Placebo inhalers had the same weight as the respective drug inhaler, were similar in appearance and were tamper-proof. Each subject received either an FC inhaler and a placebo inhaler for C or a C inhaler and a placebo inhaler for FC. Both the inhalers were administered 1 puff twice daily. The inhalers were identified by the sequential numeric code. Each subject was assigned the next inhaler in the sequence during randomization. The subjects, investigator and anyone else involved in the conduct of the study were not aware about the treatment allocation. The randomization code was broken by the statistician only after the data collection was completed and the data was entered and frozen.

Variables assessed

Subsequent visits were conducted at the end of weeks 1, 3, and 6, during which spirometry was performed with a calibrated spirometer before dosing, in compliance with ATS/ERS statement 2005 to obtain three acceptable spirograms with reproducibility of <150 ml between the best two efforts for FEV₁ and forced vital capacity. The quality of spirograms was checked and assured by a trained team of monitors. Spirograms not satisfying quality criteria were rejected. Levo-salbutamol was withheld for at least 6 h before spirometry. Subject diaries were checked for adequacy of capturing data.

The primary end point was the difference between the two groups in the mean change in morning predose FEV₁ at the end of 6 weeks from baseline. The secondary end points were: Mean morning and evening predose PEF values recorded, mean day-time and night-time symptom scores and mean number of daily puffs of rescue medication required recorded over 6 weeks.

Safety endpoints included incidence of adverse events, drug-related adverse events, severe asthma exacerbations, need for the use of oral steroids, requirement for hospitalization due to worsening of asthma, and assessment of laboratory parameters.

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The study was sponsored by Cipla Pharmaceuticals Ltd., Mumbai, India and their representatives were involved in developing the study protocol, statistical analysis and preparation of the manuscript.

Sample size and statistical analysis

Statistical analysis was performed using the IBM's Statistical Package for Social Sciences (SPSS) software version 17 (IBM). Assuming an upper limit of 150 ml for known standard deviation of our primary end-point,^[18]

mean FEV1 and using a two-sided significance test at the 5% level, we estimated that a sample size of 125 evaluable subjects would give the study a power of 80% to detect mean differences between the two groups in mean change in FEV1 from baseline of approximately 75 ml. With an expected 25% dropout rate we planned to randomize a total of 169 subjects.

The data of patients who received, at least, one dose of study medication were analyzed using the intention-to-treat approach. For normally distributed data, within-group changes from baseline were analyzed using paired *t*-test and inter-group differences were compared using *t*-test for independent samples. For data expressed as a percentage, the inter-group comparison was made using Chi-square test. The significance level for all comparisons was defined as 5%. The analysis was conducted by an independent statistician.

RESULTS

Of 199 screened subjects, 169 asthma patients were randomized to receive either FC ($n = 84$) or C ($n = 85$). 2 patients from FC group and 7 from C were discontinued from the study due to adverse events (FC = 1, C = 2), consent withdrawal (C = 2) and lost to follow-up (FC = 1, C = 3) after randomization. An intention-to-treat analysis was performed on all the 169 subjects. Missing data was dealt by using the last observation carried forward method, whereby the last available measurement of each subject at the time point before withdrawal was retained in the analysis. All 169 subjects completed week 1 assessments, 2 (FC = 1, C = 1) subjects were excluded between weeks 1 and 3 and 7 (FC = 1, C = 6) subjects were excluded between weeks 3 and 6.

Baseline characteristics of the FC and C group are described in Table 2 and were comparable except for FEV1% predicted which was lower in the FC group. Since the absolute FEV1 in the two groups was not significant we assumed the comparability at baseline.

