STUDY REPORT SYNOPSIS

J-DISCOVER Study

<< DISCOVERing the Treatment Reality of Type 2 Diabetes in a Real-World Setting in Japan >>

Background/rationale: It is estimated that 642 million adults worldwide will have diabetes by 2040, with 80–90% of these having type 2 diabetes mellitus (T2DM). While many new antidiabetic agents have been introduced in recent years, approximately 40% of T2DM patients still fail to achieve the recommended target HbA1c of <7.0%. The treatment landscape for T2DM patients has changed in recent years. From 2002 to 2012, the proportion of T2DM patients treated with insulin gradually decreased from 15.4 to 8.6%. In contrast, the proportion of patients treated with oral antidiabetic drugs (OADs) increased from 51.4 to 59.6% in the same period. The increased number of antidiabetic agents with different modes of action available has made more combination therapies possible, meaning patients are treated with OADs for longer than before. Furthermore, T2DM is a progressive disease and many patients undergo dual and higher combination therapies following monotherapy. Unlike the American Diabetes Association and the European Association for the Study of Diabetes treatment guidelines, which specify metformin as the first-line treatment, the 166 Diabetes Ther (2018) 9:165–175 treatment guidelines of the Japan Diabetes Society (JDS) do not specify first-line or combination antidiabetic drugs . The JDS guidelines largely leave the selection of antidiabetic agents to the discretion of treating physicians, especially for second-line treatments or higher. Furthermore, many patients with T2DM in Japan are treated by practitioners other than diabetes specialists; therefore, the exact treatment patterns of T2DM in Japan are difficult to quantify. Hence, a treatment reality study on second-line and greater antidiabetic agents involving primary care physicians would be valuable.

Objectives:

Primary Objectives :

The primary objective is to describe the longterm disease management patterns (type and number of medicines prescribed, and other management approaches used) and clinical evolution (clinical course, such as glycemic control, including HbA1c and hypoglycemic frequencies; degree of progression and prognosis of complications; and changes in the quality of life) of patients with T2DM inadequately controlled with a first-line antidiabetic therapy who initiate a second-line antidiabetic treatment (either adding a second therapy to the first therapy or switching the first therapy to a second therapy).

Secondary Objectives

The secondary objectives include describing the overall and medication class-specific treatment response in terms of change from baseline in HbA1c, blood glucose (fasting plasma glucose [FPG], casual plasma glucose [CPG], or postprandial plasma glucose [PPG]), body weight, blood pressure and lipid profile, and the achievement rates of HbA1c and blood glucose target goals. Furthermore, we aim to describe treatment changes, including the proportion of patients who initiate with a second, third, fourth or higher level of antidiabetic medication at each follow-up visit, the proportion that initiate insulin therapy and the dose of insulin, the proportion of patients who switch antidiabetic medication, and the changes in dose for each treatment. We also aim to describe the diabetes-associated complications in terms of microvascular complications, incidence of chronic nephropathy, dialysis, diabetic retinopathy, retinal photocoagulation, amputation of lower extremity, diabetic foot disease, peripheral nerve disorders, autonomic nervous system disorders, and erectile dysfunction in the whole population and by second-line antidiabetic medication class. Further secondary objectives include describing the incidence of macrovascular complications (heart failure, myocardial infarction, and stroke), hypoglycemic events and hyperglycemia hospitalizations in the whole population and by second-line antidiabetic medication class; describing in the whole population and in second-line antidiabetic medication class subgroups the patient-reported quality of life, diet, and level of physical activity; identifying risk factors associated with poorer clinical outcomes during follow-up, such as patient characteristics at baseline (age, gender, duration of diabetes, and presence of comorbidities); and identifying the determinants of treatment choice at baseline.

Study design:

J-DISCOVER is a 3-year multicenter prospective observational longitudinal cohort study, which will be conducted at an estimated 141 sites across Japan.

Data source:

During the study period, patients will visit the study sites for routine visits. Baseline data will be collected after informed consent, and followup data will be obtained from patient records at 6-, 12-, 24-, and 36-month time points with a ± 2-month buffer period. This is an observational study. Regardless of any change in diabetes treatment during study period, patients will be followed, and relevant data will be collected at the study sites until the end of the study wherever possible. Data will be entered into an electronic data capture system and checked by the data management team. The team will issue queries to investigators through the electronic data capture system. Following the manual provided, investigators will enter data and electronically sign off the electronic case report form.

Study population:

J-DISCOVER enrolled male and female patients (aged ≥20 years) with a diagnosis of T2DM who were initiating a second oral or parenteral antidiabetic medication (adding or switching) after first-line oral monotherapy.

Inclusion criteria:

Subjects in this study must fulfill all of the following criteria: 1. Provide written informed consent for study participation 2. Female or male aged 20 years or over 3. Diagnosed with type 2 diabetes mellitus 4. Initiating a second oral or parenteral antidiabetic therapy added to oral antidiabetic monotherapy or switching from the monotherapy to another monotherapy with a different drug class.

