SEVENTH FRAMEWORK PROGRAMME

SAFEGUARD

SAFETY EVALUATION OF ADVERSE REACTIONS IN DIABETES

Safety Evaluation of Adverse Reactions In Diabetes

S A F E G U A R D

HEALTH-282521

Executive summary Drug Utilization

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Full report available upon request

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Objectives

Medicines are prescribed to patients with type 2 diabetes mellitus (T2DM) in order to achieve improved glycemic control. Changes in therapy are largely guided by the level of glycemic control obtained, patient characteristics and comorbidities. As glycemic control tends to deteriorate as disease progresses, the medication regimen results in additions or switching of glucose lowering drugs (GLD). This drug utilization study (DUS) aimed to evaluate the utilization of GLD in the general population, the patterns of switching, persistence, concomitant and patient determinants at treatment initiation.

Methods

The DUS was a descriptive retrospective observational study using routinely collected automated healthcare data from cohort entry from January 1st, 1998 (earliest date valid data available in a contributing database (DB)) to the last data drawn down, data source transfer out, end of registration, end of membership, institutionalization, date of last data drawn down, death (database/patient specific) or December 31st 2012. Individuals had to have at least 365 days of continuous enrollment in the database. Data were retrieved from 8 European electronic healthcare DBs (Netherlands: PHARMO, IPCI; Spain: BIFAP; Germany: GePaRD; Italy: Health Search, Regional DBs of Lombardy and Puglia; United Kingdom: CPRD) and one DB from USA (Medicare) that participated in the SAFEGUARD project.

GLDs were defined as prescriptions/dispensings (depending on the type of DB) of drugs with Anatomical Therapeutic Chemical (ATC) Classification code A10. For all the analyses, fixed combinations (i.e. ATC codes beginning with A10BD) were considered for each of the individual constituents of the combination. Duration was provided by each database based on the best available data (e.g. duration calculated based on DDD, legend duration, etc.). Prescription of the same compound were concatenated if the gap between the end of the first of the two prescriptions and the start of the second of the two prescriptions was less than 1.5 times the duration of the first (permissible gap).

In the population level analysis the prevalence (number of prevalent users per 1,000 person years [py]), incidence (number of incident users per 1,000 py) and rate of days exposed (number of exposed days per 1,000 py) of GLD exposure was calculated. The impact of different duration metrics (e.g. duration based on DDD or PDD, days between 2 prescriptions) was also evaluated.

For each GLD treatment group (ATC 5 digits), the frequency and proportion of gaps that ended with a user resuming, switching or discontinuing treatment within 365 days after a period of non-persistence was calculated. In the case of switches, for each GLD category, we identified the GLD category the user was switched to.

The size of gaps was described in terms of the ratio of the size of a gap between two prescriptions of the same GLD group to the duration of the first of the two prescriptions. The size of overlaps (in days) between consecutive prescriptions of drugs from the same GLD treatment group was described. The size

of overlaps was also described in terms of the ratio of the size of a gap between two prescriptions of the same GLD group to the duration of the first of the two prescriptions.

For the analysis of patient determinant at each treatment initiation, only subjects starting treatment with an A10B (NIBGLD) or a combination of an A10B and A10A (insulin) prescription after 365 days from cohort entry were considered. Patients starting only with A10A prescriptions were excluded from the analysis. The prevalence of all covariates and drugs predefined in the study as relevant for the comparative studies was assessed at the time of the first prescription of the drugs of interest (ATC: A10B) at ATC at 5 digits (therapeutic group) or at ATC at 7 digits level (individual compound).
The start date of the first prescription was defined as the index date. The presence of covariates was assessed in different time frames:, 365, 730, 1095 days and anytime before the index date.. For diseases where prescriptions could be used as proxies, the prevalence was calculated using the prescription and the diagnosis, whatever was available. An event was considered as "history of it" if the date of the event was before but not equal to the start date of the prescription. A descriptive analysis of the main characteristics of the subjects was performed.

For all analyses performed in SAFEGUARD, the distributed network approach was followed using. Jerboa. Jerboa is a common standardized and centrally prepared Java script used to locally generate analytical dataset. The dataset were centrally analyzed in OCTOPUS, a Remote Research Environment. STATA and SAS software were used for the descriptive analysis.

Results

Metformin had the highest prevalence (3.9 to 15.9 users/1000py in European (EU) DBs and 170.6 users/1000py in Medicare) and incidence (3.5 to 8.1/1000py and 142.0/1000py respectively) followed by sulfonylureas. Sulfonylureas were preferred over metformin before 2002. The fixed combination metformin+sulfonylureas was consistently higher in the Italian DBs compared to the rest of DBs (3.0 to 4.9 vs. 0.1 to 0.9 users/1000py) as well as the use of acarbose, which increased after 2009 only in the Italian DBs. The use of sulfonylureas decreased progressively with time and TZD decreased after 2005-2007 in all DB, especially in terms of incidence and mainly rosiglitazone. Sitagliptin and exenatide were the most frequently used incretin-based therapies. The use of all drugs increased with age.

In most data sources a large proportion of prescriptions had durations of approximately 1 month (28/30 days), 2 months (56/60 days) or 3 months (84/90 days). However in all data sources prescriptions of intermediate lengths were also observed. Regarding gap analysis, the results indicate that less than 75% of gaps between prescriptions were closed for most GLDs using the permissible gap size of 1.5 times the duration of the of the preceding prescription.

In those data sources able to calculate duration based on PDD (i.e. CPRD, PHARMO, IPCI, BIFAP), the rate of exposure was higher using the PDD compared to the DDD suggesting that for biguanides, for instance, the DDD tends to overestimate the PDD resulting in underestimation of prescription duration and more frequent non-closing of gaps between prescriptions. Across all data sources duration based on the difference between consecutive prescriptions resulted in the highest rate of exposed days.

Regarding resuming/switching treatment after a permissible gap, more than 60 % of those using insulin, biguanides or sulfonylureas resume treatment. For other GLDs the proportion of subjects resuming treatment with the same GLD is lower and resume treatment with an insulin, a biguanide or sulfonylureas mainly.

Regarding subject characteristic at the first prescription, the mean age of subjects starting treatment with biguanides ranged from 59.5 to 62.8 years old in European DB and 74.3 in Medicare. Sulfonylurea users ranged from 63.2 to 66.4 years old and 75.6 in Medicare. The use of incretin based therapies (IBT) ranged for DPP-4I from 58.4 to 61.8 and 75.7 years old in European and Medicare databases respectively. Regarding the GLP-1 receptor agonists new users, the age ranged from 47.7 to 56.8 years old in Europe and 72.4 in Medicare. Hypertension, obesity (ever) and hyperlipidaemia are the most common comorbidities observed in subject treated with GLDs and history of obesity is more common in subjects starting exenatide compared to other incretin based therapies. Biguanides and sulfonylureas are the most common concomitant GLD followed by thiazolidinediones.

Conclusions

Metformin, sulfonylureas and insulin are the most prevalent NIBGLD agents, metformin leading specially after 2002. The use of therapies based on different mechanisms of patters introduced in the market in the 2000's (i.e. DPP-4I and GLP-1RA) has increased. Use of other treatment groups such as sulfonylureas and thiazolidinediones has decreased. Some patterns of use are country specific. Understandngi the patterns of use and the impact of the parameters used to define the exposure is crucial for a better interpretation of further analysis.