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PRODIG (Prevention of new onset diabetes after transplantation by a short term treatment of Vildagliptin in the early renal post-transplant period) study: study protocol for a randomized controlled study

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Study protocol

Keywords: Diabetes prevention; Vildagliptin; kidney transplantation; randomized controlled trial

Posted Date: March 22nd, 2019

DOI: https://doi.org/10.21203/rs.2.239/v2

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Version of Record: A version of this preprint was published on June 21st, 2019. See the published version at https://doi.org/10.1186/s13063-019-3392-6.

Abstract

Background: Post-transplant diabetes is a frequent and serious complication of kidney transplantation. There is currently no treatment to prevent or delay the disease. Nevertheless, identification of risk factors make possible to target a population at risk to develop de novo diabetes. We hypothesized that a short term treatment with Vildagliptin may prevent new onset diabetes after transplantation (NODAT) in high-risk patients. Method/design: This is a multicenter double-blind placebo-controlled randomized clinical trial. Patients undergoing first kidney transplantation will be included in 10 French transplant center. Included patients will be randomized (1:1) to receive either vildagliptin 100 or 50 mg/day (depending on glomerular filtration rate) during 2 months (the first dose being administered before entering the operating theatres) or placebo. Additional antidiabetic therapy could be administered according to glycemic control. The primary outcome is the proportion of diabetic patients 1 year after transplantation, defined as patients receiving a diabetic treatment, or having a fasting glucose above 7 mmol/l, or/and with an abnormal oral glucose tolerance test. Secondary outcomes include the glycated hemoglobin, the occurrence of acute rejection, infection, graft loss and patient death at 3 months, 6 months and 12 months after transplantation. Outcomes will be correlated to clinical and general characteristics of the patient, cardiovascular history, nephropathy, dialysis history, transplantation data, biological data, the health-related quality of life and the cost-effectiveness of prevention of diabetes with vildagliptin. Discussion: There are only few data concerning pharmacological prevention of post-transplant diabetes. If our hypothesis is verified, our results will have a direct application in clinical practice and could limit diabetes-associated morbidity, reduce cardiovascular complications, increase quality of life of renal transplant patients, and consequently promote graft and patient survival. Our results may possibly serve for non-transplant patients carrying a high-risk of diabetes associated with other co-morbidities. Trial registration: ClinicalTrials.gov, NCT02849899 Registered on 8 February 2016.

Background

New onset diabetes after transplantation (NODAT) affects 15 to 20% of renal transplant patients and is associated with increased morbidity and reduced survival of both transplants and patients (1,2). Furthermore, our group identified NODAT as a risk factor for atherosclerotic events (3). The majority of NODAT occurs in the first months following transplantation. Corticosteroids, anti-calcineurin, and mammalian Target Of Rapamycin (mTOR) inhibitors have a major diabetogenic impact and greatly contribute to the increase in diabetes prevalence after transplantation. Some pre-transplant risk factors have been identified offering the opportunity to define an individual risk of NODAT. Considering its impact on graft and patient survival, the ability to predict NODAT is a major issue. Chakkera *et al.* reported that a simple equation using 6 easily available parameters provided a good discrimination of risk and a good identification of high-risk population for targeted prevention (4,5). The capacity to predict NODAT occurrence is the prerequisite to efficiently prevent or delay the onset of diabetes using appropriate therapeutic interventions.

There are to date few studies concerning the pharmacological prevention of NODAT. Hecking *et al.* have recently reported that a short treatment with insulin, administered immediately after transplantation, reduce the incidence of *de novo* diabetes one-year post-transplant (6). The occurrence of diabetes, a secondary end-point, was reduced by 73% in the treated group. However, NODAT was a secondary end-point and the side-effects of insulin are not necessary compatible with a preventive strategy. Relevant experimental evidences suggest that gliptins could be used in the pharmacological prevention of NODAT. Indeed, beyond the effects on blood glucose, gliptins have other actions including a protective effect on β cells and anti-inflammatory action that could prevent or delay the occurrence of new-onset diabetes after renal transplantation in patients with risk (7–10). The gliptins are approved for the treatment of type 2 diabetes and, among the gliptins, vildagliptin was used to treat diabetes after kidney transplantation in two clinical studies (11,12). These studies showed the anti-diabetic effect of vildagliptin taken early in the disease, but not as a preventive treatment of diabetes. Our hypothesis is that a short term treatment of vildagliptin administered in the early post-transplant period may prevent the occurrence of NODAT.

