PRESERVE TRIAL:
Pancreatic beta-cell dysfunction REStorEd by Rosiglitazone and Valsartan Effects. A 52-week randomized controlled factorial study in subjects with IFG and/or IGT.

Amendment 2007: PancREatic beta-cell dySfunction rEstoRed by Valsartan Effects – PRESERVE Study.

Amendment 2007: In stead of two medicaments (Rosiglitazon and valsartan), only valsartan has been completed. Due to negative publicity, Rosiglitazon was stopped. Target number of participant is thereby decreased from 144

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23620

Source
NTR

Brief title
PRESERVE TRIAL

Health condition

Type 2 diabetes mellitus, impaired glucose metabolism

Sponsors and support

Primary sponsor: VU University Medical Center,
Amsterdam
The Netherlands
Source(s) of monetary or material Support: GlaxoSmithKline and Novartis

Intervention

Outcome measures

Primary outcome

To compare beta-cell function, as reflected by the first phase insulin secretion corrected for insulin sensitivity and/or the arginine-stimulated insulin secretion, both co-primary endpoints as measured during the eu-hyperglycemic clamp procedure, following 52 weeks of rosiglitazone, valsartan or rosiglitazone combined with valsartan in subjects with IFG (with and without a family history of DM2) and/or IGT.

Amendment 2007:

To compare beta-cell function, as reflected by the first phase insulin secretion corrected for insulin sensitivity and/or the arginine-stimulated insulin secretion, both co-primary endpoints as measured during the eu-hyperglycemic clamp procedure, following 26 weeks of valsartan in subjects with IFG (with and without a family history of DM2) and/or IGT

Secondary outcome

To compare the effects of 52 weeks of rosiglitazone, valsartan or rosiglitazone combined with valsartan in subjects with IFG (with and without a family history of DM2) and/or IGT with respect to:

1. Fasting plasma glucose;

2. Second phase insulin secretion in response to hyperglycemia during the hyperglycemic clamp test;

3. All the above-mentioned beta-cell function parameters at 12 weeks after discontinuation of therapy to assess durability/disease modifying effects;

4. The conversion from normal glucose tolerance (NGT) to IGT or diabetes (as evaluated by an oral glucose tolerance test);

5. HbA1c, fasting blood glucose and lipid/lipoprotein concentrations;

6. Insulin sensitivity assessed during the euglycemic clamp test;

7. Safety and tolerability, including assessments of hypoglycemic events, blood pressure, and urinary albumin excretion rate.

Amendment 2007:

To compare the effects of 26 weeks of valsartan in subjects with IFG (with and without a family history of DM2) and/or IGT with respect to:

1. Fasting plasma glucose;

2. Second phase insulin secretion in response to hyperglycemia during the hyperglycemic clamp test;

3. HbA1c, fasting blood glucose and lipid/lipoprotein concentrations;

4. Insulin sensitivity assessed during the euglycemic clamp test;

5. Safety and tolerability.

Study description

Background summary

Worldwide, type 2 diabetes mellitus is a major and growing health problem reaching epidemic proportions. DM2 is characterized by insulin resistance and progressive beta-cell failure, with the latter accounting for the progressive course of the disease. Current therapies fail to prevent the progressive nature of DM2, since no treatment exists that can effectively prevent or slow the decline of beta-cell function.

The PRESERVE (Pancreatic beta-cell dysfunction REStorEd by Rosiglitazone and Valsartan Effects) Trial is designed to determine whether treatment with rosiglitazone and/or valsartan will favorably affect beta-cell function in subjects with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). Since the two interventions have different mechanisms of action, it may be expected that the effects will be independent and potentially complementary (additive).

