Novel Approach to Detect the Detailed Effects of Vildagliptin on Beta-cell Dynamics in Patients with Early-onset Type 2 Diabetes

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PrimaryThe 3 months* effect of Vildagliptin on insulin synthesis and storage capacitySecondaryThe 3 months* effect of vildagliptin on- Glucose, insulin, C-peptide levels- Hormonal axes, most importantly GLP1 and GIP and Glucagon- Body weight, body…

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

Summary

ID

NL-OMON43940

Source
ToetsingOnline

Brief title
Effects of Vildagliptin on Beta-cell Dynamics

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
impaired fasting glucose/impaired glucose tolerance, prediabetes

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Ministerie van OC&W,Novartis

Intervention

Keyword: Beta-cells, dipeptidylpeptidase-4 inhibitors, South Asians, Type 2 Diabetes

Outcome measures

Primary outcome

Primary

3 months* effect of vildagliptin:

on beta-cell granule and synthesis insulin capacity during a prolonged Oral

Glucose Tolerance Test

(OGTT) using a novel isotope tracer based technique that follows biphasic

insulin response in detail.

Secondary outcome

Secondary

- 3 months* effect of vildagliptin on immunoassay based measurement of glucose,

insulin, C-peptide

levels and related OGTT indexes

- 3 months-effect of vildagliptin on hormonal axes, most importantly GLP1 and

GIP and Glucagon

- 3 months-effect of vildagliptin on body weight, body mass index, waist-to-hip

ratio, RR, plasma lipids.

Study description

Background summary

Type 2 Diabetes (T2D) is a chronic disease characterized by impaired glucose homeostasis, with a large variation in burden of disease based on family history[1] but also on ethnicity[2]. South Asians (SA) living in the Netherlands have a nearly five fold higher overall T2D prevalence than Dutch indigenous (> 25%) and among SA it is a more complicated disease[2-4].

We recently performed an in vivo study in SA families with high T2D risk and found a characteristic delayed profile in insulin secretion in persons with pre-diabetes and persons with diabetes. T2D has high heritability and most genes identified so far point at beta cell related disease processes[5]. Moreover, T2D does not occur without beta cell impairment[6]. Therefore, we developed a detailed approach [unpublished data] following beta cell dynamics to improve the early detection of individuals with predisposition for T2D enabling necessary early interventions[7]. Based on our findings, we hypothesized that a specific type of beta-cell dysfunction could contribute to the severe phenotype observed in SA. Our findings suggest that the first choice medication for this population is the Dipeptidyl dipeptidase 4 (DPP-4) inhibitor group.

Preliminary results demonstrate that individuals from high risk families already show abnormal secretion pattern with a delayed late-hyperinsulinaemic insulin release. In our model, 13C labelled leucine is administered orally prior to a prolonged and intensified OGTT. This stable isotope, given in a specific dosage and timing, is equally distributed and incorporated in de novo synthesized (pre)proinsulin, enabling us to make a difference between readily available stored insulin (releasable granules) versus de novo labelled insulin. Our method improves earlier function tests. These tests only partially explain beta-cell function, and the signal response is influenced by the insulin sensitivity. Our novel test provides insights in intrinsic beta cell function and the signalling effects on beta cell function.
The excretion of c-peptide, the 13C/12C leucine ratio and calculated insulin secretion rates give us in depth insights in beta cell dynamics. To our knowledge, a similar function test has not been performed or described. It is our hypothesis that treatment with vildagliptin stimulates

the beta-cell to increase the
storage granular capacity resulting from enhanced insulin synthesis before a glucose trigger is given.

Earlier experiences with DPP-4 inhibitors in in vivo modeling studies:
DPP-4 inhibitors stimulate insulin secretion by delayed degradation of incretin hormones Glucagon-Like
Peptide 1 (GLP1) and Glucose-dependant Insulinotrope Polypeptide (GIP), but additional glucose
lowering effects have been described as well, such as lowering of glucagon levels[8]. Notably,
hypoglycaemias and gastrointestinal side effects are less often observed on DPP-4 inhibitors compared
to all other hypoglycemic drugs[9]. The improved beta-cell function by prolonging incretin action is
promising and, of course, long-term, hard endpoint studies are required to translate in vivo responses to
disease management of different individuals and populations[9-11].