Methods/design

Study design

This is a multicenter double-blind placebo-controlled randomized clinical trial. The study will include 186 patients receiving a kidney transplant and matching the criteria of inclusions. Recruitment will be achieved in 10 French transplant units: Amiens, Besançon, Brest, Lille, Nice, Paris (Necker and Tenon), Rennes, Poitiers and Tours. Patients will be randomized into two groups: group 1 will be treated with vildagliptin and group 2 will be treated with placebo. The treatment duration will be 2 months. The dose will be adjusted during treatment, depending on the results of creatinine clearance. The administration of vildagliptin begins before entering the operating theatres. Blood glucose is controlled and if necessary hyperglycemia will be treated according to current recommendations, regardless of the group and the study.

Participants

· **Inclusion criteria**

Graft recipients aged 18 or above will be eligible for inclusion if they:

- Receive a first kidney transplant

- Are considered at high risk of developing NODAT, having at least 2 of the 3 following criteria: Age> 50 years; BMI (Body Mass Index) greater than 30 kg/m²; Direct Family history of type 2 diabetes

- Can receive immunosuppressive therapy including tacrolimus, mycophenolic acid and steroids

- Are patients in whom the cessation of steroids may be considered at the latest 3 Months post-transplant

- sign the informed consent for study participation,

- are affiliated with a medical care system.

· **Non-inclusion criteria**

Graft recipients will not be eligible for inclusion if they have the following conditions:

- Legal disability or limited legal capacity

- Patient unlikely to cooperate in the study and / or low early cooperation by the investigator

- Patient without health insurance

- Pregnancy and breast feeding

- Hepatic insufficiency

- Patient with Class IV NYHA (New York Heart Association) Heart Failure

- Patient with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption syndrome

- Patient in the period of exclusion of another study or under the "national register of volunteers."

- Inability to understand the reasons for the study; psychiatric disorders judged by the investigator to be incompatible with the inclusion in the study

- Active infection

- Infection with Hepatitis C virus

- A history of diabetes

- A history of pancreatitis

- A history of angioedema

- Multi-Organ Transplantation

· **Participant recruitment**

The study will be proposed to patients receiving a kidney transplant and matching the criteria of inclusions. The information sheet is given after admission for kidney transplant. The history of diabetes is checked during the inclusion consultation and in the medical file. Then the physician collects informed consent before going to the operating theatre. Recruitment will be achieved in 10 French transplant units (Amiens, Besançon, Brest, Lille, Nice, Paris (Necker and Tenon), Rennes, Poitiers and Tours). Delay may be

shorter than the recommended, but it corresponds to the studies on transplantation for which only a few hours are available between patient's admission and surgery. Then, patients will be randomized.

· **Randomization**

Patients will be randomized 1:1 into two groups using minimization technique with stratification according to center and the number of risk factors for developing diabetes (2 or 3).

- Group 1 (interventional group) will be treated with vildagliptin 100 or 50 mg/day for 2 months (depending on their creatinine clearance > or < to 50 ml/min; MDRD, Modification of Diet in Renal Disease, equation),

- Group 2 (placebo group) will be treated with placebo according to the same dosage.

Random allocation sequence is generated using CleanWebTM. The minimization algorithm takes into account already randomized patients in order to allocate a new treatment to minimize difference between stratification criteria. The randomization result provided by the system is attributed in 80 % of the cases; otherwise the other treatment is attributed. Neither the nurse nor the doctor nor the patient will know the nature of the ingested tablets. The blinding is created by the clinical research associate coordinator. The randomization number is assigned directly to the centers via CleanWebTM.

Interventions

· **Timing of administration of the study treatment**

First administration of the study treatment (vildagliptin or placebo) will be performed within hours prior to patient departure to the operating room. The dosage of vildagliptin will conform to the marketing authorization of data in its indication in the treatment of diabetes in kidney transplant patients. Patients will receive a half-dose of therapy until they have renal function greater than 50 ml/min of creatinine clearance (MDRD equation). Patients will receive one oral tablet in the morning and one in the evening (100 mg per day) or just one in the morning (50 mg per day) for 2 months.

· **Posology change**

The creatinine clearance will be measured each week and then the treatment will be suitable. Blood glucose is controlled and if necessary hyperglycemia will be treated according to current recommendations, regardless of the group and the study.

· **Premature discontinuation of the study treatment**

All suspected adverse reactions related to the investigational medicinal product which occurs in the present trial and that are both unexpected and serious are subject to expedited reporting. Based on the risk management plan for vildagliptin, the next adverse events will be following attentively and considered as adverse event of special interest: Gastrointestinal disorders, Pancreatitis, Hepatitis, Skin

reaction, Infection, Neurotoxicity, Pancreatic cancer, Cardiac disorders. These reactions should be recorded in the electronic case report form (e-CRF) and transmitted to the sponsor in case of serious adverse event. In this case, the investigator reserves the right to prematurely terminate the study treatment for medical reasons. The shutdown reasons should be properly documented.

