Protocol

Study 1: Exploratory study - identifying the benefits of pMDI versus Diskus for delivering fluticasone/salmeterol combination therapy in patients with chronic obstructive pulmonary disease (COPD)

To characterise patients with COPD initiating with fluticasone/salmeterol combination therapy via pMDI and Diskus and to identify and compare the potential benefits of using either device in the delivery of fluticasone/salmeterol combination therapy

Contents

OBJECTIVES

The aims of this exploratory study are to characterise patients with chronic obstructive pulmonary disease[i] (COPD) initiating with fluticasone/salmeterol combination therapy delivered via pressurised metered dose inhaler (pMDI; also known as Evohaler) or Diskus (also known as Accuhaler); and to identify and compare the potential benefits of using either device in the delivery of fluticasone/salmeterol combination therapy.

This will be carried out by:

(1) Characterising patients with COPD on fluticasone/salmeterol combination therapy via pMDI and Diskus.

(2) Identifying and comparing the potential benefits of using pMDI versus Diskus in the delivery of fluticasone/salmeterol combination therapy in terms of both efficacy and adverse events, in particular:

a. Number of COPD exacerbations
b. Development of pneumonia infections
c. Type II diabetes diagnosis
d. Therapeutic index[ii]
e. Number of severe COPD-related events, including:
    i. Lower respiratory tract infections
    ii. Oral thrush

These are more clearly defined under 'Dataset Variables' below.

BACKGROUND

Inhaled corticosteroid use by patients with obstructive lung disease is associated with increased risk of pneumonia [1], increased risk of developing type-II diabetes [2] and increased risk of oral thrush [3].

Pressurised metred dose inhaler (pMDI) and Diskus devices both deliver fluticasone/salmeterol combination therapy, but the Diskus formulation includes added lactose. A previous Research in Real Life study [4] demonstrated that asthma patients on combination therapy via pMDI have significantly greater odds of achieving asthma control and fewer exacerbations than those on dry powder inhalers such as Diskus.

This study aims to explore and identify the benefits of using either pMDI versus Diskus for delivering fluticasone/salmeterol combination therapy in patients with COPD.

This study will focus on patients with COPD initiating with Seretide® combination therapy, delivered via

- pMDI (also known as Evohaler)
- Diskus (also known as Accuhaler)

In addition, the number of patients in the following sub-populations will be reported:

[i] COPD is defined as a common, preventable and treatable disease characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lungs to noxious particles and gases.

[ii] Therapeutic index = highest dose not causing harm (side effect) / lowest dose that causes benefit (reduced number of severe COPD-related events).

- COPD without asthma
- COPD with asthma
- COPD +/- asthma AND eosinophils >0.4 X 10^9/L

DATASOURCE

This study will use the Optimum Patient Care Research Database (OPCRD), which comprises anonymous data extracted from primary care practices in order to perform reviews of their chronic respiratory services. Two types of anonymised patient data are typically collected:

(1) Routine clinical data
- OPC software interfaces with primary care practice management systems and extracts disease coding and prescribing information.

(2) Questionnaires
- Patients identified as recipients of the respiratory service under review are invited to complete validated disease assessment questionnaires to better understand their current health status (and/or possible reasons for sub-optimal status).
- Anonymised questionnaires are assigned a unique code to aid matching routine data to questionnaire results.

The OPCRD has been approved by Trent Multi Centre Research Ethics Committee for clinical research use. The anonymous, longitudinal patient data offers a high-quality data source for use in clinical, epidemiological and pharmaceutical research. It enables research to be carried out across a broad range of respiratory areas.

STUDY DESIGN

The study will be a retrospective database analysis, consisting of a (one year) baseline period, a (one year) outcome period and an index date, defined as the date of the first prescription for Seretide® combination therapy at which patients with evidence of COPD[iii] will be split into the following groups:

(1) Those using pMDI (also known as Evohaler)
(2) Those using Diskus (also known as Accuhaler)

The baseline period will be one year prior to and including the index date[iv] and it will be used for patient characterisation, such as demographics, baseline therapy, disease severity and number of COPD exacerbations. The outcome period will be one year following the index date, and the effect of device on COPD-related severe exacerbations, adverse events and therapeutic index will be investigated.

[iii] COPD diagnostic code (at any time) and recorded spirometry data supporting COPD diagnosis within 5 years window of diagnosis code. Note that individuals with asthma and bronchiectasis will not be excluded.
[iv] except for therapy prescribed at IPD (which is included in the outcome).

