Research in Real Life

Real Life Effectiveness of Aclidinium Bromide

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Project for Almirall

Real-life effectiveness evaluation of the long-acting muscarinic antagonist aclidinium bromide (Eklira®) for the management of COPD in a routine UK primary care population

Evaluating the real-life effectiveness (with optional cost effectiveness) of aclidinium bromide and the characteristics of patients prescribed aclidinium therapy for COPD following the launch of Eklira®.

PROTOCOL FOR STUDY 1

1 STUDY DESCRIPTION

1.1 STUDY DESIGN

Aim of project: To evaluate the real-life effectiveness of the antimuscarine bronchodilator aclidinium bromide (Eklira®) in three combined studies following the launch of Eklira® in the UK.

Study 1: Characterising patients prescribed aclidinium bromide from tiotropium, and determining how many patients are satisfied with their change to aclidinium therapy. This will determine the acceptability of aclidinium in clinical practice.

Study 2: (A) Examine the effects of changing COPD therapy to aclidinium bromide from LAMA therapy other than aclidinium bromide. (B: optional) Examine the effects of changing patient therapy based on patterns of use in study 1 (e.g. changing to aclidinium bromide ± LABA from ICS/LABA). This study is a before and after comparison of changes in patient outcomes in patients changing their COPD therapy to aclidinium bromide from LAMAs other than aclidinium bromide or other therapies to examine the clinical effects of the therapy change. The study will be powered for the change from baseline therapy.

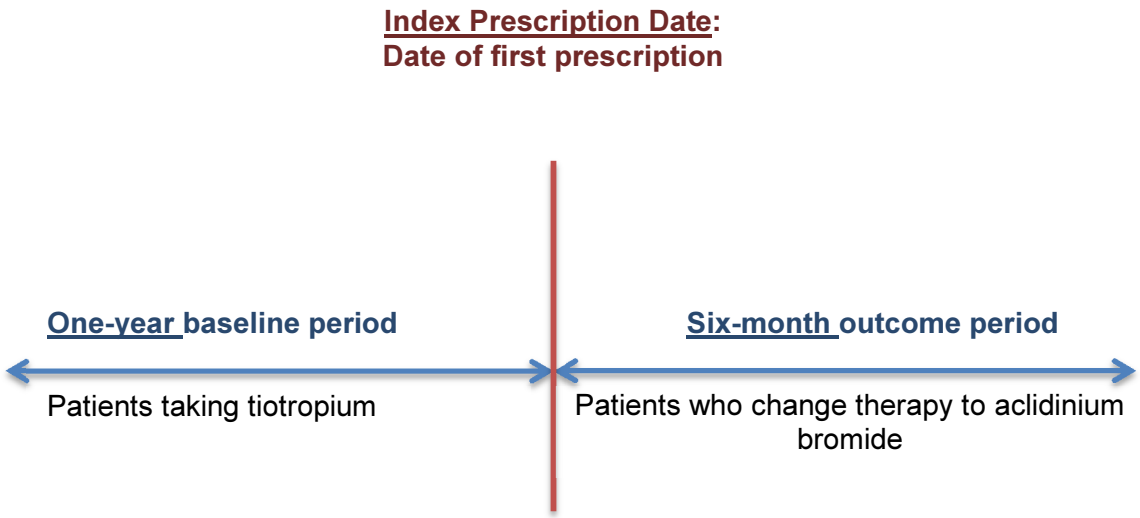
Study 3: Matched cohort study comparing COPD outcomes for patients changing to aclidinium bromide from tiotropium with patients remaining on their tiotropium therapy. This study will provide a matched comparison of the two therapies and the relative effectiveness of aclidinium bromide.

This protocol covers the procedures required for study 1.

Study 1

This is a retrospective effectiveness study consisting of a baseline and outcome period. The baseline period is a minimum of one year before the date of the patient's first aclidinium bromide prescription during which all patients were treated with tiotropium. The outcome period is defined as six months following the first aclidinium bromide prescription.

6-month therapy success evaluation and patient characterisation



During the six month outcome period, the acceptability of change will be evaluated, defined below.

1.2 STUDY PERIOD

The full study will run for three years post UK aclidinium bromide launch. Study 1 is aimed to be completed within the first year.

