CHOICE OF THE ADD-ON THERAPY TO METFORMIN IN TYPE 2 DIABETES PATIENTS IN CLINICAL PRACTICE. INITIAL RESULTS FROM A NON-INTERVENTIONAL MULTICENTER STUDY IN ROMANIA (REALITY)

C. Serafinceanu^{1,2}, R. Timar^{4,5}, D. Catrinioiu⁶, A. Zaharia^{3,*}

¹“Carol Davila” University of Medicine and Pharmacy, Dept. of Diabetes, Nutrition and Metabolic Diseases, ²“Prof. N.C. Paulescu” National Institute of Diabetes, Nutrition and Metabolic Diseases, Dept. of Diabetes 1, ³AstraZeneca Romania, Medical Department - Bucharest, ⁴County Emergency Hospital Timișoara, ⁵“V. Babes” University of Medicine and Pharmacy, Department of Diabetes - Timișoara, ⁶“Ovidius” University, Dept. of Diabetes, Nutrition and Metabolic Diseases - Constanța, Romania

Abstract

Metformin, a biguanide, remains the most widely used first-line type 2 diabetes drug. It is generally considered weight-neutral with chronic use and does not increase the risk of hypoglycaemia. Most patients eventually require more than one antihyperglycemic agent to achieve target blood glucose levels.

The primary objective of this non-interventional study was to describe and compare the main criteria used by physicians from regular outpatient setting in selecting the add-on therapy in patients with inadequately metformin-controlled type 2 diabetes in 2 time points at 1-year distance by assessment of patient, and/or agent characteristics and/or physician decision.

At the end of phase one of the study, the mean duration of type 2 diabetes was 6.8 years. The majority of patients included in the study were overweight (32%) and obese (62%), and presented diabetes complications (59.6%). In 50% of the cases, the major reason for selecting the second-line therapy was related to patient characteristics, while agent characteristics and physician decision were the main categories in 38% and 12%, respectively. Importance to achieve glycemic control and estimated treatment efficacy were selected in 73.9% and 82.4% of patients, calculated as percentage in the respective categories.

Key words: type 2 diabetes, add-on therapy, metformin, Romania, control, Haemoglobin A1c, HbA1c.

INTRODUCTION

According to the International Diabetes Federation, diabetes affects at least 415 million people worldwide, with 56.3 million in Europe (1). The numbers are expected to rise each year, with a huge

impact on human health and healthcare systems. The aims of controlling blood glucose level are to avoid acute osmotic symptoms of hyperglycaemia and instability in blood glucose over time, and to prevent and delay the development of diabetes complications without adversely affecting quality of life.

Haemoglobin A1c (HbA1c) is currently the most common marker for assessing the glycaemic status of people with diabetes and it is frequently used to guide therapy and especially medical treatment of people with diabetes. The percentage of glycosylated haemoglobin (HbA1c) reflects the glycaemic control of a patient during the previous 8-10 weeks before the blood sample was obtained. Lowering HbA1c has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes, is associated with long-term reduction in macrovascular disease (2).

The ADA/EASD's "Standards of Medical Care in Diabetes" recommends lowering HbA1c to <7.0% in most patients to reduce the incidence of microvascular disease. More stringent HbA1c targets (e.g., 6.0–6.5%) might be considered in selected patients (with short disease duration, long life expectancy, no significant cardiovascular disease) if this can be achieved without significant hypoglycaemia or other adverse effects of treatment. Conversely, less stringent HbA1c goals e.g., 7.5–8.0% or even slightly higher are appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced complications, extensive comorbid conditions and those in whom the target is difficult to attain despite intensive self-management education, repeated counselling, and effective doses of multiple glucose-lowering agents (3, 4).

*Correspondence to: Adrian Zaharia MD, AstraZeneca Romania, Medical Department, Bucharest Business Park, 12 Menuetului Street, building D, 1st floor, District 1, 013713, Bucharest, Romania, E-mail: adrian.zaharia@astrazeneca.com

Recommendations from ADA and EASD (3, 4) for the treatment of diabetes discuss advantages and disadvantages of the available medication classes and considerations for their use. A patient-centred approach is stressed, taking into account patient preferences, cost and potential side effects of each class, effects on body weight, and hypoglycemia risk.

