

Comparison of 12-Week Additional Effect Features of Formoterol Co-Inhalation and Tulobuterol Patch on Budesonide Inhalation in Elderly Patients With Asthma

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Abstract

Background: For asthma strategy, to avoid the aggravation of bronchial inflammation and contraction, the long acting beta agonist (LABA) addition on inhaled corticosteroids (ICS) has been recommended.

Objectives: To know whether there is any clinical difference between the additional efficacies of Formoterol (FOR) and Tulobuterol (TUL) onto Budesonide (BUD) may be useful for the elderly patients' asthma treatment strategy.

Methods: Eighteen outpatients with mild to moderate bronchial asthma with FEV1.0% < 80% treated by intermediate ICS dosages visited Respiratory Division of Nagasaki University Hospital or Isahaya General Hospital, Japan Community Health care Organization were subjected, and were randomly assigned (9 cases per group) to either the FBC group (BUD/FOR 160/4.5 µg, 2 inhalations twice daily) or BUD + TUL group (BUD 200 mcg; 2 inhalations twice daily + TUL 2 mg daily) and were compared in parallel with 2 arms for 12 weeks prospectively. Peak expiratory flow, forced expiratory volume in 1 second, impulse oscillometry (IOS), fractional exhaled nitric oxide (FeNO), Asthma Control Questionnaire, mini-Asthma Quality of Life Questionnaire (mini-AQLQ), and occurrence of adverse reactions were compared.

Results: The "Fres" of IOS was improved in FBC group ($p = 0.03$). The "emotion" domain of mini-AQLQ was improved in BUD + TUL group ($p = 0.03$).

Conclusion: By changing the drug formulation, the patch was superior in terms of satisfaction, but it was thought that the inhaled combination was superior in improving the respiratory function itself. It is necessary to pay attention to the characteristics of the patient when selecting treatment.

Keywords

bronchial inflammation, fractional exhaled nitric oxide, impulse oscillometry, mini-Asthma Quality of Life Questionnaire, prospective study, transdermal delivery system

Introduction

Because the bronchial eosinophilic inflammation and airway smooth muscle contraction are essential pathologies of bronchial asthma, insufficient treatments result in increased airway hyperreactivity and future exacerbations due to remodeling and smooth muscle hypertrophy.^{1,2} The long acting beta agonist (LABA) addition on inhaled corticosteroids (ICS) has been recommended in Step2 onward to treat the bronchial inflammation and

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contraction. Though ICS and LABA combination inhalation therapy has an advantage as these materials goes to almost same area in the airways,^{3,4} of which effects would be insufficient without adequate inhalation technique, e.g. elder patients with lower respiratory function. While suppression of airway inflammation by ICS is important to prevent the development of remodeling, which is a major factor in the intractability of asthma, LABA is also important because mechanical stress due to airway contraction also causes remodeling.⁵

Regarding LABA, the Tulobuterol patch (HokunalinTM Tape; TUL) with the transdermal delivery system has been used for control of asthma and chronic obstructive pulmonary disease (COPD) in Japan, Korea, and China.⁶ This patch prevents excessive increase of the concentration in blood that is useful to reduce the systemic adverse reactions.^{7,8}

There are several studies reported the additional efficacies of TUL and salmeterol (SAL) onto fluticasone propionate (FLU) inhalation,^{9–11} and the results were inconsistent. There are little studies compared the additional efficacies of TUL and Formoterol (FOR), an LABA inhalation onto Budesonide (BUD) inhalation, an ICS. Because FOR/BUD combination inhalation is quite popular for asthma control and BUD is known as an ICS with less side effects,^{3,4} to know any clinical difference between the additional impacts efficacies of FOR and TUL onto BUD may be useful for the elderly patients' asthma treatment strategy. We compared these strategies by a randomized prospective study with 2 arms for 12 weeks.

