A phase 4, monocenter, randomized, double-blind, comparator-controlled, parallel-group, mechanistic intervention trial to assess the effect of 8-week treatment with the dipeptidyl peptidase-4 inhibitor (DPP-4i) linagliptin versus the sulfonylurea (SU) derivative glimepiride on renal physiology and biomarkers in metformin-treated patients with type 2 diabetes mellitus (T2DM)

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Primary objective: What are the long-term effects (i.e. after 8-week drug exposure) of the DPP-4i linagliptin versus the SU derivative glimepiride on fasting and postprandial renal hemodynamics (glomerular filtration rate (GFR)/ effective renal...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON41714

Source
ToetsingOnline

Brief title
RENALIS: RENoprotection in diAbetes by LInagliptin versus Sulfonylurea

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Nephropathies

Synonym
Type 2 Diabetes Mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Boehringer Ingelheim,industrie

Intervention

Keyword: Diabetes, DPP-4, GLP-1, Renoprotection

Outcome measures

Primary outcome

Renal hemodynamics, measured as:

* Glomerular filtration rate (GFR; measured by the inulin-clearance technique)

* Effective renal plasma flow (ERPF; measured by the para-aminohippuric acid

(PAH) clearance technique)

Secondary outcome

To assess changes from baseline following 8-week treatment with a DPP-4i versus

SU derivative on:

* Systolic and diastolic blood pressure, mean arterial pressure

* Heart rate

* Renal tubular function, measured as:

o Fractional sodium- and urea excretion

o Urine osmolality

* Renal damage, measured by urine biomarkers as:

o Albumin/creatinine-ratio (Glomerular)

o NGAL and KIM*1 (Tubular)

Exploratory Objectives

* Resting heart rate variability

* Cardiac autonomic nervous system function

* Systemic hemodynamic variables

* Microvascular function

* Arterial stiffness

* Glycemic variables

* Lipid spectrum

* Biomarkers

* Plasma DPP4- and ACE activity

* Body anthropometrics

* Body fat content

Study description

Background summary

Diabetic nephropathy (or Diabetic Kidney Disease, DKD) is a common cause of chronic en end-stage kidney disease (CKD/ESRD). With the increasing rates of obesity and subsequent type 2 diabetes (T2DM), many more patients with DKD can be expected in the coming years. DKD is a multi-factorial condition, involving factors such as chronic hyperglycemia, Advanced Glycation End products (AGEs), oxidative stress, hypertension, glomerular hyperfiltration, as well as a

pro-inflammatory cytokines. Large-sized prospective RCTs suggest that intensified glucose and blood pressure control, the latter using agents interfering with the renin-angiotensin system (RAS), may halt the progression of DKD, both in T1DM and T2DM. However, despite the wide use of RAS-interfering drugs, both angiotensin-converting enzyme inhibitors (ACE-i) and angiotensin receptor blockers (ARB), renal function decline and the occurrence of DKD are observed during the course of diabetes in a considerable proportion of patients, suggesting an unmet need for renoprotective therapies. Based on preclinical and small-sized studies in non-diabetic individuals with normal renal function, incretin-based therapies, i.e. glucagon-like peptide -1 receptor agonists (GLP-1RA) and dipeptidyl peptidase-4 inhibitors (DPP-4i), may offer an attractive option. However, to date, the potential renoprotective effects of these agents have not been sufficiently detailed in human diabetes. The current study proposal aims to explore the mechanistic and clinical effects of DPP-4i on renal physiology and biomarkers in T2DM patients.

Hypothesis: Treatment with the DPP-4i linagliptin, as compared to the sulfonylurea (SU) derivative glimepiride, may confer renoprotection, by improving fasting and postprandial renal hemodynamics, decreasing blood pressure, and ameliorating inflammation in T2DM patients.

Study objective

Primary objective: What are the long-term effects (i.e. after 8-week drug exposure) of the DPP-4i linagliptin versus the SU derivative glimepiride on fasting and postprandial renal hemodynamics (glomerular filtration rate (GFR)/ effective renal plasma flow (ERPF)) in patients with T2DM?

Secondary objectives: blood pressure, heart rate, renal tubular function, markers of renal damage

Exploratory objectives: autonomic nervous system balance, systemic hemodynamic variables, microvascular function, arterial stiffness, metabolic/humoral biomarkers, markers of inflammation, ACE- and DPP-4 activity, anthropometrics and body fat content.

Study design

A phase 4, monocenter, randomized, double-blind, comparator-controlled, parallel-group, mechanistic intervention trial to evaluate the effect of 8 weeks of treatment with linagliptin versus glimepiride on renal physiology and biomarkers in metformin-treated patients with T2DM.

Renal hemodynamics, i.e. glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) will be measured by the gold-standard inulin- and para-aminohippurate (PAH) clearance methods, respectively; blood pressure and

heart rate will be measured using an automated oscillometric blood pressure device (Dinamap®); renal tubular function will be measured by fractional excretion of sodium and urea and urine osmolality; markers of renal damage will include urinary albumin/creatinine-ratio, neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1); autonomic nervous system balance (heart rate variability) and systemic hemodynamic variables (stroke colume, cardiac index, total peripheral resistance) will be measured by continuous beat-to-beat hemodynamic monitor (NexFin®); microvascular function will be measured by capillary videomicroscopy and Laser Doppler; arterial stiffness will be assessed by applanation tonometry, (SphygmoCor®); blood samples will be obtained to determine metabolic, biochemical and humoral biomarkers, markers of inflammation and ACE- and DPP-4 activity; anthropometrics, including body weight, height, body-mass index and waist circumference, and body fat contents (by bio-impedance analysis) will be measured.

