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Research Article

A prescription event monitoring study to assess safety and health outcomes of Airtec SF® (salmeterol fluticasone propionate combination) in Indian population

Ashok A. Mahashur[1]*, K. Korukonda[2], Vikram Sobti[2], Amit Bhargava[2]

[1]Consultant Pulmonologist, Hinduja Hospital, Mumbai, Maharashtra, India, [2]Medical Services, Glenmark Pharmaceuticals, Mumbai, Maharashtra, India

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***Correspondence to:**
Ashok A. Mahashur,
Email: mahashuraa@hotmail.com

ABSTRACT

Background: Asthma management has been fraught with several challenges especially for partly or uncontrolled cases. Incremental dosage strategy with salmeterol, fluticasone propionate combination offers stable yet effective control of symptoms preventing further exacerbations. However, there is limited evidence available on the need and safety profile of this incremental dosage strategy with the combination especially in Indian settings. To examine the safety and adverse clinical outcomes of Airtec SF when prescribed in patients with well- or poorly controlled persistent asthma.
Methods: Based on the principle of prescription event monitoring (PEM) for safety reporting, this study was conducted at 20 centers across India. PEM study booklets with study questionnaire were provided to capture information related to adverse "events" during the observation period of 30 days.
Results: Data of 384 patients were analyzed, with a mean age 44.5 years. 39% (n=150) were newly diagnosed and 61% (n=234) being in poorly controlled asthma status (i.e., partly or uncontrolled asthma). Of them, 42% (161), 44% (n=169) and 14% (54) patients were diagnosed with mild, moderate or severe persistent asthma, respectively. These were prescribed with metered-dose inhaler (n=187) or dry powder inhaler (n=197) formulations. 56% (n=216) patients suffered from concomitant allergic rhinitis. Among newly diagnosed patients with moderate to severe asthma dosage were tapered in 5.5% (n=3) cases. Dosage consistency was well-maintained in 98.2% (n=155) among partial or uncontrolled asthmatics with moderate to severe asthma with exacerbation rate of 1.9% (n=3). Adverse events including infective pneumonitis and upper respiratory tract infection were transient with none requiring treatment withdrawal.
Conclusion: Use of Airtec SF was safe and well-tolerated with a negligible rate of exacerbations in Indian population especially amongst poorly controlled asthma patients.

Keywords: Asthma, Obstructive lung disease, Salmeterol, Fluticasone propionate, Prescription event monitoring

INTRODUCTION

The management of obstructive lung diseases including Bronchial asthma has been fraught with several challenges despite the availability of several options including inhaled beta2 agonists/corticosteroids, xanthine derivatives, or anti-immunoglobulin E (IgE) therapy. The combination of inhaled corticosteroid (ICS) + long-acting β2-agonist (LABA) as maintenance therapy is often recommended in asthma management for optimal control of symptoms in Global Initiative on Asthma (GINA) guidelines.[1,2] OPTIMA, FACET,[3] and GOAL[4] studies have shown that there is a remarkable improvement in asthma control using low doses of ICS + LABA combination using formoterol-budesonide (FB) or salmeterol-fluticasone combinations (SFC). The CONCEPT study with SFC further demonstrates stable yet effective control of symptoms while minimizing the exacerbation rates. Similarly, the safety profile of the combination is well-established with few adverse effects being reported including pneumonia, hoarseness, dysphonia and candidiasis due to fluticasone propionate and headache, tremor, palpitations have been associated with clinical use of salmeterol.[5]

Since incremental dosing strategy with ICS/LABA combination forms an integral part of the management algorithm especially for partly or uncontrolled asthma patients as suggested by GINA, a prescription event monitoring (PEM) was designed to evaluate the safety profile of SFC in this critical population of asthma. PEM is a well-established, noninterventional, observational tool of post-marketing surveillance when prescribing drugs in clinical practice, on a national level while including patients with comorbidities and concomitant medications.[6] Importantly, in a PEM study, there is no need for the prescribing doctor to give an opinion about whether an "event" might have been caused by the drug. At the end of the observation period, these data would be submitted for subsequent analyses.