1.3 STUDY POPULATION

1.3.1 INCLUSION CRITERIA

The analysis includes patients who changed their therapy from tiotropium to aclidinium bromide following its launch in the UK. Patients should also meet the following inclusion criteria:

- Aged ≥40 years at index prescription date
- COPD diagnosis (diagnostic code and ≥2 prescriptions for COPD therapy in year prior to IPD)
- Evidence of COPD treatment: ≥1 prescription for tiotropium during the baseline period
- Ongoing COPD treatment: ≥1 prescription for long acting muscarinic antagonist therapy in the outcome period

1.3.2 EXCLUSION CRITERIA

As this study is exploring the demographics of patients who change their therapy to aclidinium bromide, no patients will be excluded at this stage.

1.4 STUDY OUTCOMES

The following outcome will be evaluated for all patients:

1.4.1 PRIMARY EFFECTIVENESS OUTCOME

The primary effectiveness outcome for this study is the **acceptability of change** from tiotropium to aclidinium during the six-month outcome period.

This is defined as the percentage of the patients changed to aclidinium bromide (received a prescription for aclidinium at date of first prescription) who did not receive ≥1 prescription for tiotropium during the outcome period. As some patients will change back to their previous tiotropium because of a resistance to change rather than as a reflection of dissatisfaction with their new therapy an acceptability rate of <70% is felt to be potentially indicative of dissatisfaction with the aclinidium therapy.

Potential reasons for patients who change back may be explored if required by the study sponsor.

1.4.2 PATIENT CHARACTERISATION

To provide real-world data on the utilisation of aclidinium bromide in clinical practice, the patients prescribed aclidinium bromide will be characterised according to the following in the year prior to aclidinium bromide initiation. As the study aims to characterise the patients who are prescribed aclidinium, all patients will be characterised regardless of whether or not they change back to tiotropium:

- age
- sex
- height
- weight
- BMI
- % predicted FEV1
- FEV/FVC ratio
- smoking status
- co-morbidities including asthma, rhinitis
- COPD exacerbations
- lower respiratory tract infections
- prior LAMA therapy + doses
- COPD severity (risk and symptoms) defined by GOLD group (A, B, C, D)
- lung function defined by GOLD stage (1, 2, 3, 4)

2 DATA AND ANALYTICAL METHODS

2.1 DATA

2.1.1 DATA SOURCE

Data will be sourced from one database for this study:

2.1.1.1 OPTIMUM PATIENT CARE RESEARCH DATABASE

The Optimum Patient Care Research Database (OPCRD) comprises anonymised data extracted from 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; and

(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 anonymised, 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.

2.2 DEFINITIONS

2.2.1 BODY MASS INDEX (BMI)

The **Body Mass Index** is a representative measure of body weight based on the weight and height of the subject. It is defined as the weight (in kg) divided by the square of the height (in m) and is measured in kg/m^2.

2.2.2 CHARLSON COMORBIDITY INDEX (CCI)

The **Charlson Comorbidity Index** was developed in the US in 1987 as a method of classifying prognostic comorbidity in longitudinal studies[i]. It predicts the one-year mortality for a patient who may have a range of comorbid conditions such as heart disease, AIDS or cancer. Each condition is assigned a "weight" depending on the risk of dying associated with the condition; scores are then summed to give a total score predicting mortality.

The weights were revised and up-dated (for example, mortality due to HIV has fallen) by Dr. Foster Intelligence (DFI) in their HSMR Methodology documentation[ii] and calibrated using UK data (due to differences in coding practice and hospital patient population characteristics from the US), using ICD-10 codes. As a result:

- DFI have expanded the coding definition of some conditions;
- Only secondary diagnoses (DIAG02-DIAG14) are now considered;
- There is greater variation in weights between conditions and the Charlson Index (the sum of the weights) can be treated as a continuous variable (limited to the range 0-50) for the purposes of risk adjustment. The weights, codes and conditions used in this study are summarised in **Error! Reference source not found.**.