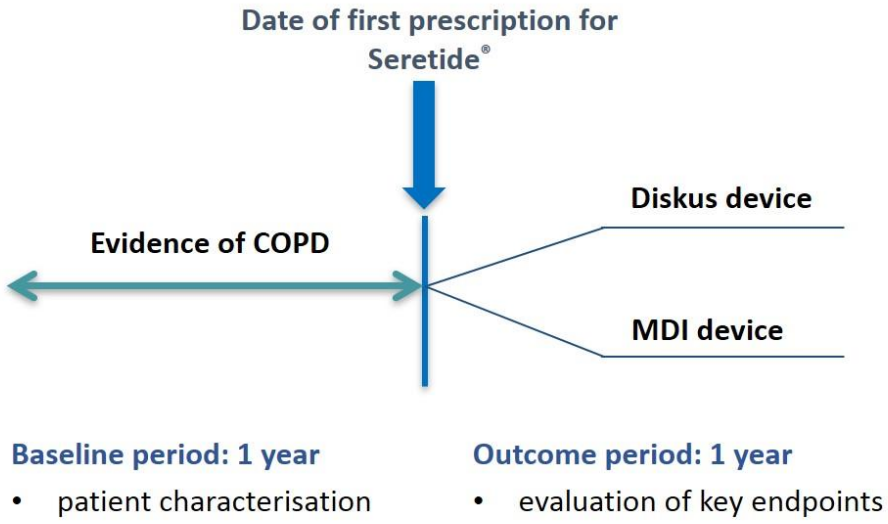

Figure 1: Study design

Inclusion Criteria

In order to be included in the study, patients must fit the following criteria:

(1) COPD diagnosis (COPD diagnostic code (at any time) and COPD confirmed by FEV/FVC ratio <0.7 ever in medical history. Note that individuals with asthma and bronchiectasis will not be excluded)
(2) Two years of continuous practice data comprising 1 year baseline data and 1 year outcome data
(3) ≥2 prescriptions for Seretide® pMDI OR Seretide® Diskus during 1 year outcome period, inclusive of IPD (i.e. 1 Seretide® prescription at IPD plus ≥1 prescriptions for the same device during 1 year outcome period).
(4) Age ≥35 at time of initiating with Seretide

Exclusion Criteria

(1) Evidence of restrictive lung disease other than bronchiectasis (diagnostic code)
(2) ≥1 prescription for inhaled corticosteroids (ICS), including as part of a fixed dose combination, during baseline period (excluding IPD)
(3) Evidence of pneumonia during baseline period (diagnostic code)
(4) No maintenance oral steroids in baseline

Dataset Variables

Demographics (gender, age, weight, height, BMI, smoking status, disease severity (FEV1 percent predicted, FEV1/FVC ratio, GOLD group, mMRC score)) will be calculated at (or closest to) the IPD. Disease severity will be regarded as missing if >5 years either side of IPD.

Treatment therapy will be recorded in the year prior to the IPD.

Baseline blood eosinophil counts will be recorded[v] (where valid is defined as a numeric value expressed /L).

Co-morbidities will be examined regardless of when diagnosis relative to the index date was made and include:

- Ischaemic heart disease
- Heart failure diagnosis
- Diabetes diagnosis
- Asthma diagnosis
- Bronchiectasis diagnosis
- Rhinitis
- Eczema
- Osteoporosis diagnosis
- Gastroesophageal reflux disease (GERD)
- Anxiety/depression diagnosis
- Chronic kidney disease
- Hypertension

Note that all of the above co-morbidities (except diabetes) are identified by GP diagnostic read code, ever recorded. Diabetes is identified by GP anti-diabetic drug prescriptions; AND/OR by GP diagnostic read code, ever recorded.

For the baseline and outcome periods, the following will be calculated:

- COPD exacerbations[vi] and the date of event (each component of the definition will also be analysed separately)

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[v] closest value to IPD (missing if >5 years either side of IPD).

[vi] Where an exacerbation is defined as an occurrence* of:

- COPD-related: Unscheduled hospital admission / A&E attendance**; OR
- An acute course of oral steroids prescribed with evidence of a respiratory review***; OR
- Antibiotics prescribed with evidence of a respiratory review***.

*Where ≥1 oral steroid course / hospitalisation / antibiotics prescription occur within 2 weeks of each other, these events will be considered to be the result of the same exacerbation (and will only be counted once).

****COPD-related Hospitalisations:** consist of either a definite COPD Emergency Attendance or a definite COPD Hospital Admission; OR a generic hospitalisation read code which has been recorded on the same day as a **Lower Respiratory Consultation**[$] (see below - excluding where the only lower respiratory code recorded on that day was for a lung function test).

*****Evidence of a Respiratory Review** - consists of the following:

a) Any **Lower Respiratory Consultation**[$] (see below) and
b) Any additional respiratory examinations, referrals, chest x-rays, or events.

[$] **Lower Respiratory Consultations -** consist of the following:

a) Lower Respiratory read codes (including Asthma, COPD and LRTI read codes);

- Development of pneumonia (recorded as absence/presence of, and confirmed via: chest X-ray within a month of a pneumonia diagnosis OR hospitalisation within a month of a pneumonia diagnosis). Note that baseline values will be zero due to study exclusion criteria.
- Development/progression of diabetes
    - Development of diabetes (recorded as absence or presence of) during outcome period for patients (for patients without diabetes at or prior to IPD)
    - Progression of ongoing type-II diabetes treatment to insulin (defined as no insulin prescription during 1 year baseline period AND any insulin prescriptions during 1 year outcome period)
    - Diabetic control (defined as change in HbA1c value prior to starting Seretide® and after IPD)
    - Diabetic medication (defined as change in anti-type-II diabetic medication dosage OR medication type)
- Number of potential severe COPD-related adverse events and date of event including
    - Oral thrush
    - Lower respiratory tract infections
    - Bronchitis
    - Dysphonia / hoarseness
    - Nasopharyngitis (common cold)
    - Sinusitis
    - Hypokalemia (low blood potassium)
    - Muscle or joint pain
- ICS dose (in outcome period only) and date of ICS prescription

Matching will be used if required.

