Multicentre Study on the Use of Innovator and Generic Salmeterol/Fluticasone Combination in Asthma Management

Khoon Hup Lim[1], Yi Ning Cheah[1], Jia Qian Chin[1], Hanafi Ikma[1], Weng Siang Foong[1], Soik Fun Lee[1], Kae Lin Looi[1], Noor Ashikin Tajudin[1], Siti Sabariah Zainuddin[1], Shobna Ramachandran[1], Vaishneve Prem Kumar[1], Ai Khiang Goon[2]

[1] Pharmacy Department, Balik Pulau Hospital, Ministry of Health Malaysia
[2] Respiratory Department, Penang Hospital, Ministry of Health Malaysia

Correspondence to: Khoon Hup Lim
huplkh89@gmail.com

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ABSTRACT

Introduction:

The Global Initiative of Asthma 2023 Guidelines recommend inhaled corticosteroid-containing treatments in asthma to reduce the risk of serious exacerbations and control symptoms. Generic substitution of the original salmeterol/fluticasone combination (SFC) has gained popularity due to cost considerations, although local studies assessing the efficacy of generic SFC are limited. This study aimed to compare the efficacy of innovator and generic SFC in asthma patients in terms of pulmonary function, asthma control symptoms, and hospitalisations.

Methods:

Conducted in Balik Pulau Hospital's outpatient department and Penang Hospital's respiratory department from January 2020 to May 2021, patients prescribed with innovator SFC in January 2020 or earlier, and were subsequently switched to generic SFC in September 2020 were enrolled. Treatment outcomes included forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), Asthma Control Test (ACT) score, and hospitalisations. Data were analysed using Statistical Package for the Social Sciences (SPSS) version 22, with paired-t test for inferential analysis of continuous data.

Results:

The study included 33 patients, primarily female (63.6%), Malay (48.5%), and aged over 71 years (45.5%). Innovator and generic SFC demonstrated comparable FEV1 (P=0.720), FVC (P=0.384), and FEV1/FVC (P=0.122) values. The ACT score significantly increased after switching to generic SFC (P=0.023). However, no significant difference in hospitalisations was observed.

Conclusion:

Spirometry improvements were comparable between innovator and generic SFC, while generic SFC exhibited superior control of asthma symptoms. This suggests that generic SFC can be considered as an effective and cost-efficient alternative to the innovator SFC in the management of asthma.

Keywords:

Asthma, innovator, generic, salmeterol/fluticasone

INTRODUCTION

The National Pharmaceutical Regulatory Agency defines generic products in Malaysia as essentially similar to already registered products, with gradual implementation of bioequivalence requirements for systemic oral solid dosage forms.[1-2] While generic and brand-name drugs share active constituents, dosage form, safety, potency, route of administration, quality, performance characteristics, and intended use, they may vary in aspects such as price and inactive constituents. Notably, innovator drugs undergo multiple animal and clinical tests that are costly meanwhile generic drugs undergo simplified registration processes, leading to significant cost advantages.[3]

Asthma, a chronic respiratory condition, presents symptoms like shortness of breath, wheezing, chest tightness, and cough. Achieving optimal asthma control is crucial for symptom alleviation, reducing the risk of exacerbations, and improving overall quality of life.[4] Seretide and Bioxitide, both combining salmeterol xinafoate and fluticasone propionate (SFC), are available in Malaysia. Salmeterol xinafoate, a long-acting beta2-agonist, relaxes bronchial smooth muscles, while fluticasone propionate, an inhaled corticosteroid, reduces airway inflammation.[4]

The Generic Medicines Policy encourages cost-effective generic substitution for interchangeable medications.[4] For instance, the use of generic salbutamol metered-dose inhalers is encouraged as previous studies have demonstrated interchangeability.[5-6] In terms of generic and innovator SFC, a study found no significant differences in anti-inflammatory activity and asthma symptom management.[7]

This study focused on comparing the effectiveness of Seretide Evohaler and the generic SFC, Bioxitide, using spirometry and Asthma Control Test (ACT) scores in patients treated at Balik Pulau Hospital and Penang Hospital. This study aimed to contribute valuable insights to the ongoing discourse on generic substitution in asthma management.

METHODS

Study Design

This study was carried out at the outpatient department of Balik Pulau Hospital and the respiratory department of Penang Hospital, with Penang Hospital serving as a tertiary hospital and Balik Pulau Hospital as a district hospital situated on Penang Island. Adhering to the drug policy implemented by both facilities on September 23, 2020, all patients previously treated with the innovator SFC, Seretide Evohaler, were transitioned to the generic SFC, Bioxitide. The study included individuals aged 18 years or older, diagnosed with asthma, who had undergone clinic follow-ups in both facilities, and who met the following criteria: (i) non-smokers or ex-smokers who had quit smoking over a year before screening; (ii) initiated treatment with the innovator SFC for at least two to three years and subsequently switched to generic SFC in September 2020; and (iii) had been using the generic SFC for at least six months.