Materials and Methods

Study Design and Population

This is a prospective, randomized, interventional, post-market feasibility study conducted at two centers in Japan. The ethics committee of Nagasaki University Hospital approved this study protocol (Na11042549) for both centers and all the participants received verbal and written information and provided the informed consent. The study is registered on UMIN Clinical Trials Registry (<https://www.umin.ac.jp/ctr/index.htm>) (UMIN000006551). All process was conducted according to the World Medical Association Declaration of Helsinki.

Patients

In this study, 18 elderly outpatients 65 years of age or older, with mild to moderate bronchial asthma, with $FEV1.0\% < 80\%$ treated by intermediate ICS dosages visited Respiratory Division of Nagasaki University Hospital or Isahaya General Hospital, Japan

Community Health care Organization (JCHO) were recruited (Table 1). All included patients fulfilled the Global Initiative for Asthma (GINA) criteria,¹ and had a history of asthmatic symptoms, including cough, wheezing, or dyspnea (mean (SD) age was 72.8 (6.2), female/male = 9/9, Non-smoker/Ex-smoker/Current smoker = 7/11/0). All patients had no findings of COPD on Chest X ray or high resolution CT. All patients retained normal diffusion capacity. Anti-asthma drugs were discontinued for at least 24 h prior to each examination. The intermediate dosages of ICS were defined as follows: 1) SAL/FUL combination, 200 to 500 µg/day or 2) BUD, 400 to 800 µg/day; beclomethason, FUL, ciclesonide, or mometasone, 200 to 400 µg/day.

Assessments

Subjects were randomly assigned to either the FBC group (n=9, BUD/FOR, 160/4.5 µg, 2 inhalations twice daily) or BUD + TUL group (n=9, BUD 200 µg, 2 inhalations twice daily + TUL 2 mg daily) and these groups were compared. The treatment period was 12 weeks and the BUD dose of both groups were set as equal. The short-acting inhaled β₂-agonists (SABA) was permitted to be used as needed (Figure 1).

At the start of the study, a full medical interview was given and a physical examination was performed. No patients had abnormal electrocardiogram findings. During a 2 week run-in period, they were asked to keep a daily diary card. This card was for record morning and evening peak expiratory flow (PEF), symptom score and the rescue use of SABA inhaler.

Measurements

PEF, forced expiratory volume in 1 second (FEV₁), impulse oscillometry (IOS), fractional exhaled nitric oxide (FeNO), Asthma Control Questionnaire (ACQ) and mini-Asthma Quality of Life Questionnaire (mini-AQLQ), and occurrence of adverse reactions were observed.

Pulmonary Function Test

Spirometry was measured using a Chestac-8900 (Chest Co., Ltd., Japan). For the predicted values of FEV₁ and vital capacity (VC), the reference data developed by the Japanese Respiratory Society were taken as the standard value.¹²

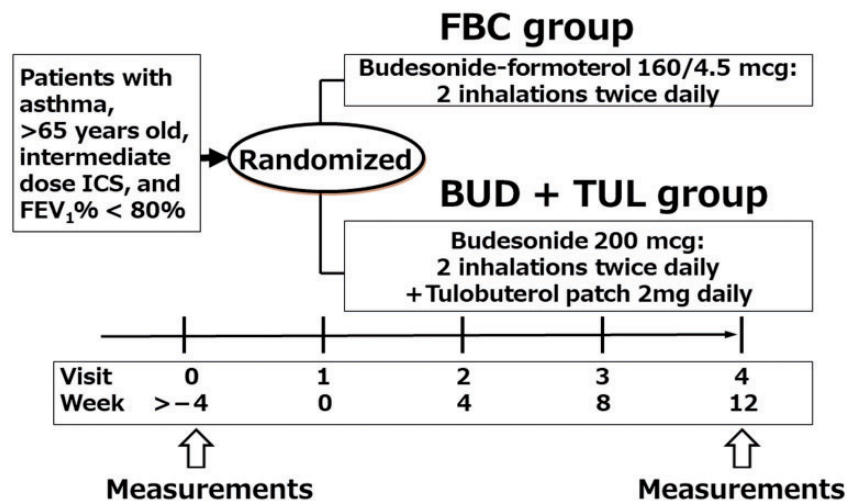
Forced Oscillation Technique

The factors of IOS were measured using a forced oscillation technique device (MostGraph-01; Chest Co., Ltd.).¹³ During tidal breath about 60 seconds in the sitting position, respiratory impedance were measured.