STUDY OUTCOMES

The primary aim of the current study is to identify baseline and outcome characteristics of patients with COPD initiating with Seretide® combination therapy via pMDI and Diskus and to identify and compare the potential benefits of using each device in the delivery of Seretide®. Among other events, the effect of device on the following outcomes will be investigated:

(1) COPD related severe exacerbations

Where an exacerbation is defined as an occurrence[vii] of:

- COPD-related: Unscheduled hospital admission / A&E attendance[viii]; OR
- An acute course of oral steroids prescribed with evidence of a respiratory review[ix]; OR

b) Asthma/COPD review codes excl. any monitoring letter codes;
c) Lung function and/or asthma monitoring.

[vii]Where ≥1 oral steroid course / hospitalisation / antibiotics prescription occur within 2 weeks of each other, these events will be considered to be the result of the same exacerbation (and will only be counted once).

[viii]**COPD-related Hospitalisations:** consist of either a definite COPD Emergency Attendance or a definite COPD Hospital Admission; OR a generic hospitalisation read code which has been recorded on the same day as a **Lower Respiratory Consultation*** (see below - excluding where the only lower respiratory code recorded on that day was for a lung function test).

[ix]**Evidence of a Respiratory Review** - consists of the following:

- Antibiotics prescribed with evidence of a respiratory review[ix].

(2) COPD related adverse events

Where adverse events include the number of incidences of:

- Oral thrush
- Lower respiratory tract infections
- Bronchitis
- Dysphonia / hoarseness
- Nasopharyngitis (common cold)
- Sinusitis
- Hypokalemia (low blood potassium)
- Muscle or joint pain

(3)Therapeutic index

Therapeutic index = highest dose not causing harm (side effect) / lowest dose that causes benefit (reduced number of severe COPD-related events).

For the highest dose not causing harm: the median dose at which no (any) adverse events occur
For the lowest dose that causes benefit (reduced number of severe COPD-related events): median dose at which patients show no increase in number of exacerbations in outcome

STATISTICAL ANALYSIS

Statistically significant results will be defined as $p<0.05$ and trends as $0.05 \leq p<0.10$

Summary statistics will be produced for all baseline and outcome variables, as a complete dataset and by device. For variables measured on the interval or ratio scale, these will include:
Sample size (n) & percentage non-missing
Mean & Variance / Standard Deviation
Range (Minimum / Maximum)
Median & Inter-quartile Range (25th and 75th percentiles)

For categorical variables, the summary statistics will include:
Sample size (n)
Range (if applicable)
Count and Percentage by category (distribution)

Treatment arms will be compared using t-test / Mann Whitney U-test (depending on distribution) for variables measured on the interval/ratio scale and using a chi square test for categorical variables.

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a) Any **Lower Respiratory Consultation*** (see below) and
b) Any additional respiratory examinations, referrals, chest x-rays, or events.

*** Lower Respiratory Consultations -** consist of the following:
a) Lower Respiratory read codes (including Asthma, COPD and LRTI read codes);
b) Asthma/COPD review codes excl. any monitoring letter codes;
c) Lung function and/or asthma monitoring.

TIMELINE, DELIVERY AND COSTINGS

Proposed timelines summary:

	Number of weeks of work required
Baseline analysis	4
Outcome analysis	8
Statistical analysis	8
Report writing	2

RESEARCH TEAM

Chief Investigator: Professor David Price, Professor of Primary Care Respiratory Medicine, Centre of Academic Primary Care, University of Aberdeen and Director of Research in Real Life.

Steering Committee: Not required for study 1.

Research Team: Research in Real Life
Commercial and Compliance Director: Catherine Hutton
Performance Director: Zlatko (Giano) Terzic
Research Team Lead: Emily Davis
Project Lead: Jessica Martin
Senior Statistician: Annie Burden
Data Analyst: Derek Skinner

REFERENCES

1. Price D, Yawn B, Brusselle G, Rossi A. Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. Prim Care Respir J 2013;22:92-100.

2. Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. Am J Med 2010;123:1001-6.

3. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775-89.

4. Price D, Roche N, Christian Virchow J, et al. Device type and real-world effectiveness of asthma combination therapy: an observational study. Respir Med 2011;105:1457-66.

5. Janson C, Larsson K, Lisspers KH, et al. Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting beta2 agonist: observational matched cohort study (PATHOS). Bmj 2013;346:f3306.