Exclusion criteria comprised of patients diagnosed with lung cancer, those with systemic diseases with pulmonary complications, or individuals contraindicated to SFC components. The research involved a retrospective review of all case notes spanning from January 1, 2020, to May 31, 2021. A total of 80 patients from both facilities were initially enrolled using a convenience sampling method. However, only 33 patients, including 9 from Balik Pulau Hospital and 24 from Penang Hospital, completed the study, as 47 patients defaulted on their appointments.

Study Outcome

Pulmonary Function Test (PFT) and Asthma Control Test (ACT) were employed to comprehensively assess asthma control, combining objective and subjective measures. PFT objectively evaluate symptom control, while ACT subjectively measures patients' perception of asthma control.[8]

PFT evaluate symptom control by assessing the forced expiratory volume (FEV1) and forced vital capacity (FVC), with the FEV1/FVC ratio calculated to evaluate asthma control. FEV1 measures the volume of air forcefully exhaled in the first second after maximal inhalation, while FVC represents the total volume of air exhaled after a maximal forced expiration. Notably, a diagnostic criterion for asthma involves confirming variable expiratory airflow limitation. In adults, an increase in FEV1 >12% and 200 mL after bronchodilator use indicates a positive bronchodilator responsiveness (reversibility) test. [4,9-11]

On the subjective front, ACT offered a concise numerical assessment for asthmatic patients aged 12 and above. Its validity and reliability has been established across diverse populations, boasting a Cronbach's alpha value of 0.79 and a commendable test-retest reliability of 0.77.[12] The test comprised of five questions, which are on (i) frequency of asthma symptoms in the past four weeks; (ii) the use of rescue inhalers or nebulisers; (iii) the impact of asthma on the patient's productivity at work, school or home; (iv) the frequency of asthma-related nighttime awakenings; and (v) the patient's assessment of asthma control over the past four weeks. Responses were recorded on a five-point scale, where 1 denoted a total absence of control and 5 represented complete control. Scores ranged from 5 to 25, with higher scores indicative of better control. Specifically, scores falling within the range of 20 to 25 were classified as well-controlled, 16 to 19 as not well-controlled, and 5 to 15 as very poorly controlled asthma. Additionally, hospitalisations served as one of the treatment outcomes.

Statistical Analysis

The data analysis was conducted using Statistical Package for Social Sciences (SPSS) version 26. The demographic characteristics were presented descriptively, including frequencies, percentages, means, and standard deviations (SD). To inferentially analyse continuous data, specifically the FEV1/FVC ratio and ACT scores, the paired-t test was employed to analyse normally distributed data.

RESULTS

Between January 2020 and May 2021, a total of 80 asthmatic patients from Balik Pulau Hospital and Penang Hospital were enrolled, with 33 successfully completing the study. Notably, the majority of participants were female (63.6%), of Malay ethnicity (48.5%), and aged over 71 years (45.5%), as detailed in Table 1. The mean duration of asthma among the study cohort was 24.38 years.

Table 2 presents a comparison of pulmonary function test results when utilising the innovator and generic SFC. The analysis of spirometric variables, including FEV1, FVC, FEV1/FVC, and the incidence of hospitalisations, revealed no statistically significant differences between the two treatment modalities. Interestingly, the study noted an episode of hospitalisation in a patient treated with the innovator SFC, contrasting with no instances of hospitalisation during the period of generic SFC use.

The details of ACT scores for patients using both innovator and generic SFC are outlined in Table 3. A noteworthy improvement in asthma symptoms was observed in the majority of patients following the switch from the innovator to the generic SFC. The overall ACT score also exhibited a statistically significant increase post-switch (P=0.023). These findings suggest a positive impact on asthma control with the adoption of the generic SFC, underscoring its potential efficacy in enhancing patient outcomes.

Table 1. Demographic Characteristics (n=33)

Characteristics	Mean (SD)	n (%)
Gender		
Male		12 (36.4)
Female		21 (63.6)
Age (years)		
31 – 50		7 (21.3)
51 – 70		11 (33.4)
>71		15 (45.5)
Race		
Malay		16 (48.5)
Chinese		13 (39.4)
Indian		2 (6.1)
Others		2 (6.1)
Duration of asthma (years)	24.38±2.45	

Table 2. Pulmonary Function Test (PFT)

Variable	Mean±SD		P value[a]
	Innovator SFC	Generic SFC	
FEV1	1.26±0.50	1.27±0.54	0.720
FVC	1.87±0.66	1.81±0.67	0.384
FEV1/FVC	67.85±12.77	70.27±15.40	0.122
Number of hospitalisations	0.12±0.55	0.00±0.00	0.211