· **Appropriate administration of treatment units**

A record of the number of tablets dispensed to and taken by each subject must be maintained and registered in the CRF. Compliance with therapy will be assessed through querying the patient during visit and examination of pillbox given back at endpoint.

· **Unblinding modalities**

If serious adverse events attributable to the study product, a blind lift procedure may optionally be initiated both by investigators and by the pharmacovigilance unit of the University Hospital. In the last case, the unblinding will be carried out by the data manager on request of the head of pharmacovigilance. Clinicians as well as biostatisticians retain the blind.

· **Concomitant medication**

Vildagliptin is an approved treatment for NODAT in patients with renal failure. This treatment will be used in these patients in preventive treatment according to the same recommendations as in curative treatment.. Vildagliptin has a low potential for drug interactions. Vildagliptin is neither a substrate nor an inhibitor or inducer of cytochrome P450 (CYP450) enzymes. Therefore, it is unlikely to interact with active substances that are substrates, inhibitors or inducers of these enzymes. Clinical studies showed no pharmacokinetic interactions clinically relevant of vildagliptin with other antidiabetic treatment (pioglitazone, metformin and glibenclamide, Digoxin, warfarin, amlodipine, ramipril, valsartan or simvastatin). Therefore no treatment (antidiabetic or not) is prohibited because of the study. As with other oral antidiabetic agents, the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid hormones and sympathomimetics. However, as in conventional treatment, these treatments are not prohibited. In conclusion, the prescription of vildagliptin for this study does not modify medical care of included patients (whether for immunosuppressive treatment or for antidiabetic treatments).

Study outcomes

The primary endpoint is the proportion of diabetic patients 1 year after transplantation, defined as one of the following proposals: Patients receiving a diabetic treatment, Patients have a fasting glucose above7 mmol/l, or/and Patients with an abnormal oral glucose tolerance test (OGTT)

The criteria for secondary assessments are: the glycated hemoglobin (HbA1c) 3 months, 6 months and 12 months after transplantation. The occurrences of acute rejection, infection, graft loss and patient death 3 months, 6 months and 12 months after transplantation. Clinical history (cardiovascular history,

baseline renal disease, dialysis, anti-Human Leukocyte Antigen antibodies, dyslipidemia, hypertension, type of donor, duration of ischemia, Cytomegalovirus (CMV) status, CMV prophylaxis, Pneumocystis prophylaxis), Biological data (creatinine, uric acid, C reactive protein (CRP), blood sugar balance, lipid profile, liver function tests, pancreatic balance and blood counts), the health-related quality of life (ReTransQoL, Renal Transplant Quality of Life, questionnaire), 8 days, 3 months, 6 months and 12 months after transplantation, and the cost-effectiveness of prevention of diabetes with vildagliptin were correlated to outcomes.

Study visits

As presented in the Figure, the study will include 5 visits (D0, D8, M3, M6 and M12) corresponding to those taking place in the context of the current follow-up after a kidney transplant. During these visits, clinical examination and a blood test will be conducted as part of the study to collect necessary clinical data in each center on a case report forms and to achieve the different dosages by hospital's laboratory, respectively. Blood glucose is controlled and if necessary hyperglycemia will be treated according to current recommendations, regardless of the group and the study. The health-related quality of life will be estimated using the ReTransQoL questionnaire and the health-utility with the EQ-5D questionnaire (EuroQol questionnaire with five dimensions). The benefits of prevention of NODAT will be evaluated by estimating the cost of patient care during the first year of transplantation (care, medicines, medical examinations, hospitalization...).

Adverse effects

The risks associated with participation in the study are those related to an additional blood sample either hematoma, redness, vagal malaise, and those related to the glucose tolerance test include nausea, vomiting, malaise, sweating, tremors, palpitations, hunger and confusion. The risks associated with taking vildagliptin are those described for use as antidiabetic treatment (vildagliptin ((S)-1-[N-(3-hydroxy-1-adamantyl)glycyl]pyrrolidin-2-carbonitrile ; N° Chemical Abstracts Service: 274901165). Based on the risk management plan for vildagliptin, adverse events will be following attentively and considered as adverse event of special interest: Gastrointestinal disorders, Pancreatitis, Hepatitis, Skin reaction, Infection, Neurotoxicity, Pancreatic cancer, and Cardiac disorders. Particular attention will be given to adverse events occurred at the national level: hepatitis, pancreatitis, rash, infections, pancreatic cancer, bullous eruption and cardiovascular serious adverse events. In addition, when combined, inhibitors of angiotensin converting enzyme and antagonists of angiotensin II receptor (ARA2) will be used with caution.