Table 1. Patient Demographics at Visit 1.

Parameters, n = 18	FBC Group, n = 9	BUD+TUL Group, n = 9	P-Values
Age, years	71.9 (5.3)	73.8 (5.0)	0.42
Female/Male	5/4	4/5	0.64
Stage, I/II/III/IV	0/3/6/0	0/2/7/0	0.78
Atopic/non-atopic	2/7	3/6	0.72
Treatment before the participating in this study, SAL/FUL, 200 µg/day/SAL/FUL, 400 µg/day/ BUD, 800 µg/day	1/ 5/ 3	1/ 4/ 4	0.88
ACQ	4.6 (4.7)	2.4 (1.5)	0.69
AQLQ	82.7 (16.8)	89.6 (9.7)	0.46
Symptom	29.4 (4.7)	31.0 (3.3)	0.64
Activity limitation	23.3 (3.7)	25.0 (2.5)	0.46
Emotional function	15.7 (6.1)	16.4 (2.8)	0.74
Environmental exposure	14.2 (5.0)	17.2 (3.6)	0.28
FVC, L	2.63 (0.98)	2.82 (0.75)	0.64
FEV1, L	1.72 (0.65)	1.82 (0.46)	0.59
FEV1%, %	66.9 (13.9)	65.0 (7.2)	0.64
%FEV1, %	81.9 (18.6)	90.0 (16.1)	0.26
V50, L/min	1.51 (0.80)	1.35 (0.56)	0.74
V25, L/min	0.43 (0.24)	0.35 (0.11)	0.79
FeNO, ppb	43.1 (28.0)	47.8 (21.4)	0.84
R5, cmH ₂ O/l/s	4.21 (1.06)	4.47 (1.61)	0.99
R20, cmH ₂ O/l/s	3.13 (0.83)	3.36 (1.29)	0.85
R5-R20, cmH ₂ O/l/s	1.08 (0.51)	1.12 (0.45)	0.99
X5, cmH ₂ O/l/s	-1.63 (1.98)	-1.00 (1.32)	0.72
Fres, Hz	10.0 (4.0)	9.1 (3.5)	0.58

Symptoms (11 items), Activity Limitation (12 items, 5 of which are individualized), Emotion (5 items), and Environmental Exposure (4 items).

**Figure 1.** Study protocol.

To reduce upper airway shunting, the subject's cheeks and mouth floor were supported by the patient's both hands. The levels of Rrs at 5 Hz (R5), Rrs at 20 Hz (R20), the difference between R5 and R20 (R5-R20), Xrs at 5 Hz (X5), resonant frequency (Fres), and also the differences of the mean Rrs and Xrs in the

expiratory phase to those in the inspiratory phase were evaluated. Whole-breath analysis and within-breath analysis were performed by programmed software automatically. These forced oscillation technique measurements were performed prior to other pulmonary function tests.

FeNO Measurement

FeNO was measured by portable sensor (NIOX MINO; Aerocrine AB, Solna, Sweden), according to ATS/ERS recommendations on measurements of FeNO,¹⁴ and the results were expressed as parts per billion. The participants were asked to inhale through the device and exhale steadily for 10 seconds at a flow rate of 50 ml/s and at a pressure of 10 cm H₂O. The measurements were done in a sitting position.

