Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/19602
DOI URL: http://dx.doi.org/10.21474/IJAR01/19602

RESEARCH ARTICLE

FLUTICASONE FUROATE AND VILANTEROL (FF/VI) VERSUS FLUTICASONE PROPRIONATE AND FORMOTEROL (FP/FM) AS MAINTENANCE THERAPY IN STABLE ASTHMATIC PATIENTS- A COMPARATIVE STUDY

Kolli Kanchana, P. Chakradhar
Department of Respiratory Medicine, Santhiram Medical College And General Hospital, Nandyal.

Manuscript Info

Manuscript History
Received: 31 July 2024
Final Accepted: 31 August 2024
Published: September 2024

Key words:-
Fluticasone Furoate (FF), Vilanterol (VI), Fluticasone Propionate (FP) and Formoterol Fumarate (FM)

Abstract

Background: Fluticasone furoate (FF) is a novel long-acting inhaled corticosteroid (ICS). Vilanterol (VI) is a long-acting beta2-agonist (LABA) that binds to the beta2-adrenoceptor on the airway smooth muscle, producing bronchodilation. The corticosteroid fluticasone propionate (FP)and the long-acting β_2-adrenoceptor agonist (LABA) formoterol fumarate (FM) have been combined in a single, pressurized, metered-dose, aerosol inhaler for the maintenance treatment of patients aged ≥12 years with persistent asthma.This study evaluated the efficacy and safety of Fluticasone furoate 100 mcgandVilanterol 6 mcg versus Fluticasone proprionate 250 mcg and Formoterol 25 mcg for 12 weeks in patients with persistent asthma as maintenance therapy.

Methods and Materials: A hospital based comparative study was conducted among stable asthmatic patients attended to Santhiram Medical College and General Hospital, Nandyal during January 2024 to June 2024(6months) by using convenient sampling method with sample size 60. Study tool was pre-designed, pre-tested, asthma control questionnaire5 (ACQ5),asthma control test (ACT) and Ask 12 adherence barrier survey.

Results: Among 60 patients, 30 patients (Group1) were given Fluticasone furoate and Vilanterol and another 30 patients (Group 2) were given Fluticasone proprionate and Formoterol. All the patients (both the treatment groups) completed the 12 weeks treatment period. Improvements from baseline in 0- to 24-h wmFEV1 were observed with both FF/VI (376 mL) and FP/FM (353 mL); the adjusted mean treatment difference was not statistically significant. There were no differences between 0- to 4-h serial wmFEV1, asthma control test, ACQ5 and Ask 12 adherence barrier survey. There was no difference in reported exacerbations between treatments. Adverse events reported in the present study were not significant. Both treatments were well tolerated.

Conclusion: The present study shows that the efficacy of once daily Fluticasone furoate and Vilanterol was not inferior as compared to the efficacy of twice daily Fluticasone proprionate and Formoterol as maintenance therapy in stable asthmatic patients. Howevertreatment with once daily FF/VI has the advantage of forgetfulness and inconvenience of inhalation.Henceonce daily FF/VI can be also useful

Corresponding Author:-Kolli Kanchana
Address:- Department of Respiratory Medicine, Santhiram Medical College And General Hospital, Nandyal.

for stable asthmatic patients as maintenance therapy as FF/VI DPI treatment.

……

Introduction:-

Despite the availability of effective preventative therapies, asthma remains a major global healthcare problem, placing a significant burden on healthcare systems, patients and their families [1,2].

According to the World Health Organization, approximately 15 million disability-adjusted life years are lost annually due to asthma and approximately 1 in every 250 deaths worldwide are attributable to the disease [3].

As the cornerstone of anti-inflammatory therapy for all severities of asthma, inhaled corticosteroids (ICS) provide a number of benefits including control of asthma symptoms, improvement in lung function, decrease in airway hyper-responsiveness [4], reductions in asthma exacerbations, and reduced asthma mortality [5, 6]. As a reflection of this, the current Global Initiative for Asthma guidelines recommend an ICS as a first-line controller therapy for asthma patients of all ages, who are not controlled on an as-needed, rapid acting beta2 agonist [2].

Despite comprehensive guidelines, a significant proportion of patients continue to have asthma symptoms that remain uncontrolled [7, 8].

24- hour coverage might be expected to provide greater asthma control; however, the complexity of asthma treatment regimens and consequent poor adherence to treatment have been cited as major contributing factors to the current poor level of global asthma control [2, 9, 10]. Once-daily treatments offer increased convenience, with the potential for improved adherence and asthma control [11].