Statistical analysis plan

· **Sample size and power calculation**

With an estimated proportion of diabetic patients 1 year after transplantation of 40% in group 2 (P2) and an expected 50% decrease in group 1 (P1) (*i.e.* 20% at 1 year) (4,5). The expected 50 % decrease is

estimated according to the results obtained with the insulin treatment of Hecking *et al.* (100% decrease at 1 year) (6). With the hypotheses H0: P2 - P1 = 0 (Null hypothesis) and H1: P2 - P1 ≠ 0 (altenative hypothesis) and by considering a group sequential design with a Z Score test (pooled estimate for variance estimation), a bilateral alpha risk = 5% and a ß risk = 20%, it will be necessary to randomize 84 patients per group (Total: 168 patients). We expect 10% of non-evaluable patients at 1 year and thus will include 186 patients in total. An interim is planned to reject H0 or H1 when at least 84 patients will be randomized with one year of follow-up (42 in each group; 50% of the information fraction) using alpha spending function and O'Brien Fleming boundaries. Sample size calculations were performed with the EAST 6 software.

Moreover as supportive analysis with this sample size we will be able to demonstrate an improvement of the time of diabetes free occurrence from 40% to 20% (Hazard ratio of 0.43) with a bilateral alpha risk = 5% and we will have a 90% statistical power with 63 events.

· **Statistical analysis**

The statistical analysis plans (final and dedicated to health-related quality of life, HRQoL, analyses) will be written and approved before the database is frozen.

Primary outcome analysis

The Intent to treat population will be used for efficacy parameters analysis (all randomized patients whatever eligibility criteria and treatment received).

A Z Score test with pooled estimate for variance estimation will be used to compare the estimated proportion of diabetic patients 1 year after transplantation between the two arms. A Lan-DeMets alpha spending function with O'Brien and Fleming boundaries (function depending on the information fraction in the ITT population) will be used. At the interim analysis with 84 informative patients at one year of follow-up (50% of the information fraction) we will reject H0 (efficacy) or reject H1 (futility) if the test p-value is lower or equal to 0.0003 and higher than 0.715, respectively. If the p-value is higher than 0.0003 but lower or equal than 0.715 we can't conclude and the study will continue. At the end of the study with 168 informative patients at one year of follow-up we will reject H0 and then accept H1only if the test p-value is lower or equal than 0.049.

Secondary outcome, exploratory and sensitivity analyses

Selected efficacy analyses will be repeated in the per protocol population (i.e., subset of the Intention-To-Treat, ITT population meeting the following criteria: all eligibility criteria fulfilled, at least one dose of allocated treatment administered). The safety population will be used for reporting the safety and treatment exposure data. Modified ITT population will be used for health-related quality of life analysis, considering all randomized patients with at least the baseline HRQoL questionnaire available. Continuous variables will be summarized using descriptive statistics, i.e. number of patients with available data (n), mean, median, standard deviation (SD), 25%-75% quartile (Q1-Q3), minimum, and maximum. Continuous

variables could be transformed to categorical variables using the median or using conventional cut-offs from bibliography or clinical practice. Frequencies in tables will be presented by arm, total frequency, percentages, and missing modality. Qualitative variables will be summarized by means of counts and percentages. Unless otherwise stated, the calculation of proportions will be based on the sample size of the population of interest. Rate of incidence of NODAT will be done with Confidence Interval (CI) and compare using Chi 2 test. Univariate and multivariate logistic analyses will be done to identify independent prognostic factor of the Rate of incidence of NODAT and to compute Odd ratio with 95% CI. The continuous variables will be treated as quantitative and qualitative data using cut-off in anticipation of elaborating a practical clinical tool. Factors will be considered for inclusion in the model if the univariate p-value is ≤ 0.1. Interactions between treatment and some variables will be tested at a two-sided 10 % level (i.e., a p-value >0.1 indicates no evidence of heterogeneity of treatment effect across the subgroups for each factor). All tests will be performed in an exploratory purpose at a two-sided 5 % significance level.

