DUS1 and DUS2 Summary for EUPAS Registry (#6559)

Rationale and background

In July 2012, Eklira/Bretaris Genuair (aclidinium bromide 322 µg twice daily) was approved in the European Union (EU) for maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). In September 2014, Duaklir Genuair (aclidinium bromide in fixed-dose combination with formoterol, 340 µg/12 µg twice daily) was approved in the EU for the same indication.

As part of the pharmacovigilance plan, a multinational database drug utilisation study (DUS) in a cohort of new users of aclidinium bromide and new users of other inhaled medications frequently used by patients with COPD was conducted (DUS1) in populations from the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK), the National Health Databases in Denmark, and the German Pharmacoepidemiological Research Database (GePaRD). DUS2 was conducted after the new fixed-dose combination of aclidinium bromide with formoterol (hereafter, aclidinium/formoterol) became available and a minimum number of users (N > 1,500-2,000) had accumulated in the same data sources.

Research question and objectives

The objectives of DUS1 were to describe the characteristics of new users of aclidinium and other selected COPD medications, evaluate the potential off-label use of aclidinium, and identify and describe users of aclidinium in patient subgroups for which there is missing information in the risk management plan (RMP). The objectives of DUS2 were the same as DUS1 with the addition of new users of aclidinium/formoterol in the study.

Study design

Non-interventional multinational European database cohort study.

Setting

DUS1 was conducted in CPRD in the UK between 1 September 2012 and 30 June 2015, the National Health Databases in Denmark from 1 September 2012 to 31 December 2015, and GePaRD in Germany between 1 October 2012 to 31 December 2013. For DUS2, new users of the study medications were identified between 1 January 2015 and 31 December 2017 in CPRD; between 4 March 2015 and 31 December 2017 in the Danish National Health Databases; and between 1 February 2015 and 31 December 2015 in GePaRD. All new users were followed up to 1 year after the date of the first prescription for aclidinium, aclidinium/formoterol, or selected COPD medications.

Subjects and study size, including dropouts

The study population comprised new users of long-acting anticholinergic (LAMA) medications—aclidinium bromide, aclidinium/formoterol, tiotropium, Other LAMA, LAMA/long-acting beta$_2$-agonists (LAMA/LABA); new users of LABA; and new users of LABA/inhaled corticosteroid (LABA/ICS). A minimum study size of 1,500 to 2,000 new users of aclidinium (DUS1) or aclidinium/formoterol (DUS2) in each data source was considered appropriate to provide an acceptable level of precision. The final number of users of aclidinium or aclidinium/formoterol included in each data source was above 2,000 at the time the data were available for extraction.

Variables and data sources

The main variables were age, sex, smoking, COPD and asthma diagnoses, comorbidity, comedications, COPD severity, indication for aclidinium and aclidinium/formoterol, and frequency of conditions with missing information in the RMP. Smoking was ascertained through recorded information in CPRD and the use of smoking-cessation drugs in Denmark and GePaRD. Medical diagnoses related to smoking were also used in GePaRD.

Results

DUS1

The study included 3,604 new users of aclidinium in CPRD, 4,613 new users in Denmark, and 13,327 new users in GePaRD. New users of LAMA medications, including new users of aclidinium, were older (median age, 69 to 71 years) than new users of LABA or LABA/ICS (median age, 55 to 66 years). Smoking was more frequent in users of LAMA medications (19.0% to 37.8% of users) than in users of LABA or LABA/ICS (7.3% to 25.9%).

A diagnosis of COPD was more frequent in users of LAMA medications (44.9% to 95.9%) than in users of LABA or LABA/ICS (25.5% to 67.4%). Asthma only (no COPD) was more frequent in users of LABA or LABA/ICS (12.5% to 59.5%) than in users of LAMA medications (2.3% to 8.9%).

In CPRD and Denmark, users of aclidinium had more severe or very severe COPD (CPRD, 45.8%; Denmark, 69.9%) than users of the other study medications (CPRD, up to 42.9%; Denmark, up to 65.2%). In GePaRD, users of aclidinium had more severe COPD (28.3%) than users of other medications except LAMA/LABA (39.0%).