Fluticasone furoate (FF) is a novel ICS and is structurally different to fluticasone propionate (FP). FF has an ester derived from 2-furoic acid at the C-17α position that replaces the simpler propionate ester [12]. This feature of FF confers both greater affinity for and longer retention in respiratory tissues than FP [13]. FF remains active 24 hours after administration; therefore it is in development for use as a once-daily inhaled treatment for asthma. Data from an early phase clinical study demonstrated that the duration of action of FF extends beyond 24 hours and is therefore longer than that of FP, making FF potentially suitable for consideration of once-daily administration [14].

Fluticasone furoate, the mainstay of asthma treatment, lead to a reduction in both airway inflammation and airway hyper-responsiveness. Regular use leads to improvement in symptoms and lung function. ICSs are currently recommended as ‘preventer’ therapy for patients who use a ‘reliever’ medication (e.g. short-acting beta2 agonist (SABA), salbutamol) three or more times per week.

Vilanterol (VI) is a long-acting beta2-agonist (LABA) that binds to the beta2-adrenoceptor on the airway smooth muscle, producing bronchodilation. LABA therapy, which is well established in adults as part of the BTS Guidelines for the Management of Asthma, leads to improvement in symptoms and lung function and reduction in exacerbations. At present, the commonly used LABAs licensed for use in asthma management (formoterol and salmeterol) require twice-daily administration, whereas VI is a once-daily therapy.

At the present time, only one once-daily ICS/LABA combination (FF/VI) is available, and several other combination inhalers are recommended for twice-daily administration [15].

The corticosteroid fluticasone propionate (FP) and the long-acting β_2-adrenoceptor agonist (LABA) formoterol fumarate (FM) have been combined in a single, pressurized, metered-dose, aerosol inhaler for the maintenance treatment of patients aged ≥12 years with persistent asthma [16].

This study evaluated the efficacy and safety of Fluticasone furoate 100 mcg and Vilanterol 6 mcg versus Fluticasone proprionate 250 mcg and Formoterol 25 mcg for 12 weeks in patients with persistent asthma as maintenance therapy.

Methods and Materials:-

A hospital based comparative study was conducted among stable asthmatic patients attended to Santhiram Medical College and General Hospital, Nandyal during January 2024 to June 2024 (6months) by using convenient sampling method with sample size 60.

Patients were divided into two groups, treated with once daily Fluticasone furoate 100mcgand Vilanterol 25 mcg pm to Group 1 patients and twice daily Fluticasone proprionate 250mcg and Formoterol 6 mcg bid to Group 2 patients for12 weeks using dry powder inhaler (DPI).

Patients are assessed using spirometry, asthma control test (ACT), Asthma control questionnaire5 (ACQ-5) and Ask 12 adherence barrier questionnaire.

Ethics committee clearance was obtained before conducting the study.

Inclusion criteria-
Stable Asthmatic Patients
Those who are willing to participate voluntarily and give written informed consent.

Exclusive criteria -
Patients who are suffering fromother obstructive airway diseases like COPD, bronchiectasis and fibrosis and tuberculosis.

Those who are not willing to participate voluntarily and give written informed consent.

Statistical analysis
Data was collected by interview methodand recorded in a master chart using a Microsoft excel spreadsheet analysed by SPSS 25version.

Results:-

The present study included total of 60 stable asthmatic patients diagnosed with spirometrydivided into 2 groups. Among 60 patients, 30 patients (Group 1) were given Fluticasone furoate and Vilanterol (FF/VI) and another 30 patients (Group 2) were given Fluticasone proprionate and Formoterol (FP/FM). All the patients (both the treatment groups) completed the 12 weekstreatment period.

Patient demographics and baseline lung function are shown in table 1.

Mean age of the patients was 40.6 in group 1, 46.6 in group 2. In this study, 12 were males, 18 were females, among the patients 7 were former smokers, 5 were non-smokers in group 1 and 10 were males, 20 were females and 6 were former smokers, 4 were non-smokers in group 2 patients.Mean BMI of patients in group 1 was 24.2, 23.7 in group 2 patients.

Mean ± Standard deviation of Pre dose FEV1 was 1.716 ± 0.367 in group 1, 1.559 ± 0.407 in group 2 and Percent reversibility of FEV1 was 21.83 ± 7.183 in group 1,21.50 ± 5.131 in group 2 and FEV1 predicted was 2.49 ± 0.519 in group 1, 2.25 ± 0.556 in group 2 patients.

In the present study, we found that post bronchodilator FEV1 was high amongst group 1 patient's compared to group 2 patients.

Table 1:- Patient Demographics and Baseline Lung Function.

