Lung deposition of extrafine vs non-extrafine triple therapies in patients with COPD using Functional Respiratory Imaging

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Background and objectives

Introduction: Functional respiratory imaging (FRI) is a validated computational fluid dynamics (CFD)-based technique using aerosol delivery performance profile, patient's high-resolution lung CT scans and patient-derived inhalation profiles to simulate aerosol lung deposition.

Across all stages of COPD, small airways dysfunction (SAD) is closely related to the high impact of disease on health status (1). Dyspnea as a hallmark symptom of the disease is directly linked to neuro-mechanical dissociation resulting from hyperinflation due to early closure of small airways and increased ERV (expiratory reserve volume) (2). Therefore, inhalation therapy (both bronchodilator and anti-inflammatory) targeting small airways is an important aspect of therapy selection in COPD (3).

The most important determinant that can improve the efficiency and lung availability of inhaled drug delivery is particle size (4). A rationale for using extrafine particles (mass median aerodynamic diameter, MMAD <2 µm) in aerosolized medicines is their ability to reach small airways compared to non-extrafine particles (5) resulting in an enhanced drug delivery to these areas. Two inhaled fixed-dose triple therapies are currently approved in Europe for maintenance treatment of COPD but little is known about their respective lung deposition patterns.

Objective: To simulate the lung deposition of an extrafine pMDI vs non-extrafine DPI fixed-dose triple combination therapies in stable COPD patient models with moderate to very severe airflow obstruction.

Methods

Study Design: The study consisted of the simulated respiratory delivery of extrafine beclomethasone dipropionate/ formoterol fumarate/ glycopyrronium bromide [BDP/FF/GB; TRIMBOW®] pressurized metered dose inhaler (pMDI) and non-extrafine fluticasone furoate/vilanterol /umeclidinium [FluF/VI/UMEC; TRELEGY® ELLIPTA®] dry powder inhaler (DPI). The FRI technique has been previously described and validated [6] and is based on four building blocks: (1) patient-specific 3-D airway geometry modelling; (2) inhaler characteristics; (3) inhalation profile; and (4) Computational Fluid Dynamics (CFD) simulations to model lung deposition.

Lung modeling: 3-D airway model was taken from the CT scans of 20 patients with stable COPD and divided into 3 parts: 1) *Extra - thoracic* (mouth and throat), 2) *Central* (large airways) and 3) *Peripheral* (small airways). *Intrathoracic* deposition is the deposition in both the central and peripheral airways.

Methods

Assessment: Intrathoracic depositions of the inhaled corticosteroid (ICS), long-acting β2 receptor agonist (LABA), and long-acting muscarinic antagonist (LAMA) components were calculated for each inhaler. Inhalation was simulated *in silico* using real-life measurement from patients with idiopathic pulmonary fibrosis with the volume and time adapted to get the desired range of flow rates (FluF/VI/UMEC), or were constructed from inspiration volume and time from patients with COPD* (BDP/FF/GB pMDI). Flow profiles were randomly assigned to each patient model corresponding to required different inhalation technique for the device (flow ranges used from 16 – 68 L/min for BDP/FF/GB and 30 – 90 L/min for FluF/VI/UMEC).

CT Scan Patient Population: In total, 5 females and 15 males with moderate to very severe airflow obstruction (7) were included with a mean (SD) age of 64 (8) years and a mean (SD) height of 169 (8) cm. Mean postbronchodilator FEV_1 was 42% of the predicted normal value (range, 19.3 – 66%) and mean FEV_1/FVC ratio was 0.41 % (range 0.17 – 0.62%).

Results

Comparing the extrathoracic and intrathoracic deposition [mean % delivered dose ± SD] the latter was higher for extrafine BDP than FluF (35.9 ± 6.7% vs 23.3 ± 4.6%) and comparable between FF and VI and between G and UM (Figure 1).

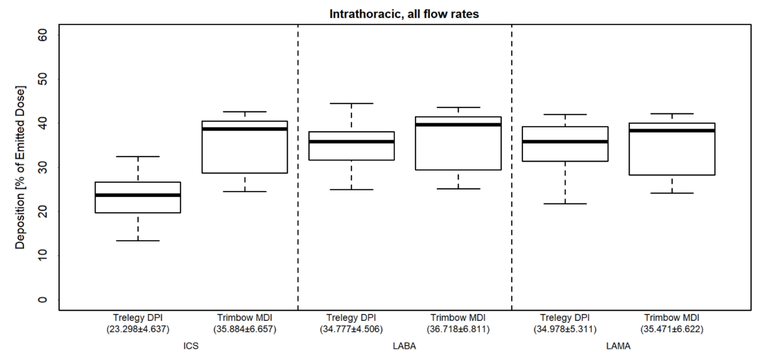

Figure 1: Intrathoracic deposition of BDP/FF/GB compared to FluF/VI/UMEC for single components.

Comparing the distribution in the intrathoracic region of all components, the central to peripheral ratios were markedly lower for BDP, FF, and GB compared to FluF, VI and UMEC, respectively (Table 1), the lower central to peripheral intrathoracic ratio indicates a better deposition of the drug in the small airways.

Results

Table 1: Central to peripheral deposition ratios (all flow rates)

Component	Extrafine BDP/FF/GB pMDI	FluF/VI/UMEC DPI
ICS	0.48 ± 0.13	1.96 ± 0.84
LABA	0.48 ± 0.13	0.97 ± 0.34
LAMA	0.49 ± 0.13	1.20 ± 0.48

Higher peripheral deposition with lower C/P ratio was achieved with all three components combined for pMDI BDP/FF/GB compared to DPI FluF/UM/VI (Figure 2).

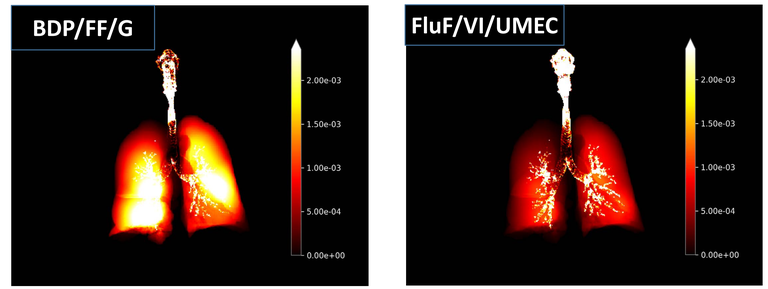

Figure 2: Visualization of deposition in entire respiratory airways showing greater peripheral deposition for BDP/FF/G (all components, all flow rates). The bright yellow color indicates greater deposition.

Conclusion

A comparison of lung deposition profiles of two inhaled fixed-dose triple therapies using *in-silico* flow estimates generated by FRI applied to COPD patient airway models showed a higher intrathoracic deposition of the ICS component and a greater peripheral (small airways) deposition of the ICS, LABA, and LAMA components with extrafine TRIMBOW® pMDI (BDP/FF/GB) compared to non-extrafine TRELEGY® ELLIPTA® DPI (FluF/VI/UMEC). These findings may be attributed to the lower inhaled particle size with TRIMBOW® pMDI.

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* A different group of COPD patients than those providing the spirometry and CT scan data .