ACQ and Mini-AQLQ

ACQ is a survey for asthma control contains seven items about limitation due to asthma measured on a 7-point scale, from 0 (no impairment) to 6 (extreme impairment), using the past 7 days recall. The mean score ≤ 0.75 was classified as “well controlled”, >1.5 as “uncontrolled”, and between these points as “somewhat controlled”. A Minimal Clinically Important Difference (MCID) of 0.5 was used.¹⁵

Mini-AQLQ is simplified version with 15 questions with four domains (symptoms, activities, emotions, and environment) from original AQLQ with 32 questions, and ask each question to have “1” if there is a serious impairment and “7” if there is no problem at all. The mean score of ≥ 1.5 indicates uncontrolled asthma and <1.5 indicates well controlled asthma. The MCID is a mean change in this mean score of greater than 0.5.¹⁶

Evaluation of the Treatment Effects

The changes of the each factor (Δ factor) was defined by subtracting the value of Visit 1 from that of Visit 4.

Statistical Analysis

Mann-Whitney test was used for comparison of the background factors and the changes of the factors (Δ factor) between the groups. The p -value < 0.05 was considered as significant difference.

Results

Participants

Regarding age, sex, classification of disease (atopic or non-atopic), severity, ACQ, AQLQ, spirometry, FeNO, and IOS parameters, there were no significant differences between the groups (Table 1).

The changes of parameters in ACQ, AQLQ, spirometry, FeNO, and IOS

Three cases (1 of FBC group and 2 of BUD + TUL group) had to use systemic steroids within 2 weeks after the commencement of the study and discontinued the trial. The remaining 15 cases were subjected for efficacy analysis. The “Fres” of IOS was improved

Table 2. Comparison of the Changes of Each Factor Between the Groups.

	FBC Group	BUD+TUL Group	P-Values
Δ ACQ	-0.11 (2.71)	0.8 (3.63)	0.95
Δ AQLQ	-2.33 (8.20)	1.80 (7.09)	0.42
Δ Symptom	-0.11 (3.52)	-0.40 (3.58)	0.84
Δ Activity limitation	-0.11 (3.52)	-0.40 (3.58)	0.84
Δ Emotional function	-1.00 (3.00)	3.20 (2.39)	0.03
Δ Environmental exposure	-0.67 (3.32)	0.00 (2.12)	0.50
Δ FVC, L	-0.00 (0.20)	0.03 (0.22)	0.74
Δ FEV1, L	0.08 (0.15)	-0.01 (0.20)	0.55
Δ FEV1%, %	4.77 (6.5)	-0.63 (2.81)	0.05
Δ %FEV, %	2.04 (4.12)	-1.98 (10.48)	0.79
Δ V50	0.22 (0.36)	-0.11 (0.33)	0.07
Δ V25	0.16 (0.33)	-0.01 (0.10)	0.16
Δ FeNO	-1.3 (12.8)	2.6 (27.0)	0.95
Δ R5	-51.8 (25.2)	-43.5 (21.7)	0.47
Δ 20	-0.95 (1.14)	-0.38 (1.00)	0.31
Δ R5-R20	-0.47 (0.37)	-0.00 (0.66)	0.20
Δ X5	1.19 (1.50)	0.30 (0.84)	0.27
Δ Fres	-5.58 (4.31)	0.54 (2.90)	0.03

($p = 0.03$) in FBC group and the “emotion” domain of AQLQ was improved ($p = 0.03$) in BUD + TUL group (Table 2, Figure 2). There were no differences between the groups in the changes of each factor of ACQ, spirometry, or FeNO.

Adverse Events

There were no drug-related adverse reactions reported in both groups.

Discussion

In this study, FBC group had better improvement on “Fres” of IOS indicators, and BUD + TUL group had better improvement on “emotion” domain of mini-AQLQ; which may suggest the differentiation of the additional effect characteristics of each drug (FOR and TUL).

