Evaluation of inhalant deposition of ICS/LABA in the peripheral airway of asthma patients using Functional Respiratory Imaging (FRI)

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Introduction

- The inflammation control not only in the central airway, but also in the peripheral airways is important to achieve total asthma control.
- Treatment with inhaled corticosteroids / long-acting β_2-agonists (ICS/LABA) is widely used for asthma control, and the drug deposition is important as well as devise operatability.
- We conducted clinical research to evaluate the inhalants deposition to the lung by using functional respiratory imaging (FRI) technology.[1)]

Aim

- To evaluate the inhalants deposition to the lung of Japanese asthma patients by FRI and to analyze the factors influencing to deposition in the peripheral airway based on the pooled data.

Methods

- Single-center, open-label study (UMIN000022840)
- This study was conducted in compliance with ethical and scientific principles based on the Declaration of Helsinki (revised in Fortaleza in 2013), the Ethical Guidelines for Medical and Health Research Involving Human Subjects (enforced on December 22, 2014), the Medical Exposure Guidelines 2006, and related laws and regulations, as well as in accordance with the protocol approved by the Ethics Committee of Kindai University Faculty of Medicine.

Patients	Mild to moderate persistent asthma as defined by the Japanese Asthma Prevention and Management Guidelines 2015
Inclusion criteria	✓ Aged 20 years or older ✓ Total or well asthma control [Asthma Control Test (ACT) ≥ 20]
Exclusion criteria	✓ Patients with evidence of chronic obstructive pulmonary disease (COPD) or respiratory infection
Analysis 1	✓ The FRI-based drug deposition in the peripheral airways
Analysis 2	✓ Correlation between peripheral deposition and respiratory function, FOT {forced oscillation technique: Impulse Oscillation System (IOS)} , FRI parameters and drug parameters
Drugs	✓ Flutiform® (ICS/LABA, pressurized metered dose inhaler: pMDI) ✓ Symbicort® (ICS/LABA, dry powder inhaler: DPI) ✓ Relvar® (ICS/LABA, DPI) ✓ Spiriva® (long-acting muscarinic antagonists: LAMA, soft mist inhaler: SMI) (Reference)

Results

Table 1 Patient Background

No. of Patients		6
Gender	Male Female	3 (50.0%) 3 (50.0%)
Age (mean±SD, years)		62.2±7.7
Duration (mean±SD, years)		11.5±17.6
Disease Type	Atopic Non-atopic	3 (50.0%) 3 (50.0%)
Severity	Mild persistent Moderate persistent	4 (66.7%) 2 (33.3%)
Treatment Step	Step 2 Step 3	4 (66.7%) 2 (33.3%)
Smoking History	Never Ex-smoker	1 (16.7%) 5 (83.3%)

Table 2 Lung function, IOS

			Mean	SD
Spirometry	FEV_1	(L)	2.43	0.21
	$\%FEV_1$	(%)	95.32	19.83
	FVC	(L)	3.06	0.34
	FEV_1/ FVC	(%)	79.87	4.57
	$\dot{V}25$	(L/s)	0.84	0.23
	$\dot{V}50$	(L/s)	3.01	0.70
	$\%\dot{V}25$	(%)	66.85	23.11
	$\%\dot{V}50$	(%)	87.67	24.05
IOS	R5	(kPa/(L/s))	0.21	0.04
	R20	(kPa/(L/s))	0.18	0.04
	X5	(kPa/(L/s))	-0.08	0.03
	Fres	(1/s)	16.68	6.51
	R5 ex-in	(kPa/(L/s))	0.05	0.02
	R20 ex-in	(kPa/(L/s))	0.06	0.04
	X5 ex-in	(kPa/(L/s))	0.00	0.01
	Fres ex-in	(1/s)	4.59	6.22

Table 3 FRI parameters

			Mean	SD
iRaw[1)]	Total (TOT)	(kPa/L)	0.0305	0.0159
	Distal (DIST)	(kPa/L)	0.0209	0.0133
iVaw[2)]	Total (TOT)	(mL)	50.42	12.20
	Distal (DIST)	(mL)	11.99	5.27

1) Airway resistance (iRaw): Total airway resistance, Distal airway resistance
2) Airway volume (iVaw): Total airway volume, Distal airway volume