Intervention

Subjects will be randomized to either of the following arms:

Treatment arm 1: Linagliptin 5 mg oral once daily
Treatment arm 2: Glimepiride 1 mg oral once daily

Study burden and risks

We are aware of the fact that in the current study participants will undergo multiple tests that demand a considerable time investment from their end. The total duration of visits are 1*/1 hour (screening- and control visit, resp.) and 7.5 - 8 hours (visits 2 and 4). The total amount of drawn blood will be 460 mL during a total period of 16 weeks. Side effects are not expected because the blood volume taken per visit is relatively small, especially in comparison with regular blood donation, which amounts 500 mL per donation (and is allowed 5 times a year for men and 3 times for women). In addition, the renal/cardiovascular test-days may be perceived as demanding: in particular, the combined renal/cardiovascular physiology test, that amongst others involves frequent blood and urine collection, infusions, blood pressure, heart rate and microvascular measurements. During the cardiac autonomous nervous system function tests participants may experience transient dizziness or lightheadedness.
However, we have gained ample experience with similarly demanding mechanistic drug intervention studies in T2DM patients. We have built in different ways to alleviate the burden for participants, including clear, repeated communication, frequent contacting, intensified (diabetes) care, 24-hour availability of research staff, study and travel reimbursement, enabling participants to receive the newest study medication (that for most of them would not be reimbursed in daily practice) and offering follow-up care in our out-patient

clinic. During test-days, we provide meals and allow participants to read or watch TV/DVDs when possible.
The study examinations/tests are considered to be safe. No invasive procedures (besides intravenous peripheral catheters) are involved. During the study tests, two *diagnostic agents* (i.e. inulin and PAH) need to be administered; both agents are inert and have no side effects.
Both study medications (linagliptin and glimepiride) have been approved (FDA, EMA) for blood-glucose lowering treatment in T2DM patients and, based on currently available data, are considered to be safe. To date, DPP-4i use has not been associated with side effects that occur more frequently than with placebo. The blood-glucose lowering effect of linagliptin is glucose-dependent and hypoglycemia rates are low when this agent is combined with metformin. Glimepiride is a 3rd generation SU derivative, the use of which is associated with relatively low hypoglycemia risk and little weight gain. Of note, the glimepiride in this study will be used at a relatively low dose (i.e. 1 mg per day) for a relatively short treatment duration of 8 weeks. Therefore, also given the inclusion- and exclusion criteria of the study participants, the overall risk of hypoglycemia is believed to be small. As these agents have been used in previous studies at the VU University Medical Center, there is ample experience. As in all drug intervention trials, in this study, we will closely monitor patients for adverse drug and study events during the follow-up visit and by telephone consultation. Moreover, the research physician is available for questions at all times.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Caucasian
* Male and Female (must be post-menopausal; no menses >1 year)
* Age: 35 - 75 years
* BMI: >25 kg/m2
* Type 2 diabetes mellitus (HbA1c: 6.5 - 9% DCCT or 48 - 75 mmol/mol IFCC) who are being treated with a stable dose of oral antihyperglycemic agents (metformin monotherapy or combination of metformin and low dose SU derivative) for at least 3 months prior to inclusion
* All patients with previously diagnosed hypertension should use a RAS-interfering agent (ACE-i / ARB) for at least 3 months

Exclusion criteria

* Current / chronic use of the following medication: thiazolidinediones, insulin, glucocorticoids, immune suppressants, antimicrobial agents or chemotherapeutics. Subjects on diuretics will only be excluded when these drugs (e.g. hydrochlorothiazide) cannot be stopped for the duration of the study
* Chronic use of NSAIDS will not be allowed, unless used as incidental medication (1-2 tablets) for non-chronic indications (i.e. sports injury, head-ache or back ache). However, no such drugs can be taken within a time-frame of 2 weeks prior to renal-testing
* Estimated Glomerular Filtration Rate <60 mL/min/1.73m2 (determined by the Modification of Diet in Renal Disease (MDRD) study equation)
* Pregnancy
* Frequent occurrence of (confirmed) hypoglycemia (plasma glucose *3.9 mmol/L)
* Current urinary tract infection and active nephritis
* Recent (<6 months) history of cardiovascular disease, including: acute coronary syndrome, chronic heart failure (New York Heart Association grade II-IV), stroke, transient ischemic neurologic disorder
* Complaints compatible with or established gastroparesis
* Active liver disease or a 3-fold elevation of liver enzymes (aspartate aminotransferase (AST) / alanine aminotransferase (ALT)) at screening
* History of or actual pancreatic disease

* History of or actual malignancy (except for basal cell carcinoma)
* History of or actual severe mental disease
* Substance abuse (alcohol: defined as >4 units/day)
* Allergy to any of the agents used in the study
* Individuals who are investigator site personnel, directly affiliated with the study, or are immediate (spouse, parent, child, or sibling, whether biological or legally adopted) family of investigator site personnel directly affiliated with the study
* Inability to understand the study protocol or give informed consent

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-05-2014
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aminohippurate Sodium 'PAH'
Generic name:	Para-aminohippuric acid (PAH)
Product type:	Medicine
Brand name:	Glimepiride Cf
Generic name:	glimepiride

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Trajenta
Generic name:	linagliptin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	11-12-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-03-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-002493-47-NL
CCMO	NL47157.029.13
Other	U1111-1143-9518