Patient characteristics	FF/VI 100/25 mcg n:30	FP/FM250/6mcg n:30
Age	40.6	46.3
Gender (M/F)	12/18	10/20
BMI (kg/m2)	24.2	23.7
Smoking status (Former/Never)	7/5	6/4

Predose FEV1	1.716±0.367	1.559±0.407
Percent reversibility of FEV1	21.83±7.183	21.50±5.131
FEV1 predicted	2.49±0.519	2.25±0.556

Efficacy Assessments

Lung Function:

Improvements from baseline in 0- to 24-hour serial wmFEV1 at week 12 were seen with both FF/VI (376 mL) and FP/FM (353 mL); however, the adjusted mean treatment difference was not statistically significant (−23mL; with in 95% CI, P = 0.128).

There were no differences in key secondary end points, including the change from baseline in individual serial wmFEV1 assessments over time at week 12. These showed sustained 24-h duration of action for both once-daily FF/VI and bid FP/FMat all time points.

There is no difference in the time to onset of bronchodilator effect (median time to ≥ 12% and ≥ 200 mL FEV1 over baseline at week 12), min in both groups61 in group 1, 60 in group 2.

No important differences were seen between FF/VI vs FP/FM for the secondary end points of time to onset of bronchodilator effect, 0- to 4-h serial wmFEV1 postdose at week 12 and change from baseline in clinic visit through FEV1 (prebronchodilator) at week 12.Secondary End Point results were shown below table 2.

Table 2:- Results of Secondary End Points.

Assessment	FF/VI	FP/FM	Difference FF/VI OD vs FP/FM BID, (95% CI)
Time to onset of bronchodilator effect (median time to ≥ 12% and ≥ 200 mL FEV1 over baseline at week 12), min	61	60	0.925 (0.767 to 1.108)
0-To 4-h serial wmFEV1 post dose at week 12, L	0.375±0.0174	0.410±0.0179	−0.035 (−0.082 to 0.018)
Change from baseline in clinic visit through FEV1 (pre bronchodilator) at week 12	0.281±0.0188	0.299±0.0193	−0.018 (−0.072 to 0.035)

Health Outcomes:

There were no significant difference present in the results of Asthma control test, Asthma control questionnaire 5 and Ask-12 adherence barrier survey that includes Adherence-related subscales likeinconvenience/forgetfulness, health beliefs and behaviourbetween group 1 and group 2 patients.

Health Outcomes Assessments and Ask-12 adherence barrier survey results were shown in table 3 and 4.

Table 3:- Results of Health Outcomes Assessments.

Assessment	Mean Score±SE From Baseline	Mean Score ± SE at Week 24	P value
ACT			
FF/VI	20.90±0.845	22.23±0.774	0.313
FP/FM	20.80±0.994	22.33±0.994	0.834
ACQ5			
FF/VI	0.35±0.42	0.39±0.51	0.748
FP/FM	0.29±0.41	0.39±0.54	0.180

Table 4:- Scoring of Ask-12 adherence barrier survey.

Ask12	FF/VI	FP/FM	P value
Total score	19.3±5.71	24.1±8.60	0.0366

Safety Assessments

There were no significant difference in the side effects in both treatment groups. However 1 (4%) patient had asthma exacerbation in treatment with FF/VI in group 1 and with FP/FM in group 2.Blood pressure and pulse rate were with in normal range in both treatment groups.

Nasopharyngitis was most common adverse event 10% in group 1, 13% in group 2 patients followed by head ache 7% in group 1, 10% in group 2 patients.

Results of adverse events and severe adverse events in the present study were shown in table 5.

Table 5:-Results of On-Treatment AEs, All SAEs.

Event	FF/VI (n:30)	FP/FM(n:30)
Nasopharyngitis	3 (10)	4 (13)
Head ache	2 (7)	3 (10)
URTI	2 (7)	1 (4)
Cough	1 (4)	1 (4)
Sinusitis	0	1 (4)
SAEs		
Asthma	1 (4)	1 (4)

24-hour Urine cortisol excretion did increase in both groups from baseline to week 12. There was no statistically significant difference between FF/VI and FP/FM in 24-hour Urine cortisol excretion at week 12 (0.95; with in 95% CI; P = 0.045).

Discussion:-

The present study of patients aged 12 years and more showed that efficacy of once daily FF/VI was not significantly different to twice daily FP/FM in stable asthmatic patients as maintenance therapy for the primary end point of 0- to 24-hour serial wmFEV1 at week 12 or for any of the secondary end points.