Table 4 Drug parameters

		ICS	LABA
Flutiform [2, 3)]	FPF (30 L / min) MMAD (30 L / min) GSD (30 L / min)	41.2% of labeled dose 3.52 μm 1.59 μm	39.1% of labeled dose 3.52 μm 1.56 μm
Symbicort [2, 4)]	FPF (60 L / min) MMAD (60 L / min) GSD (60 L / min)	35.0 % of labeled dose 2.49 μm 1.91 μm	30.0 % of labeled dose 2.53 μm 1.89 μm
Relvar [5-8)]	FPF (60 L / min) MMAD (60 L / min) GSD (60 L / min)	20.6% of labeled dose Range of 3.0 - 3.9 μm with a FPF range of 18 - 28% not found (used standard polydisperse GSD of 2.0 μm)	30.7% of labeled dose Range of 1.8 - 2.5 μm with a FPF range of 29 - 54%
Spiriva [9)]	FPF (30 L / min) MMAD (30 L / min) GSD (30 L / min)	Tiotropium: 63.0 % of labeled dose Tiotropium: 2.29 μm Tiotropium: 2.41 μm	

FPF: fine particle fraction, MMAD: mass median aerodynamic diameter, GSD: geometric standard deviation

< Analysis 1 >

Fig.1 Peripheral deposition of drug (ICS)

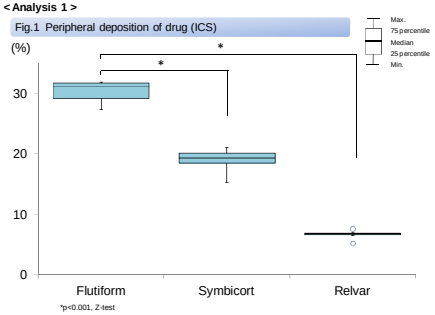
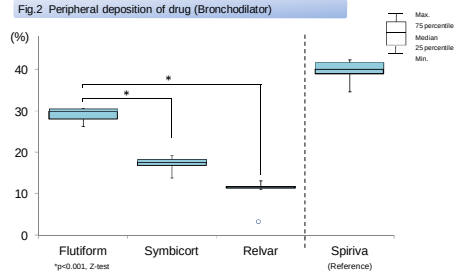


Fig.2 Peripheral deposition of drug (Bronchodilator)



< Analysis 2 >

Fig.3 Correlation between peripheral deposition and respiratory function, FOT and FRI parameters

* Spearman's rank correlation coefficient

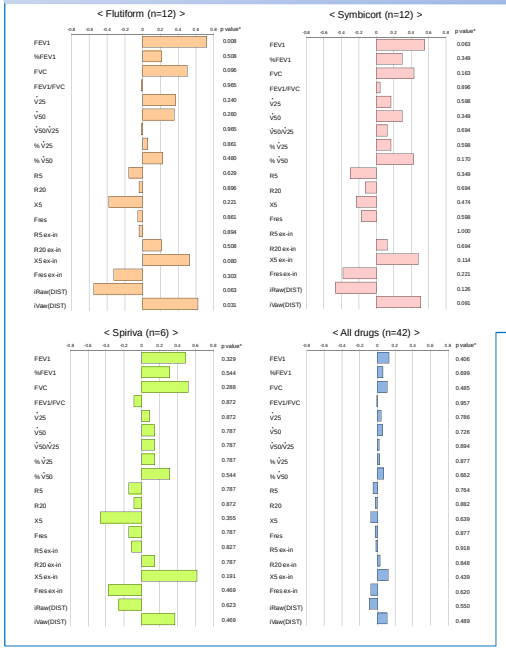
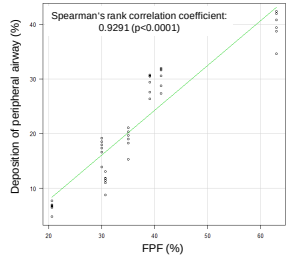


Fig.4 Correlation between peripheral deposition and fine particle fraction (FPF)



Conclusion

- Flutiform (pMDI) was shown to provide significantly higher drug deposition to the peripheral airways than Symbicort (DPI) and Relvar (DPI).
- Significant correlation between deposition and FPF of the drugs were found in peripheral airways.
- There was no correlation between deposition and respiratory function values except for FEV_1 in Flutiform.
- It is suggested that Flutiform (pMDI) may provide a potent therapeutic option to the peripheral airway for various asthma patients without being affected by peripheral airway parameters, including those who have difficulty using DPIs.

Reference

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