This PEM was, therefore, conducted, to better understand the safety profile or any adverse health outcome with SFC when administered in outpatient clinical settings of India.

METHODS

Newly diagnosed or referred cases of bronchial asthma with partly or uncontrolled asthma were prescribed Airtec SF metered-dose inhaler (MDI) (250/25 mcg) or dry powder inhaler (DPI) (250/50 mcg) formulations for 90 days. These patients were, however observed in this PEM for a period of 30 days for any adverse "events" using a standardized questionnaire or PEM report form. The PEM report forms were distributed among the clinicians seeking details of the patients at baseline i.e., (day 0) and at the end of the observation period.

The term "events" in PEM, is defined as suspected reaction to formulation, unexpected deterioration or improvement in the medical condition, any reason for referral or hospitalization or any complaint of sufficient clinical importance. During the observation period, each patient was observed for any "events" that may arise thereof that noted in PEM report form and notified immediately to sponsor pharmacovigilance center in case of serious adverse events including death, disability, hospitalization, or congenital anomaly. At the end of the observation period, the PEM booklets were collected. Based on the safety profile or observations with the drug, additional follow-up was done with the prescribing doctors for confirmation and causality assessment based on the pharmacological properties, concurrent disease or drug use.

Descriptive statistics was used to present the data.

RESULTS

This study was conducted with at 20 representative centers across India between June and September 2013. Data of 384 patients were collected at the end of the observation period with a mean age of 44.5 years with 58% and 40% (M/F), respectively. Most patients had concomitant comorbidities including Type 2 diabetes mellitus or hypertension (Table 1).

Baseline demographics showed mild (42%) moderate to severe (58%) persistent asthma that was further categorized as partly or uncontrolled patients (Figure 1).

Of all the newly diagnosed cases of mild persistent asthma, 42 (49%) were started with MDI formulation and 44 (51%) were started with DPI formulation during the study period (Figure 2).

223 (61%) patients with moderate-severe asthma were administered MDI (n=110, 49.3%) or DPI (n=113, 50.7%) formulations as highlighted in Tables 2 and 3, respectively.

Table 1: Baseline demographic characteristics of the asthmatic patients.

Demographic characteristics	n (%)
Male	221
Female	153
Age (mean)	44.5 years
Severity of symptoms	
Mild persistent asthma	161
Moderate persistent asthma	169
Severe persistent asthma	54
Medical history	
Hypertension	107
Type II DM	61

DM: Diabetes mellitus

Table 2: Dose strategy for moderate-severe asthma patients during the study (MDI).

Airtec SF MDI 250/25 mcg				
	1 puff BID		≥2 puff BID	
	Baseline	30 days	Baseline	30 days
New	0	3	21	18
Partly controlled	0	7	46	39
Uncontrolled	1	1	42	42
Total	1	11	109	99

MDI: Metered-dose inhaler, SF: Salmeterol+fluticasone propionate

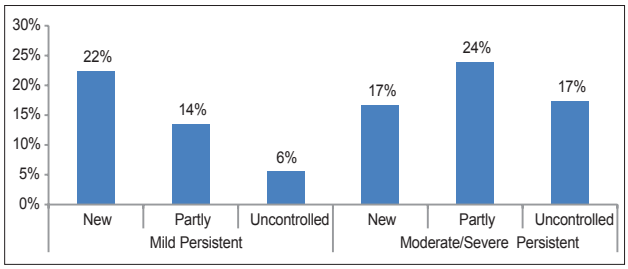

Figure 1: Baseline asthma control rates in newly diagnosed or referred cases of bronchial asthma.

Baseline symptoms

The baseline symptoms were recorded of the patients at time of enrollment in the study. 324 (84%) of the patients had daytime asthma symptoms (>2 times/week); 266 (69%) of the patients had sleep disturbance or waking up at night due to illness. Among the category distribution, 104 (27%) and 46 (12%) of the patients were suffering from partly or uncontrolled asthma, respectively (Figure 3).

