Effects on renal function and risk factors for vascular disease using DUAL blockade of the renin-angiotensin system and lanthanum treatment in patients with decreased kidney function.

DUAL study

This report on the DUAL study is carried out by principal- and sponsor investigator chief physician, PhD, ass. professor, Peter Thye-Rønn.
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Abstract

Progression of renal insufficiency necessitates either dialysis or transplantation, which is associated with high costs for both the individual and society. Recent studies have shown a renal protective effect in DUAL blockade of the renin-angiotensin system (RAS), which shows that a reduction in blood pressure and proteinuria results in an extended time to terminal kidney failure (ESRD).
In vitro models have shown increased vascular calcification in hyperphosphatemia. In a human study in uremic patients, an increase in ostepontin and Cbfa-1 and vascular calcification has been shown, which may support a hypothesis of phosphate-induced calcification.
Development of vascular calcification and cardiovascular events may be reduced by the use of calcium-free phosphate binders in combination with DUAL blockade of the RAS system.
In this DUAL study the first dimension with DUAL blockade we added losartan to standard care using ramipril. In the second dimension estimating vascular calcification we used the calcium free phosphate binder Lanthanum carbonate (Fosrenol®).
The DUAL study investigated in total 55 patients with an initial statistical plan of 100 patients. The study therefore did not achieve the relevant number to answer our hypothesis on effects on vascular calcification and protection of kidney function assessed by Cr-EDTA clearance and protein-/albuminuria.
We investigated and followed in total 55 patients in the 2 dimensions of the study with initial n=23 versus n=22 in the Losartan group and n=21 versus n=24 in the Lanthanum group. The DUAL study experienced a large number of drop-outs and were unfortunately not able to replace these patients which therefore means that our final results are not valid in regard of our initial protocol and statistical outlined parameters for our primary objectives.

Results on our study are summarized below including standard antrometric data (table 1 and 2). We have divided our data in the 2 dimensions corresponding to the Losartan and the Lanthanum group.

Table 1	Losartan			Lanthanum		
	Yes	No	p-value	Yes	No	p-value
Number (n)	23	22		21	24	
Age (years)[1]	52.4±12.8	49.5±11.3	0.42	51.0±12.8	50.9±11.6	0.98
BMI (kg/m^2)	28.5±5.1	25.7±4.3	0.052	27.5±5.1	26.9±4.7	0.69
Hip/abdomen ratio	1.08±0.13	1.05±0.11	0.41	1.09±0.11	1.05±0.12	0.21
GFR (MDRD) (randomization)	48.5±13.7	39.5±10.6	0.02	42.6±13.7	45.0±12.4	0.54
Cr-EDTA (baseline)	52.0±20.8	40.1±10.8	0.04	49.8±19.5	44.6±16.8	0.43
Systolic blood pressure (mmHg, baseline)	136±12	137±17	0.83	136±14	137±16	0.84
Diastolic blood pressure (mmHg, baseline)	78±9	82±9	0.19	80±10	80±9	0.92

1. All parameters presented as number ± 2SD

Table 1. Baseline data for the 2 study dimensions (± Losartan or ± Lanthanum)

Table 2	Losartan			Lanthanum		
	Yes	No	p-value	Yes	No	p-value
Cr-EDTA (*delta values*)[1]	-0.9±15.3 (11)	-9.2±12.1 (9)	0.19	-0.3±15.8 (9)	-8.1±12.5 (11)	0.25
Agatston (baseline)	333±758 (21)	166±297 (19)	0.36	176±222 (19)	324±783 (21)	0.41
Agatston (*delta values*)	103±171 (6)	30±73 (6)	0.37	50±68 (7)	88±198 (5)	0.70
Systolic blood pressure (*delta values*)	-5±14 (13)	1±14 (13)	0.27	1±16 (13)	-6±12 (13)	0.22
Diastolic blood pressure (*delta values*)	-6±11 (13)	-3±8 (13)	0.34	-4±8 (13)	-5±12 (13)	0.80
PWV (baseline, m/s)	7.7±2.8	8.2±2.5	0.50	7.7±2.9	8.2±2.5	0.59
PWV (*delta values*)	0.0±1.7 (13)	-0.1±2.8 (13)	0.92	0.3±2.6 (13)	-0.4±0.9 (13)	0.36
U-albuminuria (baseline, mg/l)	573±566	568±304	0.97	536±436	598±467	0.66
U-albuminuria (*delta values*)	-208±701 (9)	229±429 (10)	0.13	98±368 (9)	-46±768 (10)	0.61
U-proteinuria (baseline, g/l)	0.73±0.69	0.75±0.39	0.95	0.69±0.54	0.78±0.57	0.63
U-proteinuria (*delta values*)	-0.18±0.83 (9)	0.48±1.10 (10)	0.15	0.13±0.49 (9)	0.19±1.35 (10)	0.90

1. All parameters presented as number ± 2SD

Table 2. Values for Cr-EDTA (clearance), vascular parameters (Agatston score, blood pressure, PWV) and protein-/albuminuria for the 2 study dimensions (± Losartan or ± Lanthanum) including delta values (24 months follow-up). Patients numbers in parenthesis (n).