Health related Quality of life: The minimal clinically important difference will be fixed to 10 point for each HRQoL score. A descriptive analysis of the scores obtained for each questionnaire at baseline and at each follow-up will be performed using n, mean (SD), median (range), for all patients and according to the treatment arm. A linear mixed model for repeated measure will be applied to HRQoL scores integrating all measurement times including a treatment effect, a time effect and an interaction between time and treatment. The time to HRQoL score deterioration (TTD) approach will also be explored. The TTD will be defined as the time from inclusion in the study to the first deterioration of a least 10-point of the HRQoL score as compared to the baseline score (14,15). The TTD will be produce according to the Kaplan-Meier estimation method and compared by treatment arm using the Log-rank test. Univariate and Multivariate Cox regression models will be performed in order to estimate Hazard ratio with 95% CI to investigate potential factors independently associated with the TDD.

All tests in HRQoL analyses will be performed at a two-sided 1 % significance level to prevent inflation of the alpha type one error with a Bonferroni approach for the 5 targeted dimensions (5%/5=1%) (physical health, mental health, medical care and satisfaction, treatment and fear of losing the graft).

The EQ-5D questionnaire is a standardized tool consisting of 5 dimensions: mobility, self-care, usual activity, pain and discomfort, and anxiety and/or depression. Each patient's quality-ajusted life year will be calculated, from D0 until M12 or censoring date, by multiplying the duration of each period by the corresponding period's utility score.

For pharmacoeconomic impact: the total number of NODAT in the early post-transplant period avoided and the total number of acute rejection avoided will use as the measure of effectiveness. Because effectiveness and direct medical costs will measure over a period of one year, discounting will not apply to clinical and economic parameters according to recommendations of department of Economics and Public Health Assessment of the French Haute Autorité de Santé (21). The incremental cost-effectiveness *ratio* will be calculated comparing both interventions using the formula: (CostGroup1−Cost Group2) /

(Effectiveness Group1 – Effectiveness Group2). The robustness of the cost-effectiveness analysis (CEA) will be assessed through only deterministic sensitivity analyses. Different one-way univariate, deterministic sensitivity analyses will made on parameter likely to influence the results of the CEA.

Ethical issues

· **Ethics committee approval**

The trial has been approved nationally by the Advisory Committee on Information Processing for Research in the Field of Health (N°MEDAECNAT-2018-03-00009, N°EudraCT 2016-002023-28) and the Committee for Personal Protection (National approval by CPP Ile de France XI, n°17039).

· **Information and consent forms**

All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand. Prior to a subject's participation in the clinical study, the written informed consent form should be signed, name filled in, and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the subject.

Data quality and regulatory issues

· **Monitoring of the study**

The Sponsor of this clinical study, the Besançon University Hospital, is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the clinical study as regards ethics, clinical study protocol compliance, and integrity and validity of the data recorded on the case report forms. At regular intervals during the clinical study (every 5 or 6 patients for each center or at least every year) a representative of the monitoring team reviews study progress, Investigator and subject compliance with clinical study protocol requirements, and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: subject informed consent, subject recruitment and follow-up, serious adverse event documentation and reporting, adverse event documentation and reporting, Source document requirements. According to the ICH guidelines for Good Clinical Practice, the monitoring team must check the case report form entries against the source documents, except for the preidentified source data directly recorded in the case report form.

· **Data Management of the study**

Clinical Data Management is performed at the Methodology and quality of life unit in oncology of University Besançon hospital using the SAS version 9.4 (SAS Institute, Cary NC). Originals of all study-related report forms will be stored in the study headquarters at the trial site (according to the respective national laws). The data will be provided as SAS® files to the statistical team for data analysis under

SAS version 9.4 and R software version 2.15.2 (R Development Core Team, Vienna, Austria; http://www.r-project.org).

Investigators stores all administrative documents, patient identification log, signed patient consent forms, copies of the data documentation form and common study documentation. Original data of study patients (medical records) will be stored. A list allowing patient identification will be kept for 15 years (directive 2001/83/EG). The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical study.

Discussion

Conditions for patient selection

Patients considered at high risk of developing NODAT are included in the study. The selection of these patients is based on the Chakkera *et al.* criteria (4,5). They reported that an equation using 6 parameters provides a good identification of high-risk population for targeted prevention. These parameters include age, planned corticosteroid therapy post-transplant, prescription for gout medicine, BMI, fasting glucose and triglycerides, and family history of type 2 diabetes. The two parameter, planned corticosteroid therapy post-transplant and prescription for gout medicine, were not retained because they included a significant bias due to the subjectivity of clinician prescription. In addition, the determination of fasting glucose and triglycerides cannot be selection criteria because they both require fasting for 12 hours, which is not possible for patients selected for a kidney transplant. Nevertheless, the discriminating power of simpler algorithm is also well established. The risk of developing NODAT is multiplied by 20 in patients over 55 years of age with a BMI greater than 30 kg / m2 [unpublished data, series from (13)]. Accordingly, 3 criteria have been retained: Age over 50 years, BMI greater than 30 kg/m², and a direct family history of type 2 diabetes.