The most frequent comorbidity across the study medications in patients with COPD aged 40 years or older were hypertension (43.6% to 79.5%) and depressive disorders (23.2% to 52.6%). The most frequent comedications in these patients were short-acting beta2-agonists (24.2% to 91.0%), antibiotics (56.8% to 79.3%), and cardiovascular medications (62.2% to 77.3%).

Estimated off-label prescription of aclidinium was 4.2% in CPRD, 6.7% in Denmark, and 5.0% in GePaRD. The indication could not be evaluated in 37.7% of users of aclidinium in Denmark.

The most frequent conditions for which information was missing from the RMP were renal failure in CPRD (21.8%), angina in Denmark (17.9%), and arrhythmias in GePaRD (20.1%).

Duration of the index episode for aclidinium ranged from 3.9 months in GePaRD to 5.4 months in Denmark. In all study populations, persistence of use was higher in users of LAMA medications than in users of LABA or LABA/ICS. The highest persistence was among users of LAMA/LABA (32.3% in CPRD, 36.2% in Denmark, and 38.6% in GePaRD). The percentage of users of aclidinium bromide who discontinued with switching was 22.4% in Denmark, 11.3% in CPRD, and 9.5% in GePaRD.

DUS2

The study included 4,871 new users of aclidinium and 2,153 new users of aclidinium/formoterol in CPRD, 2,836 new users of aclidinium and 2,586 new users of aclidinium/formoterol in Denmark, and 9,961 new users of aclidinium and 10,069 new users of aclidinium/formoterol in GePaRD. New users of LAMA medications, including new users of aclidinium and aclidinium/formoterol, were older (median age, 69 to 71 years) than new users of LABA (median age, 63 to 67 years) or LABA/ICS (median age, 53 to 59 years).

Smoking was more frequent in users of LAMA medications (20.1% to 39.9% of users) than in users of LABA (15.5% to 26.8% of users) or LABA/ICS (7.9% to 23.1%). For all study medications, obesity was more frequent in CPRD than obesity proxy estimators in Denmark and GePaRD. For all study medications, the alcohol abuse proxy estimator was more frequent in Denmark than in CPRD and GePaRD.

A diagnosis of COPD was more frequent in users of LAMA medications (46.8% to 92.8%) than in users of LABA (28.4% to 65.5%) or LABA/ICS (24.2% to 43.4%). Asthma only (no COPD) was more frequent in users of LABA (13.3% to 43.7%) or LABA/ICS (24.7% to 61.8%) than in users of LAMA medications (2.6% to 12.9%). In CPRD, users of aclidinium had a higher proportion of severe or very severe COPD than users of aclidinium/formoterol or users of LABA and LABA/ICS. In Denmark, aclidinium, Other LAMA, and LAMA/LABA users had a higher proportion of severe or very severe COPD than users of other medications. In GePaRD, users of LAMA/LABA medications and users of aclidinium/formoterol had the highest proportion with severe COPD, and the proportion of severe COPD in users of aclidinium was the lowest amongst users of LAMA medications.

The most frequent comorbidity across the study medications in patients with COPD aged 40 years or older was hypertension (50.0% to 79.4%) in all data sources. The second most frequent comorbidity was depressive disorders (39.0% to 42.8%) in CPRD, urinary tract

infections (48.8% to 54.4%) in Denmark, and benign prostatic hyperplasia (BPH) (24.8% to 29.6%) in GePaRD. The most frequent comedications in these patients were short-acting beta2-agonists (25.7% to 84.4%), antibiotics (54.3% to 74.8%), and cardiovascular medications (62.8% to 75.8%).

Off-label use of aclidinium was 5.0% in CPRD, 8.9% in Denmark, and 5.4% in GePaRD. Off-label use of aclidinium/formoterol was lower than for aclidinium: 3.2% in the CPRD, 3.3% in Denmark, and 2.6% in GePaRD. The main reason for off-label use was having a diagnosis of asthma in the absence of a diagnosis of COPD.

