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Review Article

Asthma management with combination of fluticasone and formoterol: the Indian perspective

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ABSTRACT

Asthma is a major health problem globally that affects people across all the age groups. The prevalence of asthma is increasing worldwide, especially in the low- and middle-income countries. Asthma is controlled with inhaled corticosteroid (ICS) with as-needed or daily low-dose therapy. A step-up therapy to daily combination treatment with low- or medium-dose ICS/long-acting β-agonist (LABA) may be required for those with persistent symptoms. Asthma control levels are low despite the availability of many therapies. The efficacy of inhaled asthma therapy is dependent on the efficiency and reliability with which the drug is delivered to the lungs. Combination of an ICS and a LABA in a single inhaler is a safe, effective, and convenient treatment option for asthma management. Fluticasone and formoterol in combination ensure high potency action against anti-inflammation and rapid bronchodilation, and is a well-established ICS-LABA dual therapy. Rapid bronchodilator action of formoterol and fluticasone's long-term action against inflammation are vital clinical attributes for optimal asthma maintenance treatment. Fluticasone/formoterol combination therapy is an efficacious and safe alternative treatment option for patients with moderate to severe asthma. The combination of the two in a single inhaler is beneficial with regards to ease of administration and patient compliance.

Keywords: Asthma, Combination therapy, Fluticasone propionate, Formoterol fumarate

INTRODUCTION

Asthma is a major non-communicable disease worldwide. The public health consequences of asthma are major for children and adults.[1] Asthma is highly prevalent worldwide. The prevalence is high in developed countries and is increasing in the developing countries. With many countries not reporting prevalence and with no accurate

statistics, the true global burden of asthma is difficult to determine.[2]

Asthma: burden and triggers

The prevalence, severity, and mortality of asthma varies from one geographical region to the other. Though the high-income or the developed countries report higher prevalence of asthma, most of the asthma-related mortality is in the low- and middle-income or developing countries. The global epidemic of asthma is still continuing, especially in the developing world, but seems to have subsided in some of the developed countries. Globally, about 300 million people have asthma. It is estimated that by 2025, another 100 million may be affected. Asthma is ranked 16th among the leading causes of years lived with disability. Asthma ranks 28th among the leading causes of burden of disease measured by disability-adjusted life years.[1] India has more than 15 million asthmatics, and more than 10% of them are children as per the World Health Organisation.[3]

The exact prevalence and true burden of asthma in India is unknown or underestimated.[4] There were 37.9 million (35.7–40.2) cases of asthma in India in 2016.[5] The asthma-related mortality rate is the largest worldwide at 22.3%. Every year, an average of 8.4 exacerbations are reported among Indian patients with asthma, each episode lasting about 4 days.[4] Asthma is a complex multifactorial disorder. It occurs due to the interactions between genetic susceptibility, host factors, and environmental exposures.[1] Female gender, increasing age, low socioeconomic status, tobacco smoking, and family history in a 1st degree relative are associated with a higher chance of developing asthma.[3] As per the Asia-Pacific asthma insights and management (AP-AIM) survey, almost 50% of the asthmatics in India reported polluted air with dust as the main trigger factor (49%). Other asthma triggers were climate variations (27%), toxic substances (24%), smoking (23%), and cold beverages (29%).[6]

Managing asthma: recommended options

Achieving good control of the symptoms, reducing the exacerbations, and improving the quality of life are the main treatment goals in managing patients with asthma. The level of treatment depends on the level of severity of asthma (Figure 1). This approach is generally recommended by various asthma treatment guidelines and is effective in most patients.[7] Accomplishing and sustaining disease control with the lowest possible medication is the treatment strategy in asthma.[3]

Low-dose ICS/formoterol as-needed is recommended by the global initiative of asthma (GINA) guidelines in mild asthma (step 1 and 2). It is a preferred choice to reduce the risk of severe exacerbations and asthma-related deaths. ICS/formoterol is the preferred choice of reliever medication for patients on maintenance treatment across all steps of the asthma treatment algorithm. As a reliever therapy, ICS/formoterol is more effective and safer than short-acting β-agonist (SABA) across all steps of the asthma treatment algorithm.[9]

Fluticasone and formoterol in single inhaler: beneficial clinical attributes in asthma