In vivo studies showed enhanced alpha- and beta-cell function with an improved proinsulin/insulin ratio
in individuals with T2D and impaired fasting glucose[8, 12-14] Interestingly, DPP-4 inhibitors may
preserve beta cell function by reducing apoptosis and stimulating proliferation of beta cells[15] although
in vivo proof in humans is not easy to obtain. Nonetheless, a recent trial supports a clear improvement of
beta cell function[16].

In theory, direct and indirect incretin agonism both have good chances to improve beta cell function.
Based on our findings, we are convinced that the opportunity to link the medication to the meals has
great advantages. Vildagliptin is expected to restore the physiological insulin response to a meal in our
persons at risk for T2D and the patients with T2D in our SA families.

Novel beta-cell dynamics measuring technique and study goal:
We developed a method using an isotope tracer based technique to follow insulin synthesis and release
in detail. The technique has been tested in a recently performed but not yet published study.
The goal of the proposed study is to test if vildagliptin restores the delayed insulin response following
food intake in young SA persons at risk for T2D. Therefore, we will perform a small short-term,
randomized, placebo-controlled, double-blind trial in SA selected from families

with a known delayed
insulin release to test the effect of vildagliptin on the insulin release patterns.

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Study objective

Primary
The 3 months* effect of Vildagliptin on insulin synthesis and storage capacity
Secondary
The 3 months* effect of vildagliptin on
- Glucose, insulin, C-peptide levels
- Hormonal axes, most importantly GLP1 and GIP and Glucagon
- Body weight, body mass index, waist-to-hip ratio, RR, plasma lipids.

Study design

This is a randomized double blind placebo-controlled study to be conducted in two parallel study arms for
a three month period (daily doses). 20 eligible patients will be enrolled and will receive
Vildagliptin (50mg tablets twice daily) or placebo on Day 1 through 90

Intervention

Vildagliptin (50mg tablets twice daily) or placebo for the duration of 3 months

Study burden and risks

Drug interactions and adverse events:
Information about interactions of vildagliptin with other drugs is available through SmPC . Although
interactions with other oral glucose lowering drugs have been described, usage

of the class of
medications is not expected in the proposed study group. Each already prescribed medication will be
assessed by the clinician. If it is required that already prescribed drugs should be discontinued, for the
reason of participation in this study, alternatives of these already prescribed drugs will be assessed
and/or clear arguments must be delivered that discontinuation of already prescribed drugs within the
given study period is not harmful for the participant.

For possible adverse events during the use of vildagliptin, meta-analyses are available (M. Ligueros-Saylan et al Diabetes, Obesity and Metabolism 12: 495*509, 2010; A.Sweitzer et al ;Diabetes, Obesity and Metabolism 12: 485*494, 2010). They concluded that Vildagliptin was not associated with increased risk of hepatic events/injury, pancreatitis, infections, skin related toxicity, and that Vildagliptin did not increase risk for cardiovascular and cerebrovascular disease.

Benefit and group relatedness
We investigate the T2D high risk South Asian population, heavily burdened by T2D. However, our findings could also be used for other high-risk populations:
- Our results will show the effect of vildagliptin on pathologic delayed insulin release following food
intake.
- Our results will further unravel the effect of vildagliptin on beta-cell function.
- This study will increase our knowledge about the way stimuli like GLP1 and GIP alters our insulin
release pattern. This could be a direct effect on readily releasable insulin or perhaps at the level of
regulating insulin gene expression leading to faster insulin de novo synthesis.
- Finally, future expansion of the study in T2D patients with DPP-4 inhibitors (as mono therapy or
combination therapy) versus metformin for long-term usage to screen for stable/improvement of
functional beta-cell preservation followed by our stable isotope technique would be one of our next
priorities. Furthermore, other high-risk populations and measurement of their beta-cell elasticity and
related markers could be explored as well.

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

- SA individuals
- all adult; age * 18 years
- impaired fasting glucose and/or impaired glucose tolerance, which will be confirmed with a 2 hour OGTT (based on criteria of ADA)
- Informed consent

Exclusion criteria

-History of macrovascular disease
- Heart failure
- Pregnancy
- Thyroid disease
- COPD
- Infection with/without usage of antibiotics/antiviral medication

- Usage of corticosteroids
- ACE inhibitors
- Renal disease (GFR<60mL/min)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-05-2014
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Galvus
Generic name:	Vildagliptin
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	19-12-2013
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-04-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2012-002230-37-NL
CCMO	NL40868.078.12