.Condition	Condition Name	ICD-10 codes	New weight
1	Acute myocardial infarction	I21, I22, I23, I252, I258	5
2	Cerebral vascular accident	G450, G451, G452, G454, G458, G459, G46, I60-I69	11
3	Congestive heart failure	I50	13
4	Connective tissue disorder	M05, M060, M063, M069, M32,	4

		M332, M34, M353	
5	Dementia	F00, F01, F02, F03, F051	14
6	Diabetes	E101, E105, E106, E108, E109, E111, E115, E116, E118, E119, E131, E131, E136, E138, E139, E141, E145, E146, E148, E149	3
7	Liver disease	K702, K703, K717, K73, K74	8
8	Peptic ulcer	K25, K26, K27, K28	9
9	Peripheral vascular disease	I71, I739, I790, R02, Z958, Z959	6
10	Pulmonary disease	J40-J47, J60-J67	4
11	Cancer	C00-C76, C80-C97	8
12	Diabetes complications	E102, E103, E104, E107, E112, E113, E114, E117, E132, E133, E134, E137, E142, E143, E144, E147	-1
13	Paraplegia	G041, G81, G820, G821, G822	1
14	Renal disease	I12, I13, N01, N03, N052-N056, N072-N074, N18, N19, N25	10
15	Metastatic cancer	C77, C78, C79	14
16	Severe liver disease	K721, K729, K766, K767	18
17	HIV	B20, B21, B22, B23, B24	2

Table 2: Co-morbid conditions and scores used in the Charlson Co-morbidity Index (CCI)

3 THE ANALYSIS PLAN

3.1 GENERAL

Exploratory data analysis will be carried out for all baseline variables and presented in the appendix.

3.1.1 SOFTWARE

All analysis will be carried out using IBM SPSS Statistics version 20[iii], SAS version 9.3[iv] and Microsoft Office EXCEL 2007.

3.1.2 SIGNIFICANCE TESTING

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

3.2 EXPLORATORY DATA ANALYSIS

3.2.1 SUMMARY STATISTICS

Summary statistics will be produced for all baseline variables. 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)
- Count and Percentage by category (distribution).

3.2.2 PLOTS

Plots will be produced for all baseline variables. For variables measured on the interval or ratio scale, these will include:

- Frequency plots
- Box and whisker plots

Frequency plots will illustrate the distribution of the variable and whether categorisation may be necessary (for example, if heavily skewed). Box plots will illustrate the location and spread of the variable and identify potential outliers.

For categorical variables, bar charts will be produced to illustrate distributions.

3.2.3 DATA PREPARATION

The data will be prepared for analysis by:

- Investigating potential outliers;
- Indentifying and creating new variables as necessary:
    - Transformations of skewed data (for example, log transformations);
    - Categorisation of heavily skewed data;
- Investigating missing data (type of and reason for missingness).

3.3 STATISTICAL ANALYSIS

3.3.1.1 PRIMARY EFFECTIVENESS OUTCOME

The percentage of patients achieving the primary outcome will be calculated.

3.3.2 PATIENT CHARACTERISATION

Summary statistics will be produced for all baseline characteristics

3.4 STATISTICAL TESTS

Table summarises the statistical tests that may be used in the analysis as appropriate.

Test	**Use**
Chi-square (χ^2) test	Tests for the association between 2 categorical variables (data presented

	in contingency tables).
Mann Whitney U test	Nonparametric test to compare the distribution of a variable measured on the ratio / interval scale across two groups when the variable is not normally distributed.
t-test	Parametric test to compare the mean of a variable measured on the ratio / interval scale between two groups when the variable is normally distributed.

Table 3: Summary of Statistical Tests

3.5 RESEARCH TEAM & STEERING COMMITTEE

Chief Investigator: Professor David Price, Professor of Primary Care Respiratory Medicine and Director of Research in Real Life

Research Team: Research in Real Life
Chief Executive: Catherine Hutton, Research in Real Life
Researcher: Daina Lim, Research in Real Life
Project Coordinator: Victoria Carter, Research in Real Life
Senior Statistician: Annie Burden: Research in Real Life
Data Analyst: Julie von Ziegenweidt, Research in Real Life

Steering Committee: TBC

Study Sponsors: Almirall

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[i] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and Validation. *J Chronic Dis* 1987;40:373-383.

[ii] Doctor Foster Health. 2010. HSMR mortality indicators. Available online at: http://www.drfosterhealth.co.uk/docs/HSMR-methodology-Nov-2010.pdf

[iii] IBM SPSS Statistics. 2010. Statistics family. Available online at: www.spss.com/uk/software/statistics/

[iv] SAS Institute Inc. 2010. Statistical Analysis with SAS/STAT Software. Available online at: www.SAS.com/offices/europe/uk/technologies/analytics/statistics/stat/ondex.html