Co-morbid conditions

The patients enrolled in the study were carefully evaluated for the comorbid conditions. More than half of the patients, (56%) had allergic rhinitis; which was followed by history of cardiovascular diseases along with hypertension and noninsulin-dependent DM, (32%) and (9%), respectively. Gastroesophageal reflux disease (GERD) was observed in 6% of the patients and sleep disturbance was observed in 5% of the patients (Table 4).

The most common comorbid condition allergic rhinitis was observed in 218 patients with concomitant medication of either montelukast, oral antihistaminic or anti-IgE therapy (omalizumab) as highlighted in Figure 4.

These were mild to transient during the observation period with none requiring treatment (Figure 5).

Table 3: Dose strategy for moderate-severe asthma patients during the study (DPI).

Airtec SF DPI 250/50 mcg				
	1 Inhalation		≥2 Inhalation	
	Baseline	30 days	Baseline	30 days
New	10	5	33	38
Partly controlled	19	17	27	29
Uncontrolled	14	13	10	11
Total	43	35	70	78

DPI: Dry powder inhaler

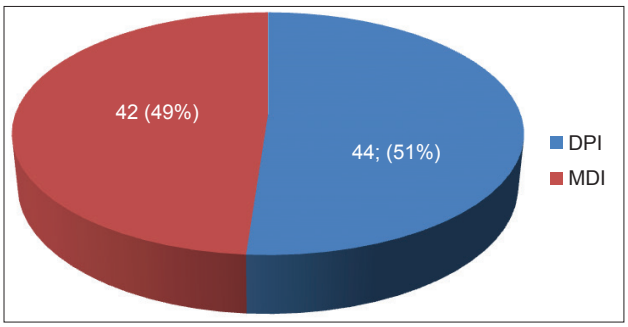

Figure 2: Newly diagnosed mild persistent cases on MDI or DPI.

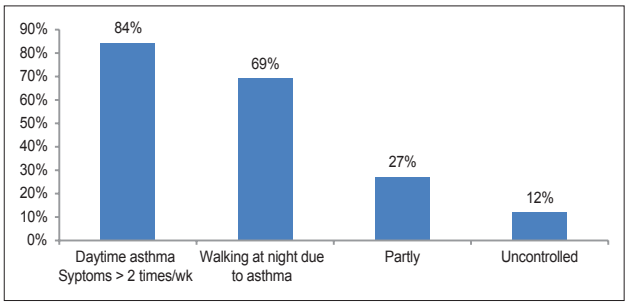

Figure 3: Severity of asthma symptoms.

DISCUSSION

Uncontrolled asthma often represents a clinical dilemma with several factors related to drug, device or patient compliance for consideration. The ensuing complications of inadequate control often presents as "exacerbation" that are often associated with high morbidity either requiring hospitalization or poor quality of life (QoL). ICS + LABA combination including SFC administered as MDI or DPI formulations for up to 3 years offers optimal yet stable control of symptoms minimizing the chances of

Table 4: Baseline demographics details for patients with comorbid conditions.

Comorbid conditions	n (%)
Allergic rhinitis	216 (56)
Cardiovascular disease	123 (32)
Type 2 diabetes	33 (9)
GERD	22 (6)
Obstructive sleep disorder	19 (5)
Others	10 (3)

GERD: Gastroesophageal reflux disease

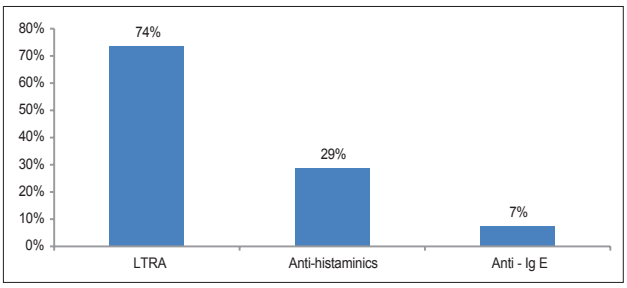

Figure 4: Medications used in allergic rhinitis patients.

