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EFFICACY OF VILANTEROL-FLUTICASONE FUROATE VERSUS FORMOTEROL-BUDESONIDE COMBINATION THERAPY IN STABLE ASTHMA

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ABSTRACT

The present study evaluates the efficacy of Vilanterol-Fluticasone Furoate (VI-FF) versus Formoterol-Budesonide (FM-BD) combination therapy in stable asthma. Both regimens led to significant improvements in asthma control, as evidenced by marked increases in FEV1 (% predicted) and ACT scores over time. The demographic characteristics, baseline respiratory symptoms, and treatment outcomes were similar between the groups, indicating that both strategies were equally effective for managing asthma. The findings indicate that both VI-FF once daily and FM-BD twice daily therapies enhance lung function and asthma control. Significant improvements in FEV1 (% predicted) and ACT scores were observed in both groups, as confirmed by intention-to-treat (ITT) and perprotocol (PPA) analyses. The equivalent efficacy of VI-FF and FM-BD, combined with the convenience of once-daily dosing, suggests that VI-FF may be preferable for patients who struggle with a twice-daily regimen. These findings highlight VI-FF as a convenient and reliable treatment, particularly can benefit patients with adherence challenges. In conclusion, our study's findings align well with other studies regarding demographic characteristics, baseline symptoms, exacerbation history, hospitalization history, and spirometry results. This consistency reinforces the validity and reliability of our results, suggesting that both VI-FF and FM-BD are effective options for stable asthma. The comparable efficacy supports flexibility in treatment choices, allowing for personalized asthma management. Future research should explore the long-term benefits and adherence patterns associated with these treatments to further optimize asthma management.

KEYWORDS: Vilanterol-Fluticasone Furoate, Versus Formoterol-Budesonide Combination, Stable Asthma.

INTRODUCTION

Control of Bronchial asthma can be evaluated in two terms i.e. symptom control and future risk of adverse outcome.1 Symptom control can be further evaluated by two tools i.e. Asthma control test and Asthma Control Questionnaire, and future risk of adverse outcome can be assessed by lung function test.1 The Asthma Control Test is a validated, patient-administered questionnaire based tool to determine patient's asthma symptoms control over the last 4 weeks. Its score ranges from 5 – 25 with patients with score range of 20 – 25 are termed as well controlled Asthma and those between 5 – 15 are categorised as very poorly controlled Asthma. It consists of total five questions, out of which 4 questions are symptoms based and one question is based on patient's asthma control over past 4 weeks.10 Its ability to accurately reflect changes in asthma status over time has been demonstrated, making it a valuable tool for monitoring treatment efficacy and

guiding therapeutic decisions. Furthermore, the ACT has been translated into several languages and tailored for different cultural settings, thereby increasing its effectiveness in managing asthma worldwide. 11 Future risk of adverse outcome can be indicated by lung function. A low FEV1 (less than 60% predicted)is an independent risk factor for exacerbations which can be modified and can also cause fixed airflow limitation.12 Exacerbation of asthma marked by sudden worsening of respiratory symptoms or a rapid decline in lung function, accompanied by the need for a change in treatment, an increase in medication, or medical intervention. These exacerbations can present as increased coughing, Introduction 3 dyspnoea, wheezing, chest tightness, or reduced peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV1). Exacerbations can range in severity from mild to severe, necessitating adjustments in treatment strategies to effectively manage the condition. Early recognition and prompt management of exacerbations are crucial to prevent complications and improve outcomes in asthma management. 11

AIM AND OBJECTIVES

To compare the efficacy of vilanterol-fluticasone furoate versus formoterol-budesonide combination therapy in stable asthma patients. 1. To compare the change in FEV1 after 8 weeks of vilanterol-fluticasone furoate versus formoterol-budesonide combination therapy. 2. To compare the change in ACT (Asthma control test) after 8 weeks of vilanterolfluticasone furoate versus formoterol-budesonide combination therapy.