The follow-up lasted for 24 months where less than 50% patients reached the final visit. This was in large due to failure to comply with the protocol and not due to exclusion with a background of adverse or serious adverse events.
The results focus on the 2 dimensions showing baseline- and delta values for selected parameters of the effects of DUAL blockade and lanthanum treatment. We found no significant relations corresponding our aims, however there where in the small number of patients a tendency towards lowering of proteinuria/albuminuria and stable kidney function in the Losartan group. In the Lanthanum group estimating vascular calcification, pulse wave velocity and blood pressure we found no changes in these parameters.
End-points for the DUAL study were not meet largely due to insufficient patient numbers included and completing our trial. The design and statistical plan described in the protocol scheduled a significant larger number of patients in order to achieve the aims. With approx. 10 patients with all data in both groups compared to expected at least 35-40 patients the study is not able to show any effects of the scheduled treatment. We found that it is difficult to obtain a sufficient number of participating patients especially with our study requirements that add up the existing offers that exists in this patient group.
We conclude due to insufficient patient numbers recruited and to a high rate of drop-outs in our DUAL study that we are not able to make final conclusions in regard to the planned study. However we see a tendency to a stable value of GFR and small decrease in protein-/albuminuria in the Losartan group but using delta-values no significant values were found. Further no effects were found in the intervention arm using lanthanum carbonate. The patient group has need for close and thorough care however we faced multiple factors that resulted in too few patients included and completing the DUAL study. Our results should still encourage a broad and intensive focus on this patient group in order to diminish the rate of decline in kidney function and ultimately avoiding need for dialysis.

Acknowledgement and financial support

The recruitment and randomization turned out to be cumbersome and resulted in only two centers (out of 4 active sites) taking in a sufficient number to initiate and continue the project. We would like to express our gratitude to colleges in all participating centers in particular nurse Jane B. Orry at Sydvestjysk hospital taking a huge task in both recruiting a large number of patients but also taking a huge responsibility in the follow-up in out-patient clinic. MD Caius Constanescu have assisted in preparation of data and statistical analysis.
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Protocol article

Introduction

Development of chronic renal failure is associated with increased risk of micro-and macrovascular complications with concomitant increased morbidity and mortality in both diabetic and non-diabetic kidney disease. Progression of renal insufficiency necessitates either dialysis or transplantation, which is associated with high costs for both the individual and society (1,2). Recent studies have shown a renal protective effect in DUAL blockade of the renin-angiotensin system (RAS), which shows that a reduction in blood pressure and proteinuria results in an extended time to terminal kidney failure (Chronic Kidney Failure (CKD) stage V) (3,4). Signs of inflammation, decreased vitamin D concentration and dysregulated calcium and phosphate metabolism as well as secondary hyperparathyroidism have been demonstrated in patients with renal impairment similar to CKD stage II-IV (5,6,7). In vitro models including a knock-out model have shown increased vascular calcification in hyperphosphatemia (8). In a human study in uremic patients, an increase in ostepontin and Cbfa-1 as well as vascular calcification has been shown, which may support a hypothesis of phosphate-induced calcification (9).
Development of vascular calcification and cardiovascular events may be reduced by the use of calcium-free phosphate binders, where possible effects are also mediated via lipid metabolism, glucose metabolism (PPAR receptors), inflammation cascades and effects of vitamin D (10,11,12). Studies in dialysis patients with a calcium-free phosphate binder show a low rate of hypercalcemia and a well-regulated phosphate level which may mean a lower risk of developing vascular calcification and optimal regulation of parathyroid (PTH) – vitamin D metabolism (13,14). Circulating calcification inhibitors such as Fetuin A and Matrix Gla protein are also important as modulators of vascular calcification in patients with ESRD (15,16). Arterial compliance assessed by pulsewave velocity (PWV) and central pulse pressure assessed by pulsewave analysis (PWA) are surrogate markers for arterial calcification and are in ACE-treatment significantly associated with cardiac vascular episodes and renal function independent of peripheral blood pressure (17,18).

Thus, it remains to be assessed how progression of renal impairment and vascular calcification is affected by the DUAL blockade of the RAS-system combined with an assessment of the effects of the calcium-free phosphate binder (lanthanum carbonate) on cardiovascular risk factors including possible effects on morbidity, mortality and other systemic effects (lipid metabolism, glucose homeostasis, degree of inflammation, etc.) than the already known effect of reduction in the intestinal phosphate uptake.
The project will therefore shed light on the preventive effect of 2 years of double blockade treatment (DUAL) of the RAS system and the effect on vascular calcification of a calcium-free phosphate binder (lanthanum carbonate, Fosrenol®).

Aims

1) To assess whether the effect of DUAL blockade (ramipril plus telmisartan) of the renin-angiotensin system compared to ACE-inhibition (ramipril) alone (with equal blood pressure) protects kidney function better assessed by albuminuria and Cr-EDTA clearance.
2) To investigate if early intervention (primary prophylaxis) with a non-calcium phosphate binder (lanthanum carbonate) reduces hyperphosphatemic calcification and increased risk for cardiovascular morbidity in patients with renal impairment.

The number of patients and study period cannot reliably detect the above, but PWV (expected to increase with increased calcification), PWA (vascular compliance) and MSCT (estimating coronary artery calcification, CAC) are all sensitive markers for changes in vascular calcification (see statistics).
3) To compare markers for vascular calcification and impaired kidney function that are sytematically collected by blood samples (see methods).

Patients.

It is planned to include 50 patients in each treatment arm (see statistics and design).

Inclusion criteria

- Age 18- 70 year
- Expected life expectancy > 2 years
- Signed informed consent form
- MDRD eGFR 25-70 ml/min. (http://www.nephron.com/MDRD_GFR.cgi)
- Proteinuria >0,5 g/day or albuminuria >300 mg/døgn.
- K < 6 mmol/l (by confirmed elevated value; reduction in medicine, increase in diuretics, dietary advice before exclusion)
- Normal safety laboratory values (within the laboratory reference values). CRP, fibrinogen, LDH, ALAT, alkaline phosphatase and bilirubin maximum 2 times upper reference.

Exclusion criteria

- Previous on dialysis or kidney