Rosiglitazone improves insulin sensitivity but may also have beta-cell protective effects, by lowering triglyceride accumulation in pancreatic islets, decrease inflammation and collagen deposition and anti-apoptotic actions. Valsartan may prevent deterioration of beta-cell function by interference with the renin-angiotensin system, both systemically and locally within the pancreatic islets. In particular, the latter action may reduce islet inflammation and scarring and increase pancreatic local blood flow. Other beneficial effects of generalized RAS blockade include an increase in disposal of glucose, a decrease in sympathetic nervous tone and the prevention of ectopic triglyceride accumulation by increasing adipogenic differentiation.
The PRESERVE study is a multi-center, randomized double-blind double-dummy trial using a balanced 2 x 2 factorial design in approximately 144 subjects with IFG (with and without a family history of DM2) or IGT. After randomization, subjects will be treated for 52 weeks, then study medication will be discontinued. At 3 months after discontinuation of the study medication, b-cell function will be re-evaluated to assess durability / disease modifying effects of the study drugs. Beta-cell function will be measured using modified euglycemic-hyperglycemic clamps prior to randomization, at 52 weeks and at 64 weeks.
The primary study endpoint is the treatment effect on beta-cell function as measured by changes in glucose induced first phase insulin secretion corrected for changes in insulin sensitivity and / or the (first phase) arginine-stimulated insulin secretion during a hyperglycemic clamp.
Secondary study endpoints include changes in fasting plasma glucose, the second phase insulin secretion in response to hyperglycemia during the clamp, conversion of NGT to IGT or diabetes, clamp-measured whole body insulin sensitivity, anthropometric and metabolic / lipid variables, as well as markers of vascular damage, inflammation and endothelial function. Those patients developing diabetes during the study (i.e. a diagnosis of diabetes will be made if 2 consecutive fasting plasma glucose (FPG) levels exceed the diagnostic thresholds of 7.0 mmol/l (126 mg/dl) or a 2 hr plasma post-load glucose 11.1 mmol/l (200 mg/dl)) and higher with FPG 10 mmol/l or above measured at 2 occasions, will be discontinued from the study after an end-point measurement.
If we can confirm our hypothesis, than it may be expected that the results will alter the guidelines, i.e. leading to earlier pharmaceutical treatment in high-risk populations.

Amendment 2007:

Worldwide, type 2 diabetes mellitus is a major and growing health problem reaching epidemic proportions. DM2 is characterized by insulin resistance and progressive beta-cell failure, with the latter accounting for the progressive course of the disease. Current therapies fail to prevent the progressive nature of DM2, since no treatment exists that can effectively prevent or slow the decline of beta-cell function. The PRESERVE (Pancreatic beta-cell dysfunction REStorEd by Valsartan Effects) Trial is designed to determine whether treatment with valsartan will favorably affect beta-cell function in subjects with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). Valsartan may prevent deterioration of beta-cell function by interference with the renin-angiotensin system, both systemically and locally within the pancreatic islets. In particular, the latter action may reduce islet inflammation and scarring and increase pancreatic local blood flow. Other beneficial effects of generalized RAS blockade include an increase in disposal of glucose, a decrease in sympathetic nervous tone and the prevention of ectopic triglyceride accumulation by increasing adipogenic differentiation. The PRESERVE study is a multi-center, randomized double-blind trial using in approximately 80 subjects with IFG (with and without a family history of DM2) or IGT. After randomization, subjects will be treated for 26 weeks, then study medication will be discontinued. Beta-cell function will be measured using modified euglycemic-hyperglycemic clamps prior to randomization and at 26 weeks. The primary study endpoint is the treatment effect on beta-cell function as measured by changes in glucose induced first phase insulin secretion corrected for changes in insulin sensitivity and / or the (first phase) arginine-stimulated insulin secretion during a hyperglycemic clamp. Secondary study endpoints include changes in fasting plasma glucose, the second phase insulin secretion in response to hyperglycemia during the clamp, clamp-measured whole body insulin sensitivity, anthropometric and metabolic / lipid variables, as well as markers of vascular damage, inflammation and endothelial function. If we can confirm our hypothesis, than it may be expected that the results will alter the guidelines, i.e. leading to earlier pharmaceutical treatment in high-risk populations.

Study objective

Type 2 diabetes is cause by progressive beta-cell dysfunction against a background of obesity and insulin resistance in susceptible individuals.

Peroxisome proliferator-activated receptor (PPAR) gamma-mediated mechanisms are involved in the regulation of important processes that may protect the pancreatic beta-cell. Local pancreatic and systemic activation of the renin-angiotensin system (RAS), as frequently observed in people with obesity/insulin resistance, may be harmful to the pancreatic beta-cell causing beta-cell dysfunction and beta-cell apoptosis.