MATERIAL AND METHODS

Study Setting: The study was conducted in the Department of Pulmonary, Critical care and Sleep Medicine at RIMD, RAIPUR, to compare the efficacy of vilanterol-fluticasone furoate (VI-FF) versus formoterol-budesonide (FM-BD) combination therapy in stable asthma patients at the equivalent corticosteroid strength. Stable asthma patients who were on treatment with formoterol-budesonide (FMBD) combination therapy twice daily for a minimum of 12 weeks attending the Pulmonary Outpatient department (OPD) were enrolled. The study was conducted after approval from institutional ethics committee and after registration in the Clinical Trials Registry – India (CTRI).

Study Design: Open label randomised control trial**.**

Sample Size: Optimum sample size for the study was calculated on the basis of anticipated 25% increase in response rate in terms of % age change in FEV1 which is our primary outcome. Assuming 80% power of the test and 5% level of significance, **sample size** came out to be 45 in each arm (Total 90).37 Patients were **randomised** in two main groups (arms)- Group A (Case group) and Group B (Active Control group). **Inclusion criteria.** Stable asthma patients on formoterol-budesonide combination with following eligibility criteria: ➢ >18 years of age ➢ On FM-BD therapy for >12 weeks prior to enrolment.

Exclusion criteria ➢ Uncontrolled asthma patient (ACT score less than 15), ➢ Severe refractory asthma ➢ Patients with history of acute exacerbation of Asthma in the preceding 6 weeks ➢ Patient with known or suspected allergy to VI-FF ➢ Asthma patients with other respiratory co-morbidities like COPD, lung cancer and interstitial lung disease. ➢ Patients who are not able to perform Spirometry. - The study was conducted after approval from the institute's ethics committee. Informed written consent were taken from all the study participants. Subjects in both the arms were evaluated on the basis for their clinical history and physical examination (specifically mentioning the total duration of disease, duration of use of MDI/DPI, the symptom control with present MDI/DPI, current grade of dyspnoea, frequency of exacerbation, history of previous hospitalization and co-morbidities if any). Their level of asthma symptom control was measured using asthma control test (ACT) score. Patients in both the arms underwent a routine spirometry in the pulmonary function lab. It was performed using a computerised spirometer (Helios 702) as per the latest ATS guidelines in which predicted percent of Forced Expiratory Volume in 1 second (%FEV1), predicted percent of Forced Vital Capacity (%FVC) and the ratio of FEV1/FVC was measured.58 Group A patients were started on VI-FF combination once daily at the equivalent corticosteroid strength at the day 0 and Group B patients continued

to use FM-BD combination twice daily at the same corticosteroid strength. Any patients who developed any clinical worsening as assessed by the investigator, side effects to the trial drugs or develops acute exacerbation during the course of treatment, were excluded from further analysis and were managed as per the standard protocols and guidelines.1 All patients were followed at 4th and 8th week to assess improvement in asthma symptoms by the asthma control test (ACT) as Material and Methods 16 well as change in predicted percent of forced expiratory volume in 1 second (%FEV1) by doing spirometry test. Thereafter change in %FEV1 and ACT score were compared within each arm as well as between the 2 arms using appropriate statistical tests. Data were coded and recorded in MS Excel spreadsheet program.

STATISTICAL ANALYSIS- Detailed analysis was carried out by using SPSS 26.0 software. Quantitative parameters were described by using mean ± SD and median with 25th and 75th percentiles (interquartile range). The presentation of the categorical variables was done in the form of frequencies and percentages. Data were presented in a graphical manner wherever appropriate for data visualization using histograms and box-and-whisker plots for continuous data and bar charts and pie charts for categorical data. Group comparisons for continuously distributed data were made using independent sample 't' test when comparing two groups. If data were found to be non-normally distributed, appropriate non-parametric tests in the form of Wilcoxon-Mann-Whitney Test were used. Chi-squared test was used for group comparisons for categorical data.