Lung function

FEV1 improved significantly from baseline in the FC group compared to Group C at each visit after randomization. At week 1, the mean FEV1 (95% confidence interval [CI]) increased by 110 (50, 160) ml in the FC group compared

to 40 (-10, 90) ml in Group C ($P = 0.01$). At week 3 and week 6, FEV1 increased by 140 (80, 190) ml and 110 (60, 170) ml, respectively in FC group compared to a corresponding increase of 20 (-30, 80) ml and 40 (-10, 90) ml in Group C ($P = 0.01$ at week 3 and $P = 0.01$ at week 6) [Table 3 and Figure 2]. The mean morning PEF increased significantly from baseline in the group FC compared to Group C at all the visits after randomization. At week 1, the mean morning PEF (95% CI) increased by 17 (11, 24) L/min in the FC group compared to a fall of PEF by 3 (-9.9, 3.1) L/min in the C group ($P = 0.01$). At week 3 and week 6, the mean morning PEF (95% CI) increased by 22 (16, 30) L/min and 30 (24-39) L/min, respectively, in FC group compared to a corresponding increase of 3 (-6, 11) L/min and 8 (-2, 17) L/min in Group C ($P = 0.01$ at week 3 and week 6). Similarly, the mean evening PEF increased significantly from baseline in group FC compared to Group C at all the visits after randomization. At week 1, the mean evening PEF (95% CI) increased by 22 (17, 28) L/min in the FC group compared to an increase of 1 (-9, 10) L/min in Group C ($P = 0.01$). At week 3 and week 6, the mean evening PEF increased by 26 (19, 33) L/min and 30 (22, 38) L/min, respectively, in the FC group compared to an increase of 6 (-5, 17) L/min and 10 (-1, 21) L/min in Group C [Figure 3].

Symptoms

The mean (95% CI) reductions in symptom-free days were 44 (28, 61) days in FC group compared to 29 (14, 43; $P = 0.146$) days in Group C and symptom-free nights were 40 (26, 53) days and 36 (24, 48; $P = 0.663$) days respectively over 6 weeks. The mean (95% CI) reductions in daytime symptom scores were 1.01 (-0.84, 1.18) days in FC group compared to 0.86 (-0.65, 1.07; $P = 0.278$) days in Group C and night-time symptom scores were 0.46 (0.31, 0.6) days and 0.36 (0.22, 0.5; $P = 0.332$) days, respectively [Table 3]. Rescue medication usage reduced by 1.51 (1.1, 1.9) puffs/day in FC group compared to a

Table 2: Baseline comparison

Parameter	Group 1 (ciclesonide + formoterol)	Group 2 (ciclesonide)	P
Number of subjects (n)	82	79	-
Age (years)	42.2±12.3	41.1±12.9	0.570
Height (cm)	160.0±9.0	161.6±10.6	0.292
Duration of asthma (years)	12.2±9.1	14.2±11.6	0.215
Smoking history (pack years)	3±5.3	1±0	-
FEV1 (L)	1.57±0.52	1.74±0.54	0.058
FEV1% predicted	60.1	63.6	0.039
FVC (L)	2.4±0.6	2.6±0.8	0.082

FEV1: Forced expiratory volume in 1 s, FVC: Forced vital capacity

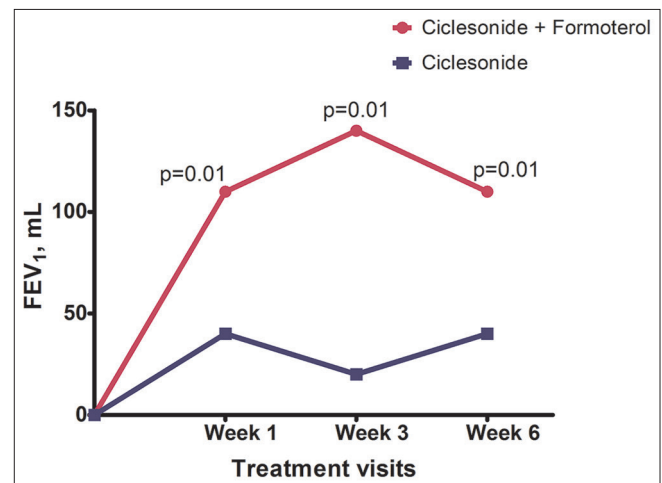


Figure 2: Change in mean forced expiratory volume in 1 s from baseline in FC and C group. FC group demonstrated significant improvement in pre-dose peak flow in comparison with C group

Table 3: Comparison of lung function and symptom scores at each visit in the two treatment groups