Metformin, a biguanide, remains the most widely used first-line type 2 diabetes drug (4). It is generally considered weight-neutral with chronic use and does not increase the risk of hypoglycaemia. Most patients eventually require more than one antihyperglycemic agent to achieve target blood glucose levels. Due to the high and increasing prevalence of type 2 diabetes, suboptimal use of second-line antihyperglycemic drugs can have a detrimental effect on health outcomes and healthcare costs (3). Hence, understanding the beliefs, perceptions and practices of healthcare providers is necessary to identify real world practice motivations for treatment strategies.

In case of inadequate control to metformin, numerous options exist for second-line therapy after metformin for type 2 diabetes, including sulfonylureas, alpha-glucosidase inhibitors, meglitinides (glinides), thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and SGLT2 inhibitors. Although many agents from all therapeutic classes are currently available for type 2 diabetes treatment in Romania, little is known about the factors taken into account by physicians in making therapeutic decisions after metformin failure in daily clinical practice.

This paper presents the first results of a non-interventional, multicentre study exploring the main criteria used by the Romanian clinicians when selecting the add-on therapies to metformin in type 2 diabetes patients.

PATIENTS AND METHODS

Eligible subjects are adult patients with type 2 diabetes inadequately controlled with metformin, receiving one add-on medication to metformin, except insulin. Patients were excluded if they had a history of type 1 diabetes, or insulin treatment, or monotherapy with an oral therapy for type 2 diabetes at the time of enrolment. Subjects participate in only one study visit, at the time of enrolment, when they provided written informed consent, thus allowing the access to their data. No patients were prospectively followed-up during the study. No additional diagnostic and monitoring

procedures were applied to patients, other than daily clinical practice. The study was conducted using the medical records and claims from clinical practice, without any intervention.

Study design

This was an observational, non-interventional study. Two time-points at approximately 1 year interval (July/August 2014 and October/November 2015) were planned to evaluate whether any changes including add on therapy or practice patterns occurred in this time frame. The patients were not prospectively followed-up. Two different study groups were defined at each evaluation, with an estimated sample size of 1070 patients per study moment.

The assignment of the patients to a particular add-on therapy was not decided in advance by the study protocol, but falls within current practice and the prescription of medicine is clearly separated from the decision to include the subject in the study.

Study objectives

The primary objective of this non-interventional study was to describe and compare the main criteria used by physicians from regular outpatient setting in selecting the add-on therapy in patients with inadequately metformin-controlled type 2 diabetes in 2 time points at 1-year distance by assessment of patient, and/or agent characteristics and/or physician decision. The Investigators were provided with a list of reasons for each category (Fig. 1), indicating which category was considered the most relevant in selecting a specific add-on class for each patient.

The secondary objectives included assessment of the add-on therapeutic classes, the prevalence of diabetes complications, as well as evaluation of glucose control at the enrolment study phase 1 by the percentage of patients with HbA1c <7%. These objectives will be detailed in this paper for the phase one of the study. Another objective of the study is to compare the changes observed in primary and secondary variables between the two moments of assessment (phase 1 and phase 2), at 1 year interval.

The study was approved by National Ethics Committee in Romania. Due to the non-interventional character of this study, only spontaneously mentioned safety events are reported as required by the post-marketing pharmacovigilance regulations.

Statistical analysis

Epidemiological methods are used for analysis

RATIONALE FOR SELECTION OF CURRENT ADD-ON THERAPY	
Patient characteristics	☐ Yes ☐ No <i>(If your answer is <<Yes>>, please select from below one or more reasons)</i>
	☐ Patient's preference ☐ Glycemic control (degree of hyperglycemia) ☐ Risk of hyperglycemia ☐ Overweight/obesity ☐ Co-morbidities ☐ Easy access to treatment
Agent characteristics	☐ Yes ☐ No <i>(If your answer is <<Yes>>, please select from below one or more reasons)</i>
	☐ Blood glucose lowering efficacy & durability ☐ Risk of inducing hypoglycemia ☐ Effect on weight ☐ Contraindications & side effects ☐ Cost
Physician decision	☐ Yes ☐ No <i>(If your answer is <<Yes>>, please select from below one or more reasons)</i>
	☐ Personal experience with medicine ☐ Other <<please specify>>

Figure 1. List of categories provided to Study Investigators to select the reasons applied when choosing the add-on therapy for each patient. If more than one category is selected, the Investigator needs to indicate which category was the most relevant for the decision.

of collected data.