RESULTS

The following observations were obtained from our study: 1. The mean age of study participants in the Group A was 42.91 ±14.71 and in the Group B was 42.53 ±13.21. Majority of participants in both Group A and Group B were from age group of 31-40 years i.e. 31.1% and 28.9% respectively. 2. Majority of participants in both the groups were females: 66.6% females in group A and 51.1% females in group B. 3. The mean BMI of the participants in the Group: A was 24.78 ±4.86 and in the Group: B was 25.33 ±3.50. 4. Dyspnoea was the most common respiratory symptom, followed by cough, in both groups. In Group A, 88.9% of participants had dyspnoea, compared to 84.4% in Group B. The majority of participants in both groups had dyspnoea mMRC grade 1, with 50% of participants in Group A and 47.4% in Group B falling into this category. 5. In Group A, 73.3% of participants had cough, compared to 80.0% of participants in Group B. 6. In Group A, the mean TDI (Total Duration of Illness in months) was 66.22 ±61.80. In Group B, the mean TDI was 71.53 ±64.88. 7. The mean Duration of FM-BD therapy taken (months) in the Group A was 27.00 ±31.08 and in the Group: B was 31.00 ±34.86.Most of the participants in both groups had no comorbidities: 73.3% in Group A and 64.4% in Group B. In both the groups of participants, hypertension was the most common comorbidity. 9. Most of the participants in both groups were non-smokers. Only 13.3% of participants in Group A and 22.2% of participants in Group B were smokers. 10. The majority of participants in both groups had correct inhaler technique: 68.9% in Group A and 60% in Group B. 11. Most of the patients had atleast one exacerbation in last one year. In Group A: 68.9 % patients and in Group B 77.8% patients had atleast one exacerbation in last one-year. The mean number of exacerbation in last one year observed in Group A was 2.02 ±1.85 and in Group B was 2.20 ±1.78. 12. A history of at least one previous hospitalization was present in 31.1% of patients in Group A and 35.6% of participants in Group B. The mean number of previous hospitalizations observed in Group A was 0.47 ±0.79, while in Group B it was 0.58 ±0.94. 13. The mean FEV1/FVC at Visit 0 observed in Group A was 73.78 ±8.48, while in Group B it was 72.66 ±8.12. The mean FVC at Visit 0 observed in Group A was 87.48 ±16.43, while in Group B it was 86.36 ±16.84. 14. The mean FEV1 (% Predicted) at Visit 0-baseline observed in Group A was 76.62 ±21.90, while in Group B it was 74.89 ±19.73. The mean ACT Score at Visit 0 observed in Group A was 18.04 ±2.37, while in Group B it was 17.82 ±2.32. 15.Intention-to-TreatAnalysis(ITT).16.Per-ProtocolAnalysis(PPA).

DISCUSSION

This study was carried out on adult patients of stable asthma attending the out-patient department (OPD) of Department of Pulmonary, critical care and sleep Medicine, RIMS,RAIPUR. Ninety patients were initially enrolled in the study based on specific inclusion and exclusion criteria; however, only 83 completed the study. Demographic data, baseline respiratory symptoms, and treatment details were recorded for all participants. Each patient underwent spirometry and Asthma Control Test (ACT) score evaluations. Follow-up assessments were conducted at the 4th and 8th weeks to measure improvements in asthma symptoms using the ACT and changes in the predicted percentage of forced expiratory volume in one second (%FEV1) through spirometry testing. Both intention to treat analysis (ITT) and per protocol analysis (PPA) were carried out. The results of the present study showed that once-daily VI-FF (Group A) and twice-daily FM-BD (Group B) therapies both improve lung function (FEV1 % Predicted) and asthma control (ACT) in asthma patients. Both intention-to-treat (ITT) and per-protocol (PPA) analyses of our study showed significant improvements in FEV1 (% Predicted) and ACT scores over time within each treatment group. However, no significant difference was observed in the trend of increase in FEV1 (% Predicted) and ACT scores over time between the two groups in both analyses. In our study, the mean age of all 90 participants was 42.72 ±13.90 years (range 18-79), with Group A having a mean age of 42.91 ±14.71 years and Group B having a mean age of 42.53 ±13.21 years. There was no statistically significant difference in the mean age between the two groups ($p = 0.898$). Most participants in both the groups were aged 31-40 years. The majority of participants in both the groups were females, with 66.6% in Group A and 51.1% in Group B, with no significant gender difference between the two groups ($p = 0.134$). Our study is in consensus with a similar study done by Bernstein et al. (2018), who reported a mean age of 43.5 ±16.04 years for all participants, with the VI-FF group having a mean age of 44.4 ±16.30 years and the SAL-FP group having a mean age of 43.0 ± 15.20 years. The majority of patients were female (64%).53 Another study by Devillier et al. (2018) reported a mean age of 48.4 ± 14.84 years for all participants, with those receiving VI-FF having a mean age of 49.3 ±14.67 years and those on twice-daily LABA-ICS combinations having a mean age of 47.5 ±14.99 years. The proportion of females was 69% in the VI-FF group and 59% in the LABA-ICS group.54 The slight variations in age distribution across these studies can be attributed to several factors, including differences in study design, target populations, and inclusion criteria. Notably, all studies reported a predominance of female participants. Asthma is more common in females due to several factors. Hormonal fluctuations, such as those of oestrogen and progesterone during the menstrual cycle, can exacerbate asthma symptoms, leading to more severe symptoms in women compared to men.59 Genetic differences, particularly in immune response genes, combined with these hormonal influences, make women more susceptible to asthma. Additionally, women generally have stronger immune responses than men, resulting in increased inflammation and asthma symptoms, particularly in adulthood. 60,61 In the current study, the mean BMI of the participants in the Group A group was 24.78 ±4.86 and in the Group B group was 25.33 ± 3.50. There was no statistically significant difference observed between the groups in terms of BMI ($t=-0.620$, $p=0.537$). The results of the study showed improvement in both the groups in terms of asthma control and lung functions. Despite the fact that all the patients were on inhaler treatment prior to enrolment, further improvement seen in both arms could be due to improvement in inhaler technique, better compliance seen under trial conditions as well as due to partially controlled asthma in many patients at baseline that showed improvement in the trial. Though the adherence rate was similar in both the treatment arms, but in real life conditions, once-daily therapy like VI-FF will generally lead to better adherence as compared to twice-daily therapy. In view of better adherence, asthma control and lung functions are likely to show better improvement after once daily regimen (VI-FF) as compared to twice a day inhaler therapy**.**