[a] Paired-T Test

FEV1 = Forced expiratory volume

FVC = Forced vital capacity

Table 3: Asthma Control Test (ACT) Scores

Variables in ACT	Mean±SD		P value[a]
	Innovator SFC	Generic SFC	
1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?	3.60±0.99	3.76±0.83	0.392
2. During the past 4 weeks, how often have you had shortness of breath?	4.00±0.66	4.00±0.66	>0.950
3. During the past 4 weeks, how often did your asthma symptoms wake you up at night or earlier than usual in the morning?	4.06±0.90	4.18±0.73	0.458
4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?	3.67±0.85	4.06±0.75	0.026*
5. How would you rate your asthma control during the past 4 weeks?	3.55±1.03	4.12±0.70	0.004*
Total ACT score	19.00±2.50	20.10±2.63	0.023*

[a] Paired-T Test

* P-value < 0.05 was considered as significant

DISCUSSION

This study aimed to compare the efficacy of innovator SFC and generic SFC in two hospitals, Balik Pulau Hospital and Penang Hospital, focusing on spirometry-function enhancements for asthma treatment. The results suggest that generic SFC is comparable with the original SFC, as evidenced by comparable measurements of FEV1, FVC, and FEV1/FVC between the two formulations. This indicates equal effectiveness between the two formulations in enhancing pulmonary function. The results align with a prior study that reported comparable lung function between innovator and generic SFC, where the generic group demonstrated superior baseline FVC.[13] In the same study, the innovator SFC exhibited superior improvement in FEV1 and FEV1/FVC during treatment, but no significant difference in FVC emerged between the two groups.[13] This consistency in findings across studies supports the notion that generic SFC can be a comparable and effective alternative to the innovator version, particularly with respect to baseline pulmonary function and spirometry-based enhancements during treatment.

In terms of asthma control, the study utilised ACT scores, revealing a statistically significant difference in favour of the generic SFC, supported by a marginal increase in the mean ACT score (P=0.023). This implies that generic SFC may be a more favourable option for asthma symptom control. While Panahi et al. observed lower ACT scores for the generic product, conflicting evidence from Maneechotesuwan et al. showed no significant differences in asthma control between the two formulations based on ACT and Asthma Control Questionnaire scores.[7,13] The conflicting evidences suggests that the choice between innovator SFC and generic SFC vary depending on individual patient responses.

This study proposes generic SFC as a viable alternative to innovator SFC for spirometry-based enhancements in asthma treatment, with potential advantages in symptom control, as indicated by improved ACT scores. However, individual patient responses should guide the choice between innovator and generic SFC, considering factors such as preferences, costs, and treatment goals. Importantly, no statistically significant differences in hospitalisations were observed between innovator and generic SFCs. However, this might be subject to regional variations.

Notably, the study underscores the interchangeability between innovator and generic SFC for asthma treatment. This finding is particularly relevant in low and middle-income countries, where access to essential medicines for treating asthma are limited.[14] The significance lies in the fact that generic medicines, which are generally more affordable and

more readily available in public facilities of such countries, can serve as a viable alternative in treating asthma.[14]

The interchangeability between innovator and generic SFC means that patients in these countries may have increased access to cost-effective asthma treatments, contributing to improved healthcare outcomes.

Limitations and Recommendations

The study outlined several limitations that should be taken into account when interpreting its findings. The most significant challenge was the substantial number of non-respondents, primarily due to patients missing their scheduled appointments. This introduces the possibility of selection bias, potentially impacting the representativeness of the sample and the generalisability of the results. The study also acknowledges the multifaceted nature of long-term asthmatic treatment adherence, citing reasons for patient dropout such as patients feeling better, logistical barriers, and medication side effects.[15] These real-world challenges can introduce confounding factors that may impact the results, highlighting the complexity of patient behaviours in the context of long-term medical treatment.

The emergence of the COVID-19 pandemic during the study further complicated matters by posing challenges to clinic follow-ups and contributing to treatment non-compliance. This external factor underscores the need for researchers to consider and account for unforeseen events or circumstances that can influence patient adherence.[16]

Another notable limitation is the absence of a compliance evaluation, which means there was no confirmation of homogeneity between the two groups of patients in terms of adherence to the prescribed treatment.

Finally, the absence of a control group in the study limits its ability to attribute observed improvements solely to the treatment being investigated. Without a control group for comparison, it becomes challenging to isolate the effects of the intervention from other potential influences.

The study also acknowledges the need for future large-scale studies to further explore and compare the long-term efficacy and safety of both the innovator and generic SFC. This recognition emphasises the importance of conducting more extensive research to validate the study's initial findings and provide a more comprehensive understanding of the implications of using generic SFC as an alternative treatment for asthma.

Researchers and readers should approach the study outcomes with caution, considering these limitations. Future research efforts should aim to address issues related to patient dropout, adherence complexities, and external factors to enhance the robustness and generalisability of the findings.

CONCLUSION

This study suggests that both the innovator and generic SFC show comparable improvements in spirometry function in asthmatic patients. Additionally, the results indicate an increase in ACT score after switching to the generic SFC. Importantly, the spirometry function and number of hospitalisations remain comparable in asthmatic patients using generic and innovator SFC. With these findings, the study suggests that generic SFC can be recommended as a viable treatment alternative to innovator SFC.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

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ETHICAL APPROVAL

This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline.

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