Exclusion criteria:

Patients will not be eligible to participate if any of the following exclusion criteria are present: 1. Diagnosis of type 1 diabetes mellitus 2. Current pregnancy 3. Current treatment for any cancer 4. Current dialysis treatment or renal transplantation 5. Current treatment with any oral steroids 6. Participation in any randomized control trials 7. Presence of any condition/circumstance that, in the opinion of the investigator, could significantly limit the complete follow-up of the patient (e.g., tourist, non-native speaker who does not understand the local language where an interpreter is not available, psychiatric disturbances, alcohol or drug abuse).

Statistical methods:

Statistical analysis will be conducted with SAS (version 9.2; SAS Institute Inc., Cary, NC, USA). Demographic variables, patient characteristics, and treatment patterns will be summarized using descriptive statistics. Descriptive statistics will include n, mean, median, standard deviation, minimum and maximum for continuous variables, and frequency for categorical variables. Inferential statistics will present data using two-sided 95% confidence intervals when considered relevant. Identification of predictors of treatment choice at baseline using baseline characteristics will be attempted using multivariable regression models. Changes in HbA1c, blood glucose, lipid profile, body weight, and blood pressure will be summarized with descriptive statistics. Stratifications will be made by antidiabetic class at baseline, and regression models will be used to see if antidiabetic class at baseline is a predictor of these outcomes. Proportions of patients switching and/or adding treatments and/or changing doses of treatments will be summarized with descriptive statistics. Kaplan–Meier estimates of the cumulative incidence of the following events will be calculated and plotted: switching of second-line treatment; initiation of insulin therapy; initiation of the third or above antidiabetic therapy. Multivariable Cox models will be applied to analyze time-to-event data to assess the association of treatment class at baseline and other baseline variables with clinical outcome variables. New and/or progression of diabetic nephropathy or neuropathy; retinal laser and/or intraocular treatment due to the development of and/or a deterioration in diabetic retinopathy; nontraumatic amputation; minor and major

hypoglycemia and/or hospitalization for hypoglycemia; and cardiovascular events will be summarized descriptively. Stratifications will be made by antidiabetic therapy class at baseline, and logistic regression or Cox model, depending on whether the outcome is binary or timeto-event, will be used to determine if antidiabetic therapy class at baseline is a predictor of these outcomes. Further information relating to the assessment of progression of complications is provided in the ESM. Quality of life results will be summarized descriptively. Stratifications will be made by antidiabetic therapy class at baseline, and 172 Diabetes Ther (2018) 9:165–175 regression models will be used to determine if antidiabetic therapy class at baseline is a predictor of these outcomes.

Results:

Primary endpoint: Mean HbA1c (unadjusted by baseline factors such as patient demographics) was 7.70%, 6.94%, 6.95%, 7.00%, and 7.06% at baseline, 6, 12, 24, and 36 months, respectively, and the mean changes from baseline at 2 6 24, and 36 months were - 0.72%, - 0.70%, - 0.64%, and - 0.58%, respectively. The mean changes of HbA1c of Sulfonylurea group from baseline at 6, 12, 24, and 36 months, was - 1.27%, - 1.07%, - 0.95%, and - 0.73%, respectively.The mean change of HbA1c from baseline at 36 month was - 0.55% and - 0.45% in the DPP-3 inhibitor and SGLLT inhibitor, respectively.

Secondary endpoint: Proption of patients who achieved the target of HbA1c (<7%) was less than 30% at baseline, but increased to 60% at 6 months. Alpha-glucosidase inhibitors gourp and thiazolidinedioes group showed a higher target achievement in HbA1C (<7%) at 36 months than other gourps. Sulfonylurea group showed a lower achievement in target of HbA1c (<7%) than other groups. Propotion of patients who achieved of HbA1c (<7%) was highest in 12 month in DPP4 inhibitors group and SGLT2 inhibitors group. Mean glucose (FPR, CPG, PPG) were lower in all drug groups compared to baseline at 6, 12, 24, 36 monts. There were non major changes in body weight, BMI, or seated blood pressure throughout the follow-up period; however, SGLT inhibitors grouo showed that body weight decreased throughout the follow uo period. Regarding the progression of the diabetes-associated complications in terms of microvascular complications, the propotion of patient who had chronic nephropathy was increased, on the other hand, this increase was not observed in diabetic retinopathy, peripheral neuropathy, and autonomic neuropathy.

Conclusion: The long term management pattern and clinical practice in patients with type 2 diabetes mellitus who implement the second line therapy were evaluated in this study. Approximately 20% to 30% of patient were changed their treatment due to the insuffient effectiveness. To assess the factors in patient group who achieved the target of HbA1c or patient who did not change the treatment with achiement of target of HbA1c will be helpful to support the management plan determination.

Publications:

Katakami N, Mita T, Takahara M, et al. Rationale and Design for the J-DISCOVER Study: DISCOVERing the Treatment Reality of Type 2 Diabetes in a Real-World Setting in Japan-A Protocol. Diabetes Ther. 2018 Feb; 9(1): 165-175.