Secondary end points in the present study receiving FF/VI are consistent with the study by Woodcock A et al [17].

A number of studies have shown that nonadherence to asthma therapy is an important reason for loss of asthma control in some [18,19].

Adherence to the treatment schedule was high during the present study, although the artificial setting of a clinical trial may have encouraged normally nonadherers to take their medication. If poor adherence to the dosing schedule is an important factor in loss of asthma control, then once-daily dosing (as opposed to bid dosing) such as that provided by FF/VI may represent a more-convenient treatment option for patients in a real-world setting [20].

There is no significant differences in Asthma Control Test scores or in measures of quality of life (ACQ and Ask 12 adherence survey) were shown in the present study. A difference of 2.1was observed between groups on the ask12 survey test, but this difference was not statistically significant. The outcomes of the post hoc (post treatment) analysissuggest that FF/VI may provide clinically relevant improvements in certain patient-reported quality-of-life measures

However FF/VI has the advantage of reduced forgetfulness and inconvenience compared to FP/FM.

A potential effect of ICS treatment is reduction in UC levels as a result of suppression of the hypothalamic-pituitary-adrenal axis, although this usually only occurs at higher doses of ICS[21,22,23].

In the current study, clinically insignificant increases in UC levels from baseline were reported, and no statistically significant differences were observed between both treatment groups at week 12.

LABAs have occasional side effects, such as headache, tremor, and hypertension [24]. In the present study, no clinically relevant effects of FF/VI or FP/FM were found in measures of BP or pulse rate.

Adverse effects were not significant in both medications, and those AEs reported with FP/FM were consistent with those previously reported with this drug combination had the most common adverse events reported more than 2% in the study population included nasopharyngitis, pharyngitis and headache [25].

And those AEs reported with FF/VI nasopharyngitis (10%) and headache (7%) were consistent with those previously reported with this drug combination had the most common adverse events reported in the study population included nasopharyngitis (11%) and headache (8%) [17].

Most of the SAEs reported in the present study were single events, and none were considered treatment related. Asthma exacerbations requiring hospitalization occurred in one patient (4%) receiving FF/VI and one patient (4%) receiving FP/FF.

Asthma exacerbations were reported by 53 patients (11.2%): 46 mild to moderate and nine severe receiving FP/FM [25].

FF/VI and FP/FM were well tolerated, and FF/VI had a similar AE profile to FP/FM.

Conclusion:-

The present study shows that the efficacy of once daily Fluticasone furoate and Vilanterol was not inferior as compared to the efficacy of twice daily Fluticasone proprionate and Formoterol as maintenance therapy in stable asthmatic patients. However treatment with once daily FF/VI has the advantage of forgetfulness and inconvenience of inhalation in inhalation adherence barriers as compared to twice daily FP/FM. Side effects were not significant for both medications. Hence once daily FF/VI can be also useful for stable asthmatic patients as maintenance therapy as FF/VI DPI treatment.

Limitations

The present study had some limitations. Study had short study conduction period and limited sample size. However we used subjective assessment for adherence barriers irrespective of objective measures like dose counter and monitoring devices in this study.

To confirm comparable clinical effectiveness including asthma exacerbation and improving adherence barriers in different inhaled devices for controlled asthma maintenance therapy, a much larger and longer study would be required.

Conflicts Of Intrest

There were no conflicts of interest in the present study.

References:-

1.Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, FitzGerald JM: Economic burden of asthma: a systematic review. BMC Pulm Med. 2009, 9: 24-10.1186/1471-2466-9-24.

2.Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention. 2009, [http://www.ginasthma.org].

3. Masoli M, Fabian D, Holt S, Beasley R: Global Initiative for Asthma (GINA) Program: The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy. 2004, 59: 469-478. 10.1111/j.1398-9995.2004.00526.x.

4. Barnes PJ, Pedersen S, Busse WW: Efficacy and safety of inhaled corticosteroids. New developments. Am J Respir Crit Care Med. 1998, 157: S1-S53.

5. Pauwels RA, Löfdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A: Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. N Engl J Med. 1997, 337: 1405-1411. 10.1056/NEJM199711133372001.

6. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B: Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med. 2000, 343: 332-336. 10.1056/NEJM200008033430504.

7. Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, Weiss ST: Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. J Allergy Clin Immunol. 2004, 114: 40-47. 10.1016/j.jaci.2004.04.042.

