Off taRget Effects of Linagliptin monothErapy on Arterial Stiffness in Early diabetes

Published: 17-05-2013
Last updated: 24-04-2024

1. To assess whether linagliptin compared with placebo improves arterial stiffness in treatment naïve subjects with type 2 diabetes.2. To assess whether linagliptin compared with placebo improves blood pressure parameters, inflammatory and...

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

Summary

ID

NL-OMON40278

Source
ToetsingOnline

Brief title
RELEASE

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Diabetes Mellitus type 2, Type 2 diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: bedrijven (Boehringer Ingelheim GmbH)

Intervention

Keyword: diabetes, Dipeptidyl peptidase (DPP)-4, linagliptin, pulse wave velocity

Outcome measures

Primary outcome

Difference in mean Pulse Wave Velocity (PWV) after 26 weeks between the Linagliptin and placebo treated group.

Secondary outcome

- Central Blood Pressure (CBP) and Augmentation Index (AI) obtained from pulse wave analysis, using Sphygmocor

- Carotid-(left) radial arterial PWV, using Sphygmocor

- Body Mass Index (BMI) and Waist-to-Hip ratio

- 24-hours ambulatory blood pressure measurement (24-ABPM)

- Urinary albumin/creatinine ratio (mean of 2 separate morning portions (ACR)

- plasma markers of inflammation (i.e. high-sensitivity C-reactive protein (hs-CRP); Interleukin-6; TNF-α, serum amyloid-A (SAA), myeloperoxidase (MPO))

- plasma markers of endothelial dysfunction (i.e. vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1), soluble E-selectin, von Willebrand factor, tissue-type plasminogen activator), in vitro stimulated cytokine production by peripheral blood mononuclear cells (PBMC)

- Glycemic indices: fasting glucose (FPG) and 2-hour post OGTT glucose (OGTT), HbA1c, fasting insulin, and derived indices (HOMA-β (as a surrogate marker for β -cell function) and HOMA-IR (insulin resistance), Matsuda index (insulin sensitivity)

- Skin AGE deposition measured as skin autofluorescence using AGE reader and

plasma levels of AGEs (N(*)-(carboxymethyl) lysine (CML), N(*)-(Carboxyethyl)

lysine (CEL)

- Intake of energy, Eating behaviour, and Physical activity

- Target-to-background ratios (TBRs) (18)F-fluorodeoxyglucose positron

emission tomography computed tomography coregistration (FDG PET-CT)

Study description

Background summary

Patients with type 2 diabetes mellitus (T2DM) are at increased risk for developing premature macrovascular complications. The process of irreversible subclinical damage to the vasculature already starts during its preceding stages. At diagnosis, patients with T2DM already have evidence of subclinical vascular damage. Recent trials have shown no benefit of glucose lowering therapy when started later in the course of the disease, implicating that early interventions could be more effective in preventing macrovascular complications. Dipeptidyl peptidase (DPP)-4 inhibitors are oral antidiabetic drugs that increase the action of the naturally gut hormone glucagon-like peptide-1 (GLP-1), leading to improvement of postprandial insulin secretion, without hypoglycaemia or weight gain. DPP4 inhibitors improve beta-cell function and insulin resistance. More importantly, off-target effects on adipose tissue inflammation, liver steatosis and atherosclerotic plaques have been extensively documented in animal studies. Furthermore, DDP4 inhibitors improve the cardiovascular risk profile in small clinical studies. Based on these considerations we hypothesize that early therapy with the DPP4 inhibitor linagliptin in subjects with type 2 diabetes will lead to beneficial effects on arterial stiffness, blood pressure, inflammatory markers and vascular inflammation, independent of its effects on glycemic control.

Study objective

1. To assess whether linagliptin compared with placebo improves arterial stiffness in treatment naïve subjects with type 2 diabetes.
2. To assess whether linagliptin compared with placebo improves blood pressure parameters, inflammatory and endothelial function markers, albuminuria, and vascular inflammation in treatment naïve subjects with type 2 diabetes.
3. To determine whether the off-target effects on arterial stiffness blood

pressure parameters, inflammatory endothelial function markers and vascular inflammation are concordant with changes in glucose parameters, including HbA1c fasting plasma glucose, and beta-cell and insulin sensitivity indices.

Study design

Single center, prospective, randomized, placebo controlled double-blind intervention trial

Intervention

Participants will be treated with:
- Linagliptin 5 mg/day + lifestyle advise, OR
- Matching placebo + lifestyle advise

Study burden and risks

Burden and risks: The efficacy and safety of linagliptin in patients with T2DM have been shown in different studies. The risks for hypoglycaemia are less with DPP4-inhibitors compared to metformin or sulfonylurea derivatives. DPP4 inhibitors do not cause weight gain, unlike sulfonylurea derivatives. Only subjects with an HbA1c that would be treated with lifestyle advice and would not directly need drug treatment in clinical practice will be included, so that the guidelines for the management of type 2 diabetes are followed. Patients visit the outpatient clinic 6 times and during each visit blood pressure is measured and 30 mL of peripheral blood is drawn by venapuncture. Additionally, an FDG PET-CT scan wil be performed. For this test, 18F-FDG wil be administrated intravenously and a scan will be performed with a radiation burden of 4.2 mSv . This is considered a moderate risk (category III, ICRP 62).

Benefits: We expect that linagliptin improves PWV and may hence have a beneficial effect on the vessel wall in patients with treatment naïve diabetes. Also, the FDG PET-CT scan may yield abnormalities (such as malignancies in early stages) that would not have been discovered otherwise and may allow earier intervention.

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

- Men and women, age 30 to 70 years, AND
- Treatment naïve type 2 diabetes, as defined as the presence of one of the following (American Diabetes Association definition:
- Fasting plasma glucose >= 7.0 mmol/l, OR
- Random plasma glucose >= 11.1 mmol/l, OR
- HbA1c >=6,5%
- written informed consent

Exclusion criteria

- Current or previous use of glycemic control medications
- Type 1 diabetes
- Gestational diabetes mellitus
- Other specific types of diabetes due to other causes
- Uncontrolled hypertension, defined as systolic blood pressure >160 or a diastolic blood pressure >100 mmHg at screening visit
- Severe dyslipidemia indicating primary dyslipidemia, defined as total cholesterol >8 mmol/l, tryglicerides >10 mmol/l of high density lipoprotein cholesterol <0.6 mmol/l
- Current use of weight loss medication or previous weight loss surgery
- History of severe gastrointestinal disease

- Clinical contraindications to DPP4-inhibitors
- Previous cardiovascular disease, defined as stable coronary artery disease or acute coronary syndrome, stroke or transient ischemic attack, peripheral artery disease
- Symptomatic heart failure, New York Heart Association (NYHA) class II-IV
- Women who are currently pregnant,planning to become pregnant,breastfeeding women, or women with child bearing potential not using appropriate contraceptive measures
- Clinically significant liver disease or hepatic function greater than 3 times upper limit of normal
- Known impaired renal function or eGFR <30 ml/min/1.73m2
- Patients who are mentally incompetent and cannot sign a Patient Informed Consent
- Current active malignancy or in the previous 6 months
- Documented HIV infection
- Use of rifampicin
- Known or suspected allergy to 18F-FDG or its components

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-02-2014
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Linagliptin

Generic name:	Trajenta
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-05-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-10-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-12-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2012-005220-15-NL
CCMO	NL43473.042.13

Study results

Date completed:	08-03-2016
Actual enrolment:	45