After signing the informed consent form at the phase 1 of the study, patient data (demographics, weight, height, diabetes history, complications, comorbidities, add-on treatment information, HbA1c level) were collected using electronic CRFs. All statistical evaluations are performed with SAS Software (Version 9.1.3). Continuous variables are summarized with the use of descriptive statistical measures (means, standard deviations, minimum, maximum, and the number of available and missing observations) and categorical/distinct variables as frequency tables (N, %). The interpretation of all results is performed in a descriptive manner and missing data are not replaced.

RESULTS

In total, at the first phase of the study, 1155 patients were included in the study in 47 study sites

in Romania from July to September 2014. Of them, 1143 patients were included in the full analysis set (FAS) population, where all subjects enrolled fulfilled all study inclusion criteria, and no exclusion criteria. Mean age of patients enrolled in 2014 was 60.9 years. The group was approximately evenly split for females (52.5%) and males. The overall details of group characteristics are presented in Table 1.

At the end of phase one of the study, the mean duration of type 2 diabetes was 6.8 years. The majority of patients included in the study were overweight (32%) and obese (62%), and presented diabetes complications (59.6%). The time on metformin monotherapy in this study was 6 years and first add-on was initiated at approximately 3 years after metformin.

HbA1c values

HbA1c values were available at the moment of study for 947 patients (83%). Mean HbA1c at

Table 1. Demographic and clinical characteristics of the patient group at the first phase of the study (July-September 2015)

Characteristic	Mean value (n=1143)
Age, years (SD) [min, max]	60.9 (9.14) [32, 90]
Females, n (%)	600 (52.5)
Weight, kg (SD) [min, max]	89.1 (16.6) [44, 155]
BMI, kg/m ² (SD)	32.1 (5.38)
<25 kg/m ² , n (%)	63 (5.5)
25-29.9 kg/m ² , n (%)	370 (32.4)
≥30 kg/m ² , n (%)	710 (62.1)
Diabetes duration, years (SD) [min, max]	6.8 (4.32) [0, 29]
Diabetes complications, n (%)	681 (59.6)
Cardiovascular	474 (41.5)
Neuropathy	326 (28.5)
Retinopathy	63 (5.5)
Nephropathy	46 (4.0)
Comorbidities	867 (75.9)
HbA1c*, % (SD)	7.4 (1.23)
≤ 7.0% Number (%) of patients	373 (32.6)
Time with metformin treatment, years (SD)	5.9 (9.14)
Time from metformin initiation and first add-on therapy, years (SD)	3.2 (2.91)
First add-on medication to metformin, n (%)	
Sulfonylurea	715 (63)
DPP-4 inhibitor	205 (18)
GLP-1 agonist	76 (7)
Alpha glucosidase inhibitor	63 (5)
Thiazolidindione	45 (4)
Glinides	39 (3)

*HbA1c measurement was not mandatory. HbA1c values at the moment of enrollment were not available for 196 patients.

first evaluation time point was 7.4%, with 33% of patients receiving combination treatment achieving the recommended target of ≤7% (Table 1).

Combination treatment

The most frequently first add-on medication to metformin was a sulphonylurea (63%), followed by a DPP-4 inhibitor (18%). GLP-1 agonists, alpha glucosidase inhibitors, thiazolidindiones, and glinides

were reported as add-on treatments in 7%, 5%, 4% and 3%, respectively.

Drivers in selecting add-on therapy to metformin

For each patient, investigators had the possibility to choose at least one category of reasons for add-on treatment to metformin from the following: patient characteristics, agent characteristics and physician decision. In case of selecting more than one category, the investigators were asked to indicate which one was the most relevant for their clinical decision.

In 50% of the cases, the major reason for selecting the second-line therapy was related to patient characteristics, while agent characteristics and physician decision were the main categories in 38% and 12%, respectively. Importance to achieve glycemic control and estimated treatment efficacy were selected in 73.9% and 82.4% of patients, calculated as percentage in the respective categories (Fig. 2).

Figure 2. Distribution of selected reasons when choosing the first add-on combination to metformin.

DISCUSSION

There is general agreement that metformin should be used as first-line therapy in type 2 diabetes, as soon as blood glucose control could not be maintained with the appropriate lifestyle interventions. This strategy could help to slow the trajectory of loss in insulin secretory capacity and glycaemic control, delaying the need for subsequent therapy intensification. However, due to progressive nature of the disease, combination therapy is required to maintain HbA1c levels at target. It has been estimated that metformin monotherapy failure occurs with a mean rate of 17% per year (5).