8. Mintz M, Gilsenan AW, Bui CL, Ziemiecki R, Stanford RH, Lincourt W, Ortega H: Assessment of asthma control in primary care. Curr Med Res Opin. 2009, 25: 2523-2531. 10.1185/03007990903218655.
9. Kandane-Rathnayake RK, Matheson MC, Simpson JA, Tang ML, Johns DP, Mészáros D, Wood-Baker R, Feather I, Morrison S, Jenkins MA, Giles GG, Hopper J, Abramson MJ, Dharmage SC, Walters EH: Adherence to asthma management guidelines by middle-aged adults with current asthma. Thorax. 2009, 64: 1025-1031. 10.1136/thx.2009.118430.
10. Hermosa JL, Sánchez CB, Rubio MC, Mínguez MM, Walther JL: Factors associated with the control of severe asthma. J Asthma. 2010, 47: 124-130. 10.3109/02770900903518835.
11.Price D, Robertson A, Bullen K, Rand C, Horne R, Staudinger H: Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study. BMC Pulm Med. 2010, 10: 1-10.1186/1471-2466-10-1.
12. Biggadike K, Bledsoe RK, Hassell AM, Kirk BE, McLay IM, Shewchuk LM, Stewart EL: X-ray crystal structure of the novel enhanced-affinity glucocorticoid agonist fluticasone furoate in the glucocorticoid receptor-ligand binding domain. J Med Chem. 2008, 51: 3349-3352. 10.1021/jm800279t.
13. Salter M, Biggadike K, Matthews JL, West MR, Haase MV, Farrow SN, Uings IJ, Gray DW: Pharmacological properties of the enhanced-affinity glucocorticoid fluticasone furoate in vitro and in an in vivo model of respiratory inflammatory disease. Am J Physiol Lung Cell Mol Physiol. 2007, 293: L660-L667. 10.1152/ajplung.00108.2007.
14. Van den Berge M, Luijk B, Bareille P, Dallow N, Postma DS, Lammers JW: Prolonged protection of the new inhaled corticosteroid fluticasone furoate against AMP hyperresponsiveness in patients with asthma. Allergy. 2010, 65: 1531-1535. 10.1111/j.1398-9995.2010.02414.x.
15. Kerry Dwan, Stephen J Milan, Lynne Bax, Nicola Walters, Colin VE Powell,corresponding author and Cochrane Airways Group: Vilanterol and fluticasone furoate for asthma. Cochrane Database Syst Rev. 2016 Sep; 2016(9): CD010758.PMCID: PMC6472525 PMID: 27582089
16. McKeage K. Fluticasone propionate/formoterol fumarate: a review of its use in persistent asthma. Drugs. 2013 Feb;73(2):195-206. Doi: 10.1007/s40265-013-0016-4. PMID: 23397367.
17. Woodcock A, Bleecker ER, Lötvall J, O'Byrne PM, Bateman ED, Medley H, Ellsworth A, Jacques L, Busse WW. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. Chest. 2013 Oct 1;144(4):1222-9.
18.Navaratnam P, Friedman HS, Urdaneta E. Treatment with inhaled mometasone furoate reduces short-acting β2 agonist claims and increases adherence compared to fluticasone propionate in asthma patients. Value in Health. 2011 Mar 1;14(2):339-46.
19. Friedman HS, Navaratnam P, McLaughlin J. Adherence and asthma control with mometasone furoate versus fluticasone propionate in adolescents and young adults with mild asthma. Journal of Asthma. 2010 Nov 1;47(9):994-1000.
20. Jentzsch NS, Camargos P, Sarinho ES, Bousquet J. Adherence rate to beclomethasone dipropionate and the level of asthma control. Respiratory medicine. 2012 Mar 1;106(3):338-43.
21Busse WW, Bleecker ER, Bateman ED, Lötvall J, Forth R, Davis AM, Jacques L, Haumann B, Woodcock A. Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial. Thorax. 2012 Jan 1;67(1):35-41.
22. Fardon TC, Lee DK, Haggart K, McFarlane LC, Lipworth BJ. Adrenal suppression with dry powder formulations of fluticasone propionate and mometasone furoate. American journal of respiratory and critical care medicine. 2004 Nov 1;170(9):960-6.
23. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. Archives of internal medicine. 1999 May 10;159(9):941-55.
24. SereventDiskus (salmeterol) prescribing information
GlaxoSmithKline website
http://us.gsk.com/products/assets/us_serevent_diskus.pdf
Accessed July 12, 2013.
25. Mansur AH, Kaiser K. Long-term safety and efficacy of fluticasone/formoterol combination therapy in asthma. J Aerosol Med Pulm Drug Deliv. 2013 Aug;26(4):190-9. Doi: 10.1089/jamp.2012.0977. Epub 2012 Oct 25. PMID: 23098325.