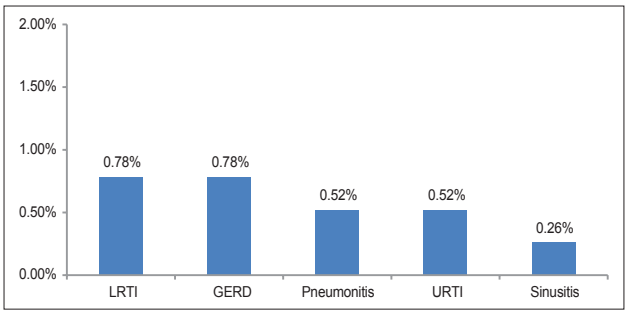

Figure 5: Adverse events during observation period (n).

exacerbations as highlighted by GOAL[4] and CONCEPT[7] studies. The reported incidence of exacerbations with SFC in GOAL study has been around 2.3% in well-controlled asthma.[4] In EXCEL study evaluating the impact of salmeterol/fluticasone propionate and FB combinations in adults with persistent asthma, the overall exacerbation rate in salmeterol fluticasone group was 2.6.[8]

This PEM successfully observed 384 patients for any adverse health outcomes while administering SFC for 30 days. Overall six cases (1.5%) reported exacerbation episodes particularly in the subgroup with baseline status of poorly controlled asthma. All of them were managed conservatively with lone case requiring hospitalization. Causality assessment revealed probable underlying continued factors like exposure to dust, smoke including noncompliance to inhalational therapy. This exacerbation rate was, however comparable exacerbation reported in GOAL study of 2.8%.

Among newly diagnosed patients with moderate to severe asthma, dosage was tapered in 5.5% (n=3) cases. Dosage consistency was well-maintained in 98.2% (n=155) among poorly controlled patients with moderate to severe asthma. Again exacerbation rate for this group of patients was just 1.9% (n=3) highlighting near optimal control with SFC in this high-risk category of patients.

Adverse events were mild and transient with none requiring treatment withdrawal. GERD was reported in three patients, which was expected in the patients who had baseline symptoms that were further aggravated by noncompliance to proton pump inhibitors therapy that were initially prescribed. Infective pneumonitis was developed during the study period in three patients. This is a well-documented clinical adverse event with SFC use.[9] These patients were managed with oral antibiotics and did not require any indoor admission for the management.

CONCLUSION

Poorly controlled asthma as partly or uncontrolled status is often associated with high morbidity and impaired QoL due to the underlying pathophysiological process with increased exposure to systemic side effects of incremental dosage strategy required in these cases. Clinical use of Airtec SF offers safe yet stable control of symptoms with a negligible rate of exacerbations in Indian population especially among poorly controlled asthma patients.

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REFERENCES

1. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. Am J Respir Crit Care Med. 2001;164:1392-7.
2. National Institutes of Health, National Heart, Lung, and Blood Institute. Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Institutes of Health; 2012.
3. Tattersfield AE, Postma DS, Barnes PJ, Svensson K, Bauer CA, O'Byrne PM, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. Am J Respir Crit Care Med. 1999;160(2):594-9.
4. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med. 2004;170(8):836-44.
5. Perrio MJ, Wilton LV, Shakir SA. A modified prescription-event monitoring study to assess the introduction of Seretide Evohaler in England: an example of studying risk monitoring in pharmacovigilance. Drug Saf. 2007;30(8):681-95.
6. Mann RD. Prescription-event monitoring -recent progress and future horizons. Br J Clin Pharmacol. 1998;46:195-201.
7. FitzGerald JM, Boulet LP, Follows RM. The CONCEPT trial: a 1-year, multicenter, randomized,double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. Clin Ther. 2005;27(4):393-406.
8. Dahl R, Chuchalin A, Gor D, Yoxall S, Sharma R. EXCEL: a randomised trial comparing salmeterol/fluticasone propionate and formoterol/budesonide combinations in adults with persistent asthma. Respir Med. 2006;100(7):1152-62.
9. Ferguson GT, Calvezley PM, Andeison ZA, Celli B, Jenkims C, Jones PN, et al. The towards a revolution in COPD health (TORCH) study: fluticasone preprionate/ salmeterol in well tolerated in patients with COPD over 3 years. Chest. 2006;130:178S.

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