By adding FOR to BUD (equal to FBC inhalation), the “Fres” associated with large and small airway resistance was improved significantly ($p = 0.03$). FOR is a LABA and provides sustained action for 12 hours which needs to be inhaled twice a day.¹⁷ It is reasonable for most patients who can inhale the medicine properly, the ICS/LABA combination will be suitable for asthma control.¹⁸

In contrast, adding TUL to BUD improved “emotion” domain significantly ($p = 0.03$). Previously, the improvement of asthma control status of patients with adult-onset mild to moderate asthma by additional TUL on FLU inhalation was reported,⁹ and additional

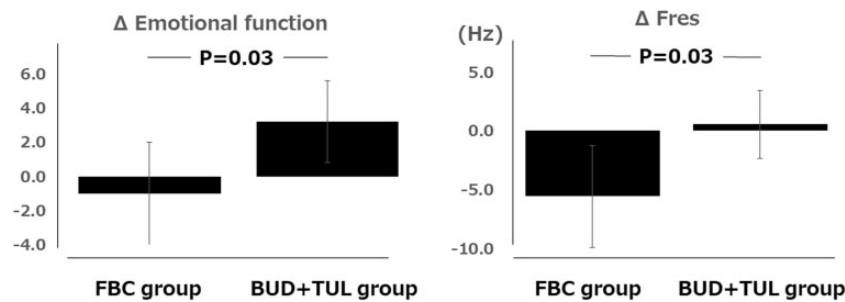


Figure 2. The changes of “emotion” domain of AQLQ and “Fres” of IOS in FBC group and BUD + TUL group.

effect of TUL on leukotriene receptor antagonist in children with asthma was also reported.¹⁰ The efficacy of TUL addition to BUD inhalation was firstly found by this study.

Other studies, however, reported that SAL addition achieved better control after switching from TUL addition in asthmatic patients with FLU treatment,¹⁰ or that SAL addition on FLU improved morning and evening PEF rates and AQLQ score but TUL addition did not, in patients with asthma on ICS therapy in 8 weeks of observation.¹¹ In our study, we have found the addition of TUL or FOR on BUD respectively showed characteristic improvements on “Fres” or “mini-AQLQ”.

For the patients with typical asthma, respiratory functions are most severely suppressed from midnight to early morning, and it is called as morning dip.¹⁹ Suppression of this morning dip may improve the patient’s QOL. TUL patch prolongs the drug’s action to 24 hours, which may improve the circadian rhythm.^{8,20} Improvements of QOL or treatment adherence are very important for chronic disease including asthma.²¹ It was reported that the therapeutic adherence of the TUL patch was significantly higher than that of other inhaled drugs, as the patch was easy to use and was applied once a day.⁶ Regarding the change in FeNO, there was no difference between the groups, and the BUD dose was consistently the same in both groups, so this is understandable.

In the study, there are some limitations. Firstly, the patients were recruited from the asthma specialist outpatient department, which might induce any bias compared with general medical clinics, and the numbers were very small. Secondly, because the TUL may suppress the Rhinovirus infection and may be effective on upper respiratory tract infection symptoms,^{22,23} the setting period include the winter season and for at least half year might be desired.

Conclusion

By changing the drug formulation, the patch was superior in terms of patients’ satisfaction, but it was thought

that the inhaled combination was superior in improving the respiratory function itself. It is necessary to pay attention to the characteristics of the patient when selecting treatment.

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We would like to thank the physicians, patients, and volunteers for participating in this study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The ethics committee of Nagasaki University Hospital approved this study protocol (Na11042549) for both centers.

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Statement of Human and Animal Rights

The study adhered to good clinical practices and ethical standards. The STROBE reporting guidelines for cohort studies were applied.

Statement of Informed Consent

All the participants received verbal and written information and provided the informed consent.

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References

1. Global strategy for asthma management and prevention. NHLBI/WHO Report. Bethesda National Institutes of Health, National Heart, Lung and Blood Institute.

