Pattern of use of incretin-based drugs in clinical practice

Protocol version 1.0

Title	Pattern of use of incretin-based drugs in clinical practice.
Medicinal product(s) / Device(s)	GLP-1 analogues and Dipeptidyl Peptidase-4 Inhibitors
Event(s) of interest	Not applicable
Research question and objectives	To describe the pattern of use of incretin-based drugs in large sample of the Italian general population.
Country(ies) of study	Italy
Protocol author(s)	Giuseppe Roberto (ARS), Rosa Gini (ARS)

List of abbreviations:

ARS	Agenzia Regionale di Sanità della Toscana (Regional Health Agency of Tuscany)
GLP-1	Glucagon like peptide-1
DDP-4i	Dipeptidyl Peptidase-4 inhibitors
T2DM	Type 2 diabetes mellitus
ATC	Anatomical Therapeutic Chemical classification

Responsible parties

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Amendments and updates

Version	Description of changes	Study protocol section	Date of effectiveness

Background

Diabetes is a chronic metabolic condition causing sustained hyperglyemia due to a deficit o insulin secretion and/or a reduced response of target tissues to this hormon [1]. In particular, type 2 diabetes (T2DM), in which insulin-resistance is the predominant pathogenetic mechanism, represents the about the 90% of all diabetes cases worldwide [2]. In patients with T2DM, the chronic exposure to hyperglycemia can causes the occurrence of serious and potentally fatal micro- and macrovascular complications [1]. Therefore, if diet and life style modification are not sufficient for an adequate glyemic control, pharmacological treatment is strongly recommended [1,3,4].

Current national [3] and international [4] guidelines on the treatment of T2DM recommend metformin as the initial treatment of T2DM and the subsequent addition (or switch in case of intollerance) of one or more ipoglicemic drugs or insulin in order to maintain the recommended glycemic target.

In addition to older hypoglycemic drugs such as metformin, sulphonylureas, glinides, glitazones and acarbose, in February 2008 the Italian Healthcare Service approved the reimbursement of the first incretin-based medicines [5]. The clinical efficacy of this class of drugs in the treatment of T2DM relies on the potentiaton of the activity of the Glucagon-like peptide 1 (GLP-1), an endogenous hormon belonging to the family of incretin hormones that exerts an important role in the glycemic omeostasis [3,6,6]. Currently, available incretin-based terapie are distinguished in two main groups: i) GLP-1 analogues, which possess a longer half-life compared to the endogenous GLP-1 hormon and are administered subcutaneously, and ii) the dipeptidyl peptidase-4 inhibitors (DPP-4i), which reduces the activity of the enzyme responsible for the degradation of the endogenous GLP-1 and are admistered orally [3,6].

Results from clinical trials have suggested a positive risk/benefit balance of these drugs in the treatment of T2DM [6,7]. However, given the recent commercialization, available literature on the pattern of use of incretin-based therapy in the real world clinical practice is still scarce [5,8-10]. A study based on the administrative data of an Italian Local Health Authority reported a trend of increase of the use of these drugs between 2009 and 2012 [8] however, no specific information was provided with respect of GLP-1 analogues and DDP-4i respectively, as well as for individual molecules belonging to the two groups. Since the effectiveness and safety profile of these drugs cannot be considered completely established yet [7,11], evidence on the exposure of the general population to these medications, as well as the characterization of treated patients, becomes of paramount importance for the planification of large scale observational pharmacoepidemiological studies[12,13].

Therefore, the aim of this study is to describe in greater details the pattern of use of incretin-based drugs in large sample of the Italian general population through the analysis of the analysis of routinely collected data from the Regional Health Agency of Tuscany (ARS - Agenzia Regionale di Sanità).

Materials and Methods

Data source

Italy has a tax-based, universal coverage National Health System organised in three levels: national; regional (21 regions); and local (on average 10 Local Health Authorities per region). Healthcare is managed for every inhabitant by the Local Health Authority where he/she has her regular address.
This study will be based on the analysis of the ARS databases which collects pseudonymized patient-level information on the utilization of healthcare services dispensed to all subjects who are residents and registered with a general practitioner in Tuscany, corresponding to a population of around 3.5 million people. For each subject in the data base, demographic information, such as age, sex and pertinent Local Health Authority, can be linked to records of dispensings of prescription drugs intended for outpatient use and reimbursed by the National Healthcare Service. Prescription records include information on the dispensed drugs (e.g. active principle, ATC code) as well as the date of dispensation.
Although this version of the protocol concerns the use of the ARS data base only, the possibility to use also data from other Italian Regions and/or Local Health Authorities is currently under assessment. In case other data bases are included, the protocol will be updated accordingly.

Study population and design

This is a descriptive, population-based, pharmacoepidemiological study on the utilization of incretin based drugs in clinical practice. All subjects registered in the ARS data base between January 1, 2008 and December 31, 2014 will be considered and data from dispensed drug prescriptions will be analyzed. Per each year of observation, the reference study population will correspond to all subjects active into the data base at January the 1st that, at this date, will have ≥18 years of age and at least 365 days of look-back period. Within such population, all subjects with ≥1 prescription of any antidiabetic drug (**ATC**: A10*) will be identified as well as those with ≥1 prescription containing an incretin-based drug (i.e. GLP-1 analogues- **ATC**: A10BX04, A10BX 07, A10BX10; DPP-4i - **ATC**: A10BH01, A10BH02, A10BH03, A10BH04, A10BH05, A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD12, A10BD13; see Table 1).