Combination of fluticasone and formoterol (FF), a potent ICS and a LABA in a single aerosol inhaler is found to have a rapid onset and longer duration of action (due to LABA), and good topical potency and low systemic bioavailability (due to ICS) (Figure 2).[10]

Dual therapy of fluticasone along with formoterol (ICS-LABA dual therapy) is well-established and widely available globally. Fixed combination inhalers of ICS/LABA are clinically preferred for initiating therapy in Indian asthmatic patients as it is convenient and improves patient compliance. The vital clinical attributes with the combination are long-term action against inflammation with fluticasone, and quick and sustained bronchodilation with formoterol for ideal maintenance therapy.[4]

A pooled analysis of 5 randomised studies in patients with asthma demonstrated fluticasone/formoterol to improve lung function, asthma symptoms, control of asthma, and reduce the risk of exacerbation. It has a good safety and tolerability profile compared to the fluticasone monotherapy.[11]

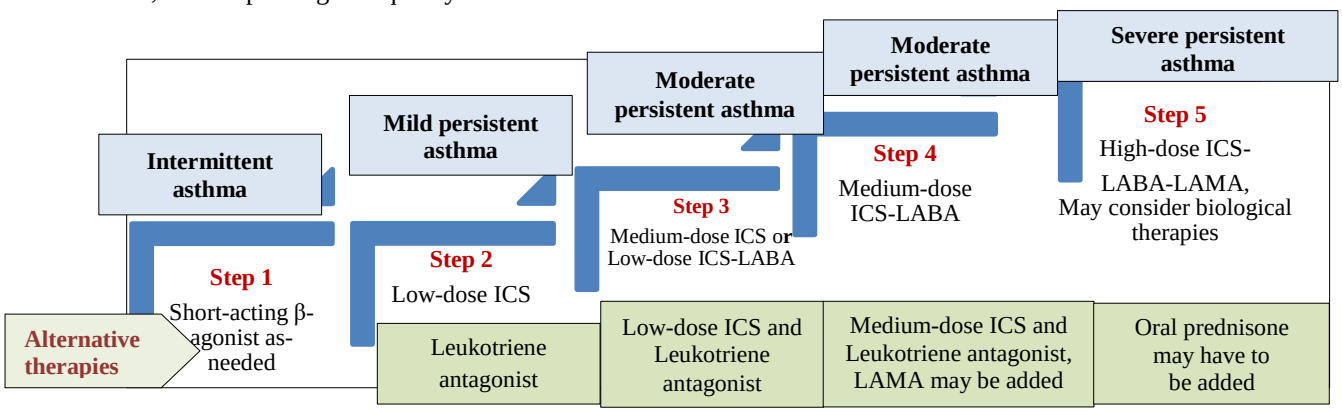

Figure 1: Stepwise treatment approach of asthma.[8]

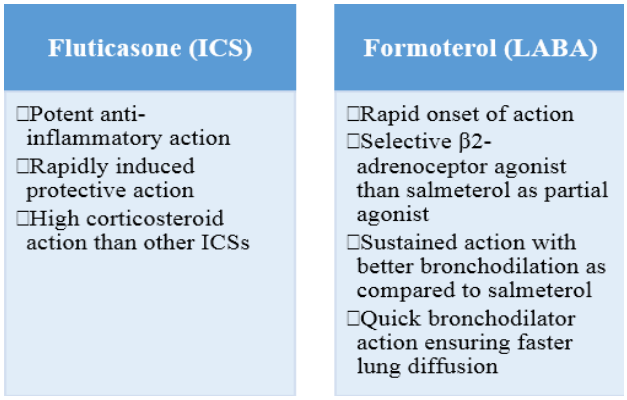

Figure 2: Benefits of fluticasone and formoterol.