	Group 1 (ciclesonide + formoterol)				Group 2 (ciclesonide only)				P (Group 1-Group 2)		
	Baseline	Week 1	Week 3	Week 6	Baseline	Week 1	Week 3	Week 6	Week 1	Week 3	Week 6
FEV1 (L)	1.57±0.52	1.68±0.56	1.71±0.61	1.68±0.58	1.74±0.54	1.78±0.61	1.76±0.63	1.78±0.63	0.01	0.01	0.01
Mean morning PEF (L/min)	259±95	277±98	282±93	291±94	275±101	271±95	277±96	282±97	0.01	0.01	0.01
Mean evening PEF (L/min)	257±96	280±100	283±96	287±93	266±102	267±97	272±98	276±96	0.01	0.01	0.01
Day-time symptom score	2.27±0.58	1.64±0.59	1.55±0.64	1.27±0.45	2.29±0.59	1.68±0.55	1.58±0.7	1.42±0.64	0.46	0.75	0.27
Night-time symptom score	1.56±0.46	1.34±0.43	1.38±0.52	1.2±0.35	1.49±0.43	1.35±0.41	1.29±0.46	1.2±0.42	0.30	0.94	0.33
Rescue use/day	2.52±1.61	1.76±1.74	1.51±1.92	1.02±1.15	2.32±1.46	1.77±1.54	1.68±1.61	1.36±1.49	0.61	0.32	0.03

Group 1 (FC group) demonstrated significant improvement in lung function from baseline and in comparison with ciclesonide group. Ciclesonide did not produce any lung function improvement but lead to symptomatic improvement equivalent to FC group. Values are expressed as mean±standard deviation. FEV1: Forced expiratory volume in 1 s, PEF: Peak expiratory flow

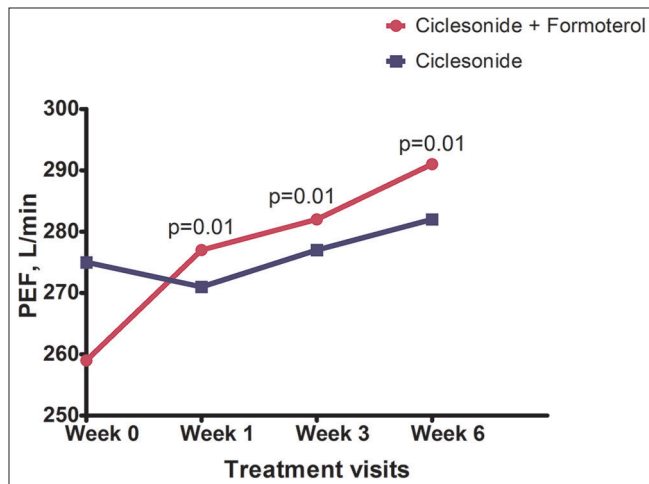


Figure 3: Change in mean morning pre-dose peak flow from baseline in FC and C group. FC group demonstrated significant improvement in pre-dose peak flow in comparison with C group

reduction of 0.95 (0.5, 1.4) puffs/day in Group C ($P = 0.03$). Furthermore, the number of puffs of rescue medication used per day reduced significantly in both the groups, although, the difference between the two groups was not significant.

Safety variables

29 adverse events (FC = 12, C = 17) were reported during the study period. One subject in the FC group suffered from a Serious Adverse Event of parotitis which was considered nondrug-related by the study investigator.

The group-wise distribution of adverse events was: Tremors (FC 3), cramps (FC 1, C 1), palpitations (FC 1), asthma exacerbations (C1), cough (C1), increased breathlessness (C 1), headache (FC 1, C 1), viral fever (FC 1), viral hepatitis (C 1), common cold (FC 1), fever (C 2), edema (C 1), hypochondriac pain (FC 1), abdominal pain (FC 1), nausea (C 1), parotid swelling (FC 1), pharyngitis (FC 1), sinusitis (C 1), cellulitis (C 1), and tonsillitis (C1). The differences in the adverse events between the two groups were statistically nonsignificant ($P > 0.05$).

The random blood glucose levels in the FC and C group decreased from 94.8 mg/dl and 92.0 mg/dl at baseline to 93.8 mg/dl and 89.8 mg/dl at week 6, respectively (between group $P = 0.29$). The serum potassium levels in the FC and C group decreased from 4.3 mEq/L and

4.4 mEq/L at baseline to 4.1 mEq/L and 4.2 mEq/L at week 6, respectively (between group $P = 0.43$).

DISCUSSION

In this study, the combination of ciclesonide and formoterol in asthma patients with moderate-to-severe airflow limitation produced a significant improvement in lung function, peak flow monitoring, and symptoms. Except for symptoms all other improvements were significantly better than the improvements seen in the ciclesonide group. There was no difference in the adverse event profile between the two study groups. To the best of our knowledge, this is the first study demonstrating a better efficacy of FC combination inhaler compared to C in asthma subjects with moderate-to-severe airflow limitation. In a previous study, Korn and Buhl demonstrated noninferiority of FC combination compared to Fluticasone-Salmeterol combination.^[19] The improvement (356 ml) seen in their study with FC was higher than that seen in our study (110 ml). This could be because of the use of a higher daily dose (F = 18 µg, C = 640 µg) in their study compared to the dose in our study (F = 9 µg, C = 160 µg).

The dose of ciclesonide in the run-in period was doubled during the treatment period, and this doubling did not produce significant improvement in lung function parameters like FEV1, morning peak expiratory flow rate (PEFR) and evening PEF, although it produced significant improvement in symptoms and rescue medication use. This is consistent with findings from other studies comparing various doses of fluticasone, beclomethasone, budesonide, triamcinolone, and mometasone in which only budesonide showed significant dose-response with FEV1 while triamcinolone and fluticasone demonstrated dose-response in terms of morning and evening PEF improvements.^[20]

Our study demonstrated that addition of a long-acting bronchodilator (formoterol, in this case) can produce better bronchodilation and symptomatic improvement in asthma patients having moderate-to-severe airflow limitation. This finding will help clinicians and those patients whose asthma is uncontrolled on low-dose ciclesonide to take a better informed decision. Such patients are more likely to benefit from the addition of bronchodilator than doubling the dose of inhaled steroid.

Our study could be criticized for comparing ciclesonide 160 µg/day with a combination containing formoterol and an equivalent dose of ciclesonide (160 µg/day). It might appear obvious that addition of LABA would produce an additional improvement over similar dose of ciclesonide. However, the efficacy of adding LABA to ciclesonide over conventional dose of ciclesonide has not been demonstrated. In our study, we found that addition of formoterol to ciclesonide produces additional significant improvement while doubling the run-in dose of ciclesonide during treatment period did not produce improvement in lung function.

We included patients having FEV1 between 40% and 80% predicted at a screening in spite of receiving a stable dose of ICS equivalent to fluticasone 500 mcg daily suggesting the inclusion of moderate-to-severe asthma patients. Asthma patients having severe airflow limitation are usually excluded from drug trials as severe asthma may be associated with airway remodeling, emphysema, and COPD. However, we included such patients as the combination inhalers are used most prevalently in moderate-to-severe asthma patients. Besides, patients having a diagnosis of emphysema or COPD were excluded from the study.

We did not find a significant difference between the adverse events between the two groups, although, adverse events such as tremors, palpitation, and cramps were more in the combination group. However, the duration of the trial (6 weeks) may be too short to capture long-term adverse effects and trials of at least 48 weeks might be appropriate. Furthermore, higher use of beta-agonist salbutamol in the steroid group might confound the adverse effects of LABA in such studies. In addition, it might have been valuable to study adrenal function in order to capture concerning adverse effects of steroid and study electrocardiogram and QTc to specifically capture the adverse effects of formoterol. It would also be useful to study the efficacy and safety of FC combination in COPD patients.

CONCLUSIONS

Formoterol and ciclesonide combination in a single inhaler shows better therapeutic efficacy and comparable safety than ciclesonide alone in asthma patients with moderate-to-severe airflow limitation. This combination could be a new option to currently available ICS/LABA combination inhalers for obstructive airways disease.

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Conflicts of interest

There are no conflicts of interest.

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