Justification of the choice of vildagliptin, dosing and timing of drug administration

Hecking *et al.* previous study reported that insulin, administered immediately after transplantation, was an efficient pharmacological prevention of NODAT. This study included 50 renal transplant patients and showed that a three months treatment of Neutral Protamine Hagedorn insulin decreased HbA1c and the occurrence of diabetes (73%) in the treated group. However, NODAT was a secondary end-point and hypoglycemia occurred five times in the treatment group (6). This strategy seems incompatible with preventive treatment. Moreover, the few numbers of patients and the absence of double blind hamper the conclusions of the study.

Other non-hypoglycemic antidiabetic drugs seem to be better candidates for the prevention of diabetes. Among them, gliptins seem to be the appropriate therapy because of their mechanistic properties. These drugs are inhibitors of dipeptyl peptidase-4 (DPP-4), which inactivates the incretins, the glucagon-like peptide-1 (GLP-1) and the gastric inhibitory polypeptide (GIP). DPP-4 inhibition causes an increase in the

GLP-1 and GIP concentrations which induce insulin secretion and inhibition of glucagon secretion. Beyond the effects on blood glucose, gliptins have pleiotropic effects including:

- A protective effect on β cells: Many preclinical studies have demonstrated the anti-proliferative and apoptotic effects of gliptins on β cells (7). The diabetogenic effects of Tacrolimus are the consequence of increased insulin resistance, but also a direct effect on β cells. Tacrolimus induces apoptosis in β cells, decreases insulin exocytosis and inhibits transcription of the insulin gene (8). Gliptins could prevent these deleterious effects.

- Anti-inflammatory: DPP-4 is strongly expressed on many immune cells, including monocytes and T lymphocytes. Inhibition of DPP-4 reduces the production of various cytokines, including interleukin (IL)-2, IL-12 and interferon-γ. Transforming Growth Factor-β is up-regulated after inhibition of DPP-4. Inhibition of DPP-4 also exerts effects on chemokines (9). It follows from these properties an anti-inflammatory action from gliptins. Inflammation plays an important role in the onset of NODAT (10). These different effects of gliptins could prevent or delay the occurrence of NODAT in patients with risk. There are several members of gliptins that can be used in the treatment of diabetes. Sitagliptin and vildagliptin are the best candidates. However, there is a significant risk of acute pancreatitis with sitagliptin therapy, and sitagliptin should not be used in patients with moderate to severe renal impairment (16). Vildagliptin was used to reduce diabetes after kidney transplantation in two clinical studies. Haidinger *et al.* conducted a randomized, double-blind Phase II to assess the efficiency of the administration of 50 mg of vildagliptin per day versus placebo for 3 months to 32 patients (16 per group) transplanted for at least 6 months and newly diagnosed for diabetes by NODAT score (11). Treatment with vildagliptin significantly improved oral glucose tolerance and reduced the glycated hemoglobin ($p < 0.01$) but did not affect fasting glucose. The differences were not maintained one month after treatment. Werzowa et al. conducted a similar study comparing vildagliptin and Pioglitazone versus placebo. Forty-eight patients (16 per Group) were recruited using the same method as above and followed until the end of treatment, namely 3 months (12). As in the study of Haidinger *et al.*, treatment with vildagliptin improved oral glucose tolerance and reduced glycated hemoglobin but did not alter fasting blood glucose. Given the important effect of vildagliptin taken early in diabetes, we can reasonably expect a preventive effect. Vildagliptin is prescribed according to the dosage indicated by the High Health Authorities in its use in NODAT.

Justification of the primary outcome

The primary endpoint is the proportion of diabetic patients 1 year after transplantation, defined as patients receiving a diabetic treatment, patients have a fasting glucose above 7 mmol/l and/or patients with an abnormal OGTT. Unlike Hecking *et al.* study, we chose *de novo* diabetes, a clinically relevant criterion, as the main criterion and not a surrogate marker (6). This will actually determine if this preventative treatment effectively protects from the disease. Consequently, the results will be expressed as the number of patients with diabetes, as defined previously, at a given time. At transplant, 100% of patients will be considered as diabetic because all patients will be treated, at least, with vildagliptin (or placebo) for two months. At 2 months, treatment with vildagliptin, prescribed in the context of the study,

will be stopped and only some patients will be considered diabetic (abnormal dosages and/or prescription of a new antidiabetic treatment) at 3 months. This number of patients may still vary at 6 months and one year post-transplant (6). The main criterion is the number of patients with diabetes at one year.