Based on data collected in this non-interventional study, metformin was initiated in less than 1 year after diagnosis of type 2 diabetes, with the first add-on therapy started in more than 3 years after metformin. We are aware that these results provide only a snapshot of clinical management in Romania, however this insight is important for further in-depth analysis and research on measures to overcome clinical inertia and to stimulate a more aggressive treat-to-target attitude.

Inability of metformin alone to sustain normal blood glucose levels brings both the clinician and patient into an important decision moment, especially given the fact that available guidelines are less prescriptive for second-line therapies (3, 4). Although each class of these agents broadly shows similar efficacy as monotherapy with hardly any clinically meaningful differences in glucose-lowering potency at least in short term, each therapeutic class has distinct safety profile that either could be related to their specific mechanism of action.

In our study, the data collected in the first phase of evaluation show that patient characteristics represented the major component (50%) of the clinical decision process when selecting the first add-on agent. With the complexity of type 2 diabetes management increasing over the last years, physicians now have many pharmacological options available to tailor the treatment to patients' specific needs.

It is important to note that answers selected for patient characteristics correlated very well with agent characteristics. Therefore, the main reason for choosing the combination treatment appears to be related to glycaemic control and add-on medication efficacy, respectively. These rational grounds are followed by the effect on body weight, emphasising a lot more the importance of weight gain and

obesity in the management of type 2 diabetes. As presented here, and also in another recent report of an epidemiological study in Romania (6), a dramatically high prevalence of overweight and obesity in these population is seen. Supporting patients to lose weight should be considered a key goal of diabetes care for all overweight and obese patients with type 2 diabetes. Adjunctive treatment with metformin, SGLT2 inhibitors, DPP-IV inhibitors and GLP-1 analogues may limit weight gain and obesity-related complications.

In a survey performed in Canada exploring perceptions of healthcare providers and type 2 diabetes patients related to add-on therapy (7), patients described the disappointment and sense of failure they feel following the addition of second-line agents. Hypoglycaemia and weight gain were cited most frequently as important concerns when choosing antihyperglycemic therapy, even greater than glucose-lowering efficacy. Patients also described the importance of having a provider who can take the time to listen and answer questions, emphasising the importance of appropriate education and shared decision making as changes to diabetes treatment are made.

Not surprisingly, based on the confidence gained over several decades of use and also its cheaper cost, our results show that sulfonylureas are the most commonly used oral drugs to initiate in combination with metformin. Although large randomised trials could not associate this class with any obvious increase in cardiovascular mortality, some recent larger databases showing divergent results suggest an increase of cardiovascular safety signals (8) and this may put sulphonylureas at a disadvantage given the availability of safer alternatives. In recent years, incretin-based therapies and SGLT 2 inhibitors are gaining popularity primarily because of their advantage of weight reduction or neutrality and minimal hypoglycaemia along with the perception of possible pleiotropic cardiovascular benefit mainly derived from pooled data of their trials.

To our knowledge, this is the first study in Romania to assess the reasons for selecting the combination therapy in type 2 diabetes patients. When final results are available, after completion of the second moment of evaluation, it will be possible to determine if any change has occurred in treatment patterns, and potential clinical and economic implications for the patients and healthcare system in Romania.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 7 ed. Brussels, Belgium: International Diabetes Federation, 2015.
2. Irene MS, Amanda IA, Andrew WN, David RM, Susan EM. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study, *BMJ* 2000; 321: 405–412.
3. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; 35(6): 1364-1379.
4. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015; 38(1): 140-149.
5. Brown JB, Conner C, Nichols GA. Secondary failure of metformin monotherapy in clinical practice. *Diabetes Care* 2010; 33: 501-506.
6. Mota M., Prevalence of diabetes mellitus and prediabetes in the adult Romanian population: PREDATORR study. *Journal of Diabetes*, 2016; 8 (3): 336-344.
7. Gauthier B, Singh SR, Virani A, Staples H, Colbourne A. Perspectives and experiences of healthcare professionals and patients regarding treatment for type 2 diabetes. *Cann Pharm J (Ott)* 2013; 147:45-54.
8. Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab.* 2013; 15 (10): 938-953.