Rotation for Optimal Targeting of Albuminuria and Treatment Evaluation (ROTATE-1)

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A better understanding on the individual response to different albuminuria lowering drugs and a better understanding why these drugs, of which some are developed for another indication, may help to tailor optimal therapy. Therefore in this study...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Nephropathies
Study type	Interventional

Summary

ID

NL-OMON43438

Source
ToetsingOnline

Brief title
ROTATE-1

Condition

- Nephropathies

Synonym
Albuminuria in patients with diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: PROTON project;Novo Nordisk Fonden

Intervention

Keyword: albuminuria, diabetes, individual

Outcome measures

Primary outcome

Primary Objective:

To determine the degree of albuminuria lowering response of four different albuminuria lowering drug classes in individual patients with type 1 diabetes and microalbuminuria.

Secondary outcome

Secondary Objective(s):

* To correlate the albuminuria-lowering response within individuals between different drug classes.

* To correlate the albuminuria-lowering response within individuals with the thickness of the glycocalyx.

Study description

Background summary

Current guidelines advise treatment with angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEi) in patients with diabetes and persistent albuminuria, as these drugs assert renoprotective effects. Despite being standard of care, it is known that a large proportion of patients treated with ARBs/ACE-i do not respond to the treatment. This means that a large proportion of patients receives suboptimal treatment, which highlights the necessity for a more personalized approach to albuminuria-lowering treatment. Alternative treatment regimens may be more suited to lower albuminuria and reduce the risk of renal failure in individual patients.

It is known that ARBs/ACE-I mainly assert their renoprotective effects in patients with diabetes through their albuminuria-lowering effect. Albuminuria

is a strong risk marker for renal and cardiovascular disease in different patient populations including patients with type 1 diabetes. Various drugs, other than ARBs/ACE-I are available that also decrease albuminuria. Examples include drugs such as atorvastatin, sulodexide, SGLT-2 inhibitors, and endothelin antagonists. By analyzing multiple large clinical trials we have shown that in diabetes (but also in non-diabetes) that the treatment group with more effective reduction of albuminuria during the first weeks/months of treatment invariably shows more renal/cardiovascular protection indicating that the initial albuminuria lowering response is crucial for long-term renal/cardiovascular protection.

Although these different drugs decrease albuminuria on a group level, a large variability exist in the albuminuria lowering response between individuals. Whether individual patients show different albuminuria responses to different drug classes has not been prospectively investigated but could be expected given the variable pathogenesis of diabetes.

Study objective

A better understanding on the individual response to different albuminuria lowering drugs and a better understanding why these drugs, of which some are developed for another indication, may help to tailor optimal therapy. Therefore in this study individual patients will be subjected to four different drug classes that have all been shown to reduce albuminuria on a group level. The drug that induces the strongest albuminuria-lowering response will be repeated in a fifth treatment period to assess whether this particular drug again produces the strongest albuminuria-lowering response. This design will allow us to determine whether an individual patient truly responds more strongly to a particular drug, or whether the albuminuria-lowering response is based on chance.

Study design

The study is designed as a randomized multicenter crossover trial with a total duration of 48 weeks and a total of 26 patients diagnosed with type 1 diabetes and microalbuminuria. Eligible patients are not allowed to use drugs intervening in the renin-angiotensin-system. Patients who are using such medications will be subjected to a 4 week run-in period in which their angiotensin-converting enzyme inhibitor, angiotensin receptor blocker or direct renin inhibtior will be discontinued. After the 4-week run-in period, patients will be randomly assigned to a four way treatment schedule consisting of an angiotensin receptor blocker (telmisartan 80 mg/day), SGLT-2 inhibitor (empagliflozin 10 mg/day), a DPP-4 inhibitor (linagliptin 5 mg/day) or sulodexide (200 mg/day) with each treatment period lasting four weeks. After each four weeks treatment period a wash-out period of four weeks will follow. For each patient, the drug that induced the strongest albuminuria-lowering

response will be repeated on completion of the rotation. If contraindicated by an adverse event, the drug will be substituted by the next most effective drug. This rotation schedule is repeated until each patient has received all treatment periods.

Intervention

Drugs (telmisartan, empagliflozin, linagliptin, sulodexide) are commercially bought and prepared by the hospital pharmacy of the University Medical Center Groningen. Patients will be randomized to a treatment schedule consisting of each of the four drugs with washout periods in between based on the treatment schedule set up by the pharmacy. Study medication is received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location. The study medication is stored according to the instructions specified on the drug labels. Storage conditions are adequately monitored. Subjects are asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation or in every visit to the outpatient nephrology clinic. Appropriate documentation of the subject specific dispensing process is maintained. Unused drugs are destroyed by the pharmacy department at the end of the study.

Study burden and risks

Patients will visit the clinic 14 times during the study period of 48 weeks. At every visit blood and urine samples will be taken. The risks for this study include increased blood pressure due to stopping ACE inhibitors and AII antagonists. Blood pressure will therefore be monitored and if needed (>180mmHg systolic blood pressure) amlodipine will be started at an initial dose of 1 dd 5mg, which will be uptitrated to 1 dd 10mg if necessary. The medication used in the study is deemed safe as it is registered for use in the European Union and adverse events are generally mild in nature. No risks are associated with the glycocalyx measurement as it is a non-invasive measurement with a camera. It is placed under the tongue for several minutes, which does not infer a high burden on the patient.

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

* Type 1 diabetes
* eGFR > 45ml/min/1.73m2
* Albumin:creatinine ratio >50mg/g and *500 mg/g
* Age * 18 years
* Written informed consent

Exclusion criteria

* Pregnant women and women of child-bearing potential who are not using reliable contraception
* Cardiovascular disease: myocardial infarction, angina pectoris, percutanous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, heart failure (NYHA I-IV) < 6 months before inclusion
* Uncontrolled blood pressure (office bp > 160/ 100 mmHg)
* Known malignancy
* History of autonomic dysfunction (e.g. history of fainting or clinically significant orthostatic hypotension)
* Any medication, surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of medications

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-11-2016
Enrollment:	17
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Jardiance
Generic name:	empagliflozin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Micardis
Generic name:	telmisartan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Trajenta
Generic name:	linagliptin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Vessel Due F
Generic name:	sulodexide

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-06-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-07-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-12-2019
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	EUCTR2015-005691-26-NL

Register	ID
CCMO	NL56183.042.15