The onset of diabetes at other times (3 and 6 months) as well as abnormal glucose indicators (fasting glucose, OGTT, glycated hemoglobin) at each time will be assessed as secondary endpoints. These data will also be correlated with the clinical events (occurrence of acute rejection, infection, graft loss and patient death at 3 months, 6 months and 12 months after transplantation), the medical history and the biological assessment of the patients.

Health-related quality of life, renal transplantation and diabetes

The HRQoL assessment significantly predicts patient survival, particularly in patients with chronic kidney disease (17,18). Moreover, transplantation resulting in one of the best increases of patients' quality of life, its estimate is essential in the treatment evaluation of this population (19–22). It has been shown that cardiovascular complications, dialysis method, hypertension, method of diabetes treatments (oral or injectable) and hypoglycemia influence the quality of life (18,23,24). Furthermore, in patients with type II diabetes, hypoglycemia is associated with depressive symptoms and heightened anxiety and others setting important for quality of life (25). Prospective reports have indicated that diminished HRQOL among adults with type II diabetes is associated with subsequent mortality risk (26). Kizilisik et al have demonstrated in a cohort of 86 kidney transplant patients that transplantation and diabetes have direct, opposite and independent effects on the quality of life of patients (27).

Although the most commonly questionnaire used for assessing health-related quality of life is the Short Form 36 (SF-36), Gentile *et al.* have developed a quality of life questionnaire to specifically assess the quality of life associated with renal transplantation in France (28). This questionnaire was analyzed, evaluated and validated by French public health priorities (29). That is why the health-related quality of life questionnaire, ReTransQoL, will be used in our study (28,30). The ReTransQOL questionnaire was completed at t0, 8 days, 3 months, 6 months and 12 months after transplantation. The questionnaire is done on Day 0 and Day 8 for two reasons; to get rid of the beneficial effect on patient’s quality of life due to transplant announcement and to overcome the impossibility of filling out the form just before entering the operative block. The EQ-5D questionnaire allows evaluating a wide variety of interventions. It is widely used in utility calculations. It has evidence of validation in type 2 diabetes with a variety of different profiles (treatment, symptoms, and complications) (31).

Health economics analysis

The additional cost associated with NODAT could be also significantly reduced by efficient prevention. A United State study found that, for the period between 1994 and 1998, a newly diagnosed diabetic patient has cost $21,500 of medical expenses 2 years after transplantation (32). The increase in cardiovascular diseases due to post-transplantation diabetes may be accounted for this additional cost.

The purpose of this health economics analysis will be to investigate the cost-effectiveness of prevention of diabetes with vildagliptin in patients included in the PRODIG clinical trial. The CEA will be performed on resources and effectiveness collected prospectively and aggregated from all patients included in the PRODIG clinical trial. The analysis will be performed from a health care payer perspective. Only direct medical costs will be computed from the inclusion visit of patient (D0) until the last visit (M12) (i.e. 1-year-long time horizon; (21)). They will include: medication (as preventive treatment of diabetes and kidney transplant rejection, lipid-lowering therapy, diabetes treatment, treatment of diabetes and renal transplant complications, treatment of adverse event), hospitalization (complications related to the kidney transplant and/or new diabetes, serious adverse event management, follow-up), inpatient and outpatient consultations, biomedical analyses (creatinine clearance, OGTT, Hba1c, proteinuria, serology for Human Immunodeficiency Virus, Hepatitis B and C Viruses, CMV) and transport. Minor costs and cost considered to be independent of the treatment arm will not take into account. Nor will be indirect medical and intangible costs. Costs will express in Euros (€) (reference year 2018). Each cost will be calculated using the official tariff, as, for example, for each hospitalization, the national health-insurance provider's tariffs for Diagnosis-Related Group.

Furthermore, health-utility based measures of quality of life are recommended by some decision makers in health care. No studies have addressed changes in utility in patients with the same profile as patients included in PRODIG clinical trial. The purpose of this secondary analysis will be to assess the association of change in health-utility with changes in other variables as complications or treatment. Some preference-based measures of health status have been developed to facilitate the use of utilities in economic analyses. The EQ-5D is one of the most widely used health states descriptive system, especially recommended by the National Institute for Health Care and Excellence in the UK for the incorporation of health benefits in cost-utility analysis and for which validated preference-based scores are available in France (19,20,22,30).