- NIH Publication: 02-3659. <http://www.ginasthma.org>. Updated 2015.
2. Ichinose M, Sugiura H, Nagase H, et al. Japanese guidelines for adult asthma 2017. *Allergol Int*. 2017;66(2):163–189.
 3. Patel M, Pilcher J, Pritchard A, et al.; SMART Study Group. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med*. 2013;1(1):32–42.
 4. Sobieraj DM, Weeda ER, Nguyen E, et al. Association of inhaled corticosteroids and long-acting β -Agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and Meta-analysis. *JAMA*. 2018;319(14):1485–1496.
 5. Grainge CL, Lau LC, Ward JA, et al. Effect of bronchoconstriction on airway remodeling in asthma. *N Engl J Med*. 2011;364(21):2006–2015.
 6. Tamura G, Ichinose M, Fukuchi Y, et al. Transdermal tulobuterol patch, a long-acting β (2)-agonist. *Allergol Int*. 2012;61(2):219–229.
 7. Park SI, Kim BH. Bioequivalence assessment of tulobuterol transdermal delivery system in healthy subjects. *Int J Clin Pharmacol Ther*. 2018;56(8):381–386.
 8. Iikura Y, Uchiyama H, Akimoto K, et al. Pharmacokinetics and pharmacodynamics of the tulobuterol patch, HN-078, in childhood asthma. *Ann Allergy Asthma Immunol*. 1995;74(2):147–151.
 9. Inoue H, Niimi A, Matsumoto H, et al. A 12-week, randomized, parallel-group, proof-of-concept study of tulobuterol patch and salmeterol inhaler as add-on therapy in adult-onset mild-to-moderate asthma. *Clin Exp Pharmacol Physiol*. 2017;44(1):21–29.
 10. Kobayashi Y, Yasuba H, Kudou M, et al. Addition of transdermal or inhaled long-acting Beta2-agonists in adult asthmatic patients treated with inhaled corticosteroids: switchover study from tulobuterol patch to salmeterol dry powder inhaler. *J Asthma*. 2007;44(2):77–81.
 11. Fujimoto K, Komatsu Y, Yasuo M, et al. Comparison of the clinical efficacy of salmeterol and sustained-release tulobuterol (patch) on inadequately controlled asthma patients on inhaled corticosteroids. *J Asthma*. 2006;43(7):501–507.
 12. Sasaki E, Nakamura M, Kida K. Reference values for spirogram and blood gas analysis in Japanese adults. *J Jpn Respir Soc*. 2001;39:S1–S17.
 13. Shirai T, Kurosawa H. Clinical application of the forced oscillation technique. *Intern Med*. 2016;55(6):559–566.
 14. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med*. 2005;171:912–930.
 15. Juniper EF, O'Byrne PM, Guyatt Gh, et al. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14(4):902–907.
 16. Juniper EF, Guyatt GH, Cox FM, et al. Development and validation of the mini asthma quality of life questionnaire. *Eur Respir J*. 1999;14(1):32–38.
 17. Janjua S, Schmidt S, Ferrer M, et al. Inhaled steroids with and without regular formoterol for asthma: serious adverse events. *Cochrane Database Syst Rev*. 2019;9:CD006924.
 18. Masoli M, Weatherall M, Holt S, et al. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. *Thorax*. 2005;60(9):730–734.
 19. Turner-Warwick M. On observing patterns of airflow obstruction in chronic asthma. *Br J Dis Chest*. 1977;71(2):73–86.
 20. Patel KR. Tulobuterol in the management of obstructive airways disease in adults. *Clin Ther*. 1985;7(4):452–467.
 21. O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: time for a new approach? *Eur Respir J*. 2017;50(3):1701103.
 22. Yamaya M, Nishimura H, Nadine L, et al. Tulobuterol inhibits rhinovirus infection in primary cultures of human tracheal epithelial cells. *Physiol Rep*. 2013;1(3):e00041.
 23. Katsunuma T, Ohya Y, Fujisawa T, et al. Effects of the tulobuterol patch on the treatment of acute asthma exacerbations in young children. *Allergy Asthma Proc*. 2012;33(3):e28–e34.