Limitations- This study has several limitations. It was conducted at a single centre without blinding, which may introduce bias. The sample size was relatively small, and specific patient backgrounds such as blood eosinophil count and airway reversibility were not examined. Additionally, the study did not compare specific inhaler devices, which could influence the results. Adherence was self-reported, which might not accurately reflect true adherence rates. The short duration of the study (8 weeks) is another limitation. A longer follow-

up period might provide a more comprehensive understanding of the long-term efficacy particularly the exacerbation frequency and safety of these treatments.

Future Research- Future studies should aim to include a larger, more diverse patient population and a longer follow-up period to better assess the long-term outcomes of VI-FF and FM-BD therapies. Investigating the impact of specific inhaler devices and using objective measures to track adherence could also provide more robust data. Additionally, examining biomarkers such as blood eosinophil counts might help in understanding the differential effects of these treatments on various asthma phenotypes. Studies like those conducted by Averell et al. (2021) and Furuhashi et al. (2019) emphasize the importance of comprehensive and longterm data to validate the efficacy and safety of asthma therapies.

CONCLUSION

The present study evaluates the efficacy of Vilanterol-Fluticasone Furoate (VI-FF) versus Formoterol-Budesonide (FM-BD) combination therapy in stable asthma. Both regimens led to significant improvements in asthma control, as evidenced by marked increases in FEV1 (% predicted) and ACT scores over time. The demographic characteristics, baseline respiratory symptoms, and treatment outcomes were similar between the groups, indicating that both strategies were equally effective for managing asthma. The findings indicate that both VI-FF once daily and FM-BD twice daily therapies enhance lung function and asthma control. Significant improvements in FEV1 (% predicted) and ACT scores were observed in both groups, as confirmed by intention-to-treat (ITT) and perprotocol (PPA) analyses. The equivalent efficacy of VI-FF and FM-BD, combined with the convenience of once-daily dosing, suggests that VI-FF may be preferable for patients who struggle with a twice-daily regimen. These findings highlight VI-FF as a convenient and reliable treatment, particularly can benefit patients with adherence challenges. In conclusion, our study's findings align well with other studies regarding demographic characteristics, baseline symptoms, exacerbation history, hospitalization history, and Spirometry results. This consistency reinforces the validity and reliability of our results, suggesting that both VI-FF and FM-BD are effective options for stable asthma. The comparable efficacy supports flexibility in treatment choices, allowing for personalized asthma management. Future research should explore the long-term benefits and adherence patterns associated with these treatments to further optimize asthma management.

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