Clinical implications

The incidence of type 2 diabetes is steadily increasing after solid organ transplantation (33). In kidney transplantation 30 percent of patients develop diabetes within 6 months of transplantation. Controlling this impaired glucose metabolism is a challenge in transplantation. There are only few data concerning pharmacological prevention of NODAT. In our study, we hope to show that the use of the antidiabetic, Vildagliptin, will achieve similar results that Hecking *et al.* study without the inconvenience of direct insulin treatment (subcutaneous administration, hypoglycemia). Indeed, in addition to the side effects of treatment (hypoglycemia, malaise...), the use of insulin therapy is very controversial. Hecking *et al.* indicates in his study that the administered treatment results in too low HbA1c rate (<6%) (6). And low HbA1c rate is correlated with increased cardiovascular complications (34). If our hypothesis is verified, our results will have a direct application in clinical practice. Moreover direct benefit is expected for the patients in the experimental group. Indeed, vidalglipin administration should prevent the occurrence of NODAT and thus limit the associated morbidity, reduce cardiovascular complications and consequently promote graft and patient survival. Prevention of NODAT would also increase the quality of life in renal

transplant patients. Importantly, a double-blind study has never been accomplished in this area. Our results may serve for non-transplant patients carrying a high-risk of diabetes associated with other co-morbidities such cardiovascular disease.

Trial status

At the time of submission, the regulatory authorizations have been obtained (protocol version 6 dated May 22, 2018), three patients were enrolled in the study in our center (first inclusion 2018/10/26) and the implementations are in progress in the participating hospitals (signing of conventions, implementation meeting). The recruitment will be completed approximately in November 2020.

List Of Abbreviations

ARA2: Antagonists of Angiotensin II Receptor

BMI: Body Mass Index

CEA: Cost-Effectiveness Analysis

CI: Confidence Interval

CMV: Cytomegalovirus

CPP: Committee for Personal Protection

(e)CRF: (electronic) Case Report Form

CRP: C Reactive Protein

CYP450: Cytochrome P450

DPP-4: DiPeptyl Peptidase-4

EQ-5D: EuroQol questionnaire with five dimensions

GIP: Gastric Inhibitory Polypeptide

GLP-1: glucagon-like peptide-1

HbA1c: glycated hemoglobin

HRQoL: Health-Related Quality of Life

ICH: International Council for Harmonisation

IL: InterLeukin

(m)ITT: (modified) Intention-To-Treat

MDRD: Modification of Diet in Renal Disease

mTOR: mammalian Target Of Rapamycin

NODAT: New Onset Diabetes After Transplantation

NYHA: New York Heart Association

OGTT: oral glucose tolerance test

ReTransQoL: Renal Transplant Quality of Life

SD: Standard Deviation

SF-36: Short Form-36

TDD: Time to Definitive Deterioration

Declarations

Ethics approval and consent to participate

The trial has been approved nationally by the Advisory Committee on Information Processing for Research in the Field of Health and the Committee for Personal Protection protocol version 6 dated May 22, 2018.

Written informed consent will be obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interest

Funding

PRODIG study was supported by a grant from the French Ministry of Health (Programme Hospitalier de Recherche Clinique 2015).

Author contributions

EG, FB, AA, VN, SL, DV, DD, LK, TC, JB, CC, MB, EC, GC, MH, LK, CL, YLM, AT, contributed to conception and design of protocol

EG, AA, VN, SL, DV, DD, LK, were involved in drafting or revising the manuscript

EG, AA, VN, SL, DV, DD, LK, TC, JB, CC, MB, EC, GC, MH, LK, CL, YLM, AT, LA, JMC, NO give final approval of the version to be published.

Acknowledgments

We thank the Fédération Hospitalo-Universitaire INCREASE for its help to the realization of the study.

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Figures

	STUDY PERIOD							
	Enrolment	Allocation	Kidney transplant	Post-transplantation				Close-out
TIMEPOINT	*Kidney transplant visit*	*Day 0*		*Day 8*	*Month 2*	*Month 3*	*Month 6*	*Month 12*
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS:								
Vidagliptin (100 or 50 mg per day)		D0 ←			→ M2			
Placebo (100 or 50 mg per day)		D0 ←			→ M2			
ASSESSMENTS:								
Physical examination		X			X	X	X	X
Collect of necessary clinical data		D0 ←						→ M12
Blood sample		X			X	X	X	X
OGTT (primary endpoint)					X	X	X	X
Fasting Glucose test (primary endpoint)		X			X	X	X	X
Glycated hemoglobin (HbA1c) test		X			X	X	X	X
Questionnaire ReTRANSQUOL		X		X	X	X	X	X
Cost-effectiveness ratio (EQ-5D)		X		X				X
Adverse events		D0 ←						→ M12

Figure 1

SPIRIT-Figure of PRODIG study

Supplementary Files

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- supplement1.pdf