Treatment of subjects at high risk to develop type 2 diabetes, including those with impaired fasting glucose and/ or impaired glucose tolerance (with/without a familiy history of diabetes) with a PPAR gamma agonist and/or an angiotensin II receptor blocker may improve beta-cell function.

Amendment 2007: Type 2 diabetes is caused by progressive beta-cell dysfunction against a background of obesity and insulin resistance in susceptible individuals. Local pancreatic and systemic activation of the renin-angiotensin system (RAS), as frequently observed in people with obesity/insulin resistance, may be harmful to the pancreatic beta-cell causing beta-cell dysfunction and beta-cell apoptosis. Treatment of subjects at high risk to develop type 2 diabetes, including those with impaired fasting glucose and/ or impaired glucose tolerance (with/without a familiy history of diabetes) with an angiotensin II receptor blocker may improve beta-cell function.

Study design

N/A

Intervention

Participants will be randomized into 1 of the following 4 treatment groups for a 52-week intervention:

1. Rosiglitazone 8 mg daily and valsartan-placebo;

2. Valsartan 320 mg daily and rosiglitazon-placebo;

3. Rosiglitazone 8 mg daily and valsartan 320 mg daily;

4. Rosiglitazon-placebo and valsartan-placebo.

Amendment 2007:

Participants will be randomized into 1 of the 2 treatment groups for a 26-week intervention:

1. Valsartan 320 mg daily;

2. Placebo.

Contacts

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Eligibility criteria

Inclusion criteria

Male and female subjects (aged 35-70 years) with impaired fasting glucose (IFG; fasting plasma glucose 6.1 or higher and less than 7.0 mmol/l) and/or subjects with IFG (fasting plasma glucose 5.6 or higher and less than 7.0 mmol/l) ánd a family history of DM2 (i.e. first and second degree (i.e. grandparents) relatives), and/or impaired glucose tolerance (IGT; 2-h plasma glucose during 75-g oral glucose tolerance test 7.8-11.1 mmol/l) are eligible.

Exclusion criteria

Drug use:

1. Current use of ACE-I, ARB and/or TZDs and inability to discontinue these drugs;

2. Known hypersensitivity to any of the study drugs;

3. Prior use of blood glucose lowering medications except during pregnancy;

4. Use of systemic glucocorticoids or niacin.

Cardiovascular co-morbidities:

1. Ejection fraction known to be <40% or congestive heart failure, or existing clinical CV disease (previous MI or stroke; angina with either >50% stenosis in >=2 major coronary arteries, or ST depression of >=2mm, or a positive nuclear test, previous coronary angioplasty, stent or bypass; previous limb bypass or vessel angioplasty or angiographic evidence of >50% stenosis, or intermittent claudication with an ankle/arm pressure <=0.8);

2. Uncontrolled hypertension requiring ACE I or ARB.

Other Criteria:

1. History of diabetes (except gestational DM) or on antidiabetic medication;

2. Renal or Hepatic Disease:

A. Renal artery stenosis;

B. Creatinine clearance <40 ml/min or serum creatinine 200 umol/l or higher;

C. Clinical proteinuria (1 or above, + proteinuria on dipstick or 300 mg and above albuminuria/day, in the absence of urine);

D. Measured alanine transferase (ALT) 2.5 or more times the upper limit of normal;

E. Active liver disease including jaundice, chronic hepatitis, previous liver transplant.

3. Major illness with life expectancy < 5 years or that may interfere with participation;

4. Use of another experimental drug;

5. Pregnant or unwilling to use reliable contraception (fertile women will have a pregnancy test prior to randomization);

6. Major psychiatric disorder;

7. Diseases and medications that affect glucose tolerance (e.g. pheochromocytoma, Cushing’s syndrome, acromegaly, steroid-dependent asthma, protease inhibitors, antipsychotics);

8. Unwillingness to be randomized or sign informed consent);

9. Known uncontrolled substance abuse;

10. Inability to understand study information and/or communicate with clinic staff.

Study design

Design

Study type:	Interventional
Intervention model:	Factorial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2006
Enrollment:	80
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	03-08-2006
Application type:	First submission

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
NTR-new	NL711
NTR-old	NTR721
Other	- : N/A
ISRCTN	ISRCTN42786336

Study results

Summary results
N/A