The most frequent conditions with missing information in the RMP that were identified prior to initiation of study medications were renal failure and BPH in CPRD, arrhythmias and angina in Denmark, and BPH and arrhythmias in GePaRD. These conditions affected between 15% and 29% of users of aclidinium or aclidinium/formoterol.

For all study medications, duration of the index episode was longer in Denmark than in CPRD or GePaRD. Median duration of the index episode for aclidinium ranged from 3.0 months in GePaRD to 6.0 months in Denmark; median duration of the index episode for aclidinium/formoterol ranged from 3.0 months in GePaRD to 8.9 months in Denmark. In all study populations, persistence of use was higher in users of LAMA medications than in users of LABA or LABA/ICS. Approximately one-third of users of aclidinium and aclidinium/formoterol continued treatment at 1 year of follow-up in CPRD. This proportion was higher in users of aclidinium/formoterol in Denmark and it was lower in users of aclidinium in GePaRD.

The proportion of patients who discontinued the study medications and switched to another study medication was in general higher in new users of LAMA medications than users of LABA and LABA/ICS medications. Amongst users of aclidinium, the percentage discontinuing with switching to another medication was 28.1% in CPRD, 29.2% in Denmark, and 19.2% in GePaRD. For aclidinium/formoterol, the percentage discontinuing with switching to another medication was 31.7% in CPRD, 30.2% in Denmark, and 14.1% in GePaRD.

Discussion

In both studies, characteristics of users of the study medications were consistent with the potential indication of COPD in users of LAMA medications and of COPD and/or asthma in users of LABA and LABA/ICS medications.

In DUS1, the higher severity of COPD in users of aclidinium is compatible with a selective prescribing of a new medication to more severely affected patients not responding to other available treatments.

DUS2 found that amongst users of LAMA medications, users of tiotropium in CPRD had the lowest frequency of a prior diagnosis of COPD and the highest frequency of a diagnosis of

asthma. This finding could be explained to some extent by the approval of tiotropium for the treatment of asthma in Europe 2014.

The higher severity of COPD in Denmark than in CPRD or GePaRD is consistent with the available information in CPRD, where patients with COPD were identified based on primary care and hospital discharge diagnoses. In GePaRD, identification was based on ambulatory care and hospital diagnoses, whilst in Denmark, only hospital inpatient and outpatient codes were available (no primary care data were available). Thus, in Denmark, patients with COPD were expected to have more severe disease, as patients with COPD are mostly managed in primary care, whereas worsening of the condition or complications are mainly managed in a hospital setting.

The lack of information about primary care diagnoses in Denmark could result in underascertainment of comorbidity and potential indications amongst users of the study medications.

Overall, in these studies, users of aclidinium and users of LAMA medications were older; had a higher prevalence of COPD, current smoking, comorbidity, and use of comedications; and had a lower prevalence of asthma than users of LABA or LABA/ICS. In DUS1, hypertension, depressive disorders, ischaemic heart disease, diabetes, and urinary tract infections were the most frequent comorbidities in users of the study medications with COPD. In DUS2, hypertension, depressive disorders, and urinary tract infections were the most frequent comorbidities in users of the study medications with COPD. In both studies, severe COPD was more frequent in users of LAMA medications and in users of aclidinium and aclidinium/formoterol than in users of other study medications. Off-label use of aclidinium bromide was low in the three study populations, although in Denmark information on diagnoses was limited to the inpatient and outpatient hospital setting. Aclidinium and aclidinium/formoterol were prescribed in patients with a history of conditions with missing information in the RMP, most frequently renal failure. Overall, these studies indicate that users of aclidinium and aclidinium/formoterol have a high prevalence of chronic comorbidity and use of comedications and more severe COPD than users of other COPD medications; also, aclidinium and aclidinium/formoterol are mainly prescribed according to the labelling.