Table 1. **Antidiabetic drugs of interest for the study as available in Italy during the study period.**

Classe farmacologica	ATC	Principio attivo
DDP-4 inhibitor	A10BH01	sitagliptin
	A10BH02	vildagliptin
	A10BH03	saxagliptin
	A10BH04	alogliptin
	A10BH05	linagliptin
	A10BD07	metformin and sitagliptin
	A10BD08	metformin and vildagliptin
	A10BD09	pioglitazone and alogliptin
	A10BD10	metformin and saxagliptin
	A10BD11	metformin and linagliptin
	A10BD13	metformin and alogliptin
GLP-1 analogues	A10BX04	Exenatide
	A10BX07	liraglutide
	A10BX10	Lixisenatide
Biguanides	A10BA01	Fenformin
	A10BA02	Metformin
Sulphanylureas	A10BB01	Glibenclamide
	A10BB02	Chlorpropamide
	A10BB03	Tolbutamide
	A10BB06	Carbutamide
	A10BB07	Glipizide
	A10BB08	Gliquidone
	A10BB09	Gliclazide
	A10BB12	Glimepiride
Thiazolidinediones	A10BG02	Rosiglitazone
	A10BG03	Pioglitazone
Alfa glicosidase inhibitors	A10BF01	Acarbose
Meglitinides	A10BX02	Repaglinide
Insulins	A10A*	Insulin and analogues
Other hypoglicemic drugs in fixed combinations	A10BD01	phenformin and sulfonamides
	A10BD02	metformin and sulfonamides
	A10BD03	metformin and rosiglitazone
	A10BD05	glimepiride and pioglitazone
	A10BD14	metformin and repaglinide

In particular, the following analyses will be performed:

A) trends of annual prevalence and incidence of use of 1) overall incretin-based drugs, 2) GLP-1 analogues and 3) DPP-4i in the general population. The prevalence of use will be calculated as the ratio between the total number of prevalent users (subjects with ≥1 prescrition of interest during the year) and the total number of subjects in the reference population for that year. The annual incidence of use will be computed by dividing the number of new users of that year (i.e. patients

with ≥1 prescription interest during the year and none during the previous 365 days) for the number of subjects at risk to receive the drug of interest in the reference population in the same year (i.e. the reference population for that year minus prevalent users of the previous year). The assessment of each of the three exposure categories (i.e. incretin-based drugs, GLP-1 analogues and DPP-4i) will be independent from the other two and non mutually exclusive;

B) trend of the annual percentage of prevelent users of incretin-based drugs, GLP-1 analogues and DPP-4i on the total prevalent users of antidiabetic drugs (**ATC** A10*), as well as the trend of the annual percentage of new users of incretin-based drugs, GLP-1 analogues and DPP-4i on the total number of new users of antidiabetics (**ATC** A10*). As for the latter analysis, incident users will be classified in the relevant exposure category on the basis of the first prescription of interest dispensed during the year of reference;

C) percentage of incident users of GLP-1 analogues and PP-4i on the total number of incident users of incretin-based drugs per each year of observation. Patients will be categorized in the relevant exposure category considering the first prescription of interest during the year of reference. Moreover, this analysis will be also performed at active substance level (i.e. V° level of the ATC classification, see Table 1).

D) incident users of incretin-based drugs, divided per year of observation and metropolitan area, will be characterized in terms of percetage of women, mean age, and antidiabetic drugs used during the 365 day before the first prescription of an incretin-based drug. In particular, these subjects will be classified in the following mutually exclusive categories (see Table 2):

1) No previous antidiabetic treatment,

2) Insulin with or without hypoglicemic drugs (i.e. ≥1 insulin prescription),

3) hypoglycemic drugs in monotherapy (i.e. drugs belonging to one pharmacological class of hypoglycemics excluding insulin and fixed combinations),

4) Politherapy with hypoglycemic drugs (drugs belonging to more than one class of hypoglycaemic medicines or fixed combination)

Results will be reported as percentages of incident incretin-based drug users classified in each of the four categories described above on the total number of incident incretin-based drug users.

Statistical analysis

Both prevalence and incidence of use, the latter intended as the incident risk of receiving the drug of interest, will be reported as proportions per 1000 subjects, with relevant 95% confidence intervals (95%CI). The Cochran–Armitage test will be used to verify the statistical significance of the trends

of prescribing patterns and users characteristics between 2008 e 2014 with a preestablished significance threshold equal to $p< 0.05$.

Table 2. Exposure categories for the caracterization of incident incretin-based drug users.

Exposure categories	**Description (ATC)***
Insulin with or without hypoglicemic drugs	≥1 insulin prescription (A10A*)
hypoglycemic drugs in monotherapy	Drugs belonging to only one of the following groups: - Biguanides (A10BA*) or - Suphanylureas or Glitinides (A10BB01, A10BB02, A10BB03, A10BB06, A10BB07, A10BB08, A10BB09, A10BB12, A10BX02) or - Tiazoledindiones (A10BG*) or - Alfa glucosidase inhibitors (A10BF01)
Politherapy with hypoglycemic drugs	- Drugs belonging to more than one groups among those reported above or: - Fixed combination (A10BD01, A10BD02, A10BD03, A10BD05, A10BD14)

*drugs dispensed during the 365 days before the first dispensing of a incretin-based drug.

Data management and processing

Data will be analyzed using the software TheMatrix (http://thematrix.isti.cnr.it/) and statistical software STATA version 12.1.

Limitations of study methods

The data source used for this study cannot track prescription drugs used in inpatent setting. Given the design and the descriptive nature of the study this limitation is unlikely to have any significant impact on the study results.

Ethical considerations

The study was approved by the governance board of ARS.

Disseminations and communication strategy

Data generated through this research will be shared among all study participants before December 2015. A study report summarizing all main results will be produced and shared with data partners before February 2016.

The findings from this study will be submitted to a peer-review international journal before June 2016.

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