Rapid bronchodilation with FF

The efficacy of FF is comparable to fluticasone/salmeterol (FP/SAL) in mild to moderate severe asthma and persistent asthma. FF is superior to FP/SAL in terms of time to onset of action. FF as a treatment option is as effective as FP/SAL, but with more rapid onset of action.[12] Patients with well-controlled asthma can be switched to FF from FP/SAL with no compromise in control of asthma and risk of exacerbation. However, one needs to be cautious while stepping down ICS/LABA in patients with a history of 1 or more exacerbations in the previous year, even if the patient is stable and well-controlled in the past 3 months.[13]

FF (twice-daily) has shown rapid and sustained improvements in lung function and asthma control in mild to moderate severe asthma. The improvements with combination of FF is greater than that with placebo or either of them in monotherapy, and similar to either of them administered concurrently via separate inhalers. The onset of bronchodilation with FF is faster and the rapid onset of action perceived by the patient could have a positive impact on adherence to therapy.[14]

FF provides more rapid onset of bronchodilation than FP/SAL over the first 120 min post-dose on day 0 (hazard ratio [HR] equals to 1.47 [95% confidence interval {CI} 1.05-2.05]) and day 84, HR equals to 1.77 [95% CI 1.14-2.73]).

Odds of achieving bronchodilation within 5 min of dosing almost 4-times higher on day 0 (OR=3.97 [95% CI 1.96-8.03]).

Odds of achieving bronchodilation within 5 min of dosing almost 10-times higher on day 84 (OR=9.58 [95% CI 2.14-42.90]).

Odds of achieving bronchodilation within 120 min post-dose about 2-fold higher on both days.

Overall percentage increase in least-squares (LS) mean forced expiratory volume in 1 second (FEV1) during the 120 min post-dose period was significantly greater on day 0 (LS mean treatment difference: 4.70% [95% CI 1.57-7.83]; p=0.003) and day 84 (2.79% [95% CI 0.65-4.93]; p=0.011).[15]

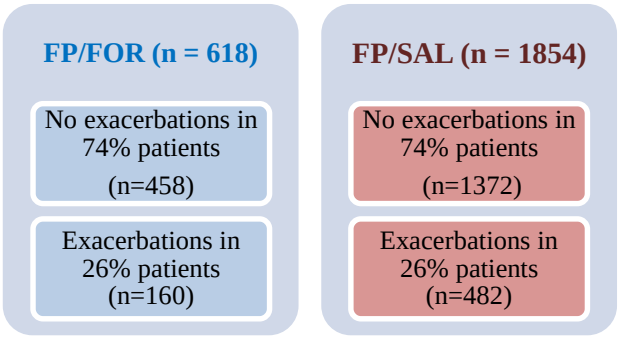

Figure 3: Asthma exacerbations (ATS/ERS definition) with FP/FOR versus FP/SAL16.

Effects of initiating/switching treatment to FF

FF, a novel combination has proven to be a promising option for managing asthma and is highly valued by most physicians. Changing to, or initiating combination therapy with FF, is non-inferior to continuing or initiating FP/SAL treatment with no severe exacerbation and lower average annual cost compared to continuing or initiating treatment with FP/SAL (Figure 3).[16] Formoterol-based combinations are usually preferred by physicians due to its faster action. It is a preferred choice for patients with difficult asthma and non-compliance. The symptom control is better with fewer side effects with FF when compared to budesonide/formoterol (BF). FF is mostly preferred in younger, or uneducated patients where compliance post using the inhaler like gargling would be difficult, and in patients with severe asthma, and patients who require long-term management of asthma. FF has sustained FEV1 over a longer period of time and also provides a better response than BF.

Real-world effectiveness and safety of fluticasone and formoterol

The real-world evidence has found FF to be a safe and efficacious treatment option for asthma (Table 1).

FF versus other ICS/LABA in asthma control

The therapeutic profile ICS/LABA in fixed-dose combinations (FDCs) is well-documented in asthma and the safety and efficacy of Bud/Form is well-established, and it is widely prescribed. However, FF in a single inhaler (administered via pMDI) which is a relatively newer option offers the advantage of a highly potent anti-inflammatory agent and a rapid-acting bronchodilator. FF may be an efficacious alternative that could have a positive impact on asthma outcomes (Table 2).[20]

FF when compared with other ICS-LABA formulations, provides faster onset of action, superior improvement in

lung function, comparable asthma control, and better safety with lower occurrence of pneumonia (Table 3).[21]

Use of FF in asthma: Indian perspective

A prospective, open-label, non-comparative, observational, 24-week multicentre study which was the 1st real-world study from India by Ghoshal et al compared the efficacy and safety of FF in adult patients with persistent asthma. The study included patients >18 years of age with persistent asthma who were already taking FF combination capsules (100/6 mcg or 250/6 mcg) or were uncontrolled on other treatments and required a change in their treatment to FF FDC as per the treating physician's discretion. The mean change in asthma control test (ACT™) at 4, 8, 16, and 24 weeks were the primary outcome measures. The mean ACT™ score increased from 14.9±3.26 (95% CI: 14.58, 15.22) at baseline to 21.6±2.75 (95% CI: 21.28, 21.83) at week 24; a mean change in ACT™ score of 6.7 (95% CI: 6.32, 7.06; p<0.0001). There was a significant continuous increase in the mean change in ACT™ score from baseline - at week 4, week 8, and week 16 that were also significant (p<0.0001) (Figure 4). The proportion of patients achieving asthma control increased from 8.4% at baseline to 80.78% at week 24 (10-fold increase), and the proportion of patients with uncontrolled asthma (as per ACT™) decreased from 59.8% at baseline to 2.3% at week 24. There was a continuous increase in the proportion of patients experiencing symptom-free days and nights from baseline to week 24. FF was safe and well-tolerated with a good safety profile over a period of 24-weeks and a well-tolerated treatment option for long-term asthma management.[22]

Table 1: Real-world studies on efficacy and safety of combination of fluticasone and formoterol.

Study	Study design	No. of subjects	Efficacy and safety of FF single inhaler
Mansur et al, 2013[17]	A 12-month open-label study in 5 European countries in patients ≥12 years with mild to moderate severe asthma for >1 year and treated with twice-daily FF	413	Exacerbations of asthma in 11.2% patients
			No abnormal trends or clinically important or dose-response–related changes in vital signs or laboratory tests
			AEs in 36.9% of the patients, mostly mild to moderate, only 3.8% study was drug–related (most common - nasopharyngitis, dyspnoea, pharyngitis, and headache in >2% of the patients)
Backer et al, 2018[18]	Post-authorisation safety study in 8 European countries – a 12-month observational study of outpatients with asthma aged ≥12 years (mean age 47.7 years)	2539	Patients with controlled asthma: increase from 29.4% at baseline to 67.4% at the end of study based on the ACT score ≥20
			Patients with severe exacerbation: decrease to 9.8% during the study compared to 35.8%, in the year prior to enrolment
			AE in 60% patients, only 10.2% possibly related to FF combination (exacerbation of asthma, 2%; dysphonia, 1.8%; cough, 1.1%) with no serious AEs with FF
Price et al, 2020[19]	Historical, longitudinal cohort database study - CPRD database (UK primary care) of patients with asthma ≥18 years prescribed either FF versus another comparator (licensed product)	41,609	Incidence of adverse outcomes with FF is similar to, or lower than other combinations
			incidence of any new adverse outcome: 24.75/100 person years with FF; 31.19/100 with FP/SAL; 25.16/100 with BUD/FORM
			Lower risk of cardiac arrhythmias and ischaemia with FF: 1.81/100 person years compared to FP/SAL DPI (3.34/100 person years), and BUD/FORM (1.93/100 person years)
			Lower risk of pneumonia with FF: 0.56/100 person years compared to FP/SAL DPI (1.34/100 person years), and BUD/FORM (0.67/100 person years)
			Lower risk of anxiety/depression with FF: 5.72/100 person years with FF compared to FP/SAL DPI (6.87/100 person years), and BUD/FORM (6.54/100 person years)

ACT: Asthma control test; AE: adverse event; CPRD: clinical practice research data link; FF: fluticasone/formoterol; BDP: beclomethasone; BUD: budesonide; SAL: salmeterol; DPI: dry powder inhaler; MDI: metered-dose inhaler; FORM: formoterol

Table 2: FF versus bud/form: efficacy on multiple measures at 12 weeks in moderate to severe persistent asthma.[20]

Efficacy endpoints	Flu/form	Bud/form	P value
Improvement in mean pre-dose morning PEF	48.07 (±56.58) l/min	49.03 (±46.20) l/min	<0.0001

Continued.

Efficacy endpoints	Flu/form	Bud/form	P value
	[90% CI of mean change=38.87, 57.28]	[90% CI of mean change=41.40, 56.66]	
FEV1	0.19 L	0.21 L	<0.001
Median symptom-free days	0.71	0.91	0.03 NS
Median symptom-free nights	0.96	0.96	NS
Rescue medication use	0	0	-
Day- and night-time symptom scores	0	0	-

PEF: Peak expiratory flow; FEV1: forced expiratory volume in one second; flu/form: fluticasone/formoterol; bud/form: budesonide/formoterol

Table 3: FF versus other ICS-LABA: clinical outcomes.[21]

Outcome	Comparators	Result
Onset of action	FF versus sal-flu	FF provides faster onset of bronchodilation
Lung function	FF versus sal-flu or form-bud	FF provides better improvement in lung function
Asthma control	FF versus sal-flu or form-bud	FF offers superior asthma control
Asthma-related QoL	FF versus sal-flu or form-bud	FF offers better QoL
Long-term risk of pneumonia	FF versus sal-flu or form-bud	Least with FF

FF: Formoterol/fluticasone, sal: salmeterol; flu: fluticasone; form: formoterol; bud: budesonide; QoL: quality of life

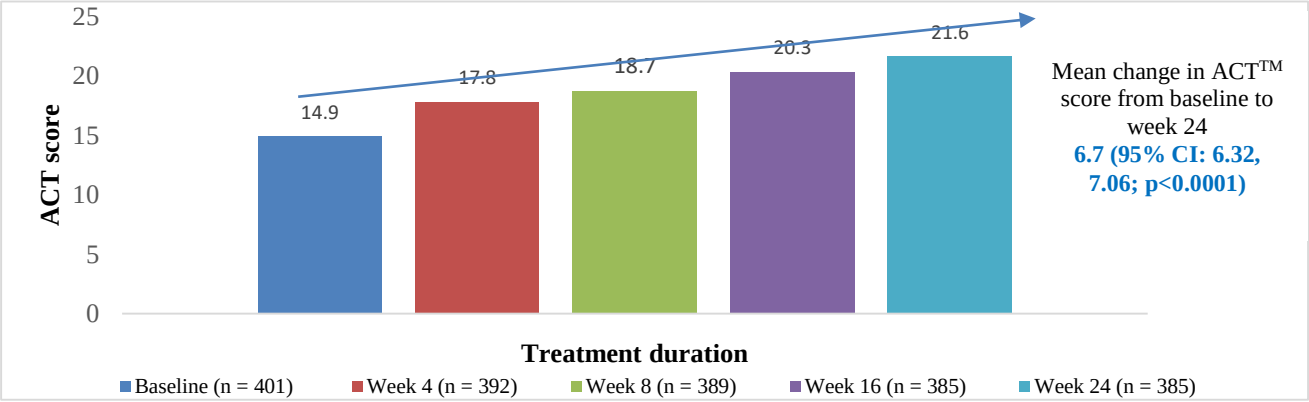

Figure 4: ACT score over 24 weeks.

Improved adherence with fluticasone and formoterol

FF FDC is a promising treatment option for asthma in single inhaler therapy that can improve patient compliance. It could help reduce the risk of symptom-guided isolated bronchodilator overuse and also the discontinuation of therapy. It helps reduce health care costs (separate drug inhalers), and also respiratory-related deaths and life-threatening episodes.

FF with its unique peculiarities is delivered via a single inhaler, and is a valuable treatment option for asthma. The combination of fluticasone and formoterol is unique due to their pharmacologic properties that are advantageous when it comes to treatment of asthma. The rationale behind combining both is to provide adequate symptomatic relief with a high-potency topical anti-inflammatory effect and rapid onset of bronchodilation. Single inhaler helps avoid the risk of bronchodilator overuse without ICS by using two drugs or two separate inhalation devices. The potency of the ICS and the speed of onset of the LABA is crucial in ICS/LABA combination for its quick and sustained action.[10]

CONCLUSION

Asthma control is suboptimal many times despite the treatment. Fluticasone and formoterol used in combination is uniquely advantageous in the treatment of asthma due to its unique pharmacologic properties. Fluticasone/formoterol used in combination in a single inhaler is superior to either of the components administered as a monotherapy or concurrently via separate inhalers. The efficacy and safety profile of fluticasone/formoterol is similar to fluticasone/salmeterol and budesonide/formoterol, but fluticasone/formoterol has the additional benefit of rapid bronchodilation. The real-world evidence shows that fluticasone/formoterol in a single inhaler has excellent efficacy and safety profile with good tolerance. These attributes may have better patient compliance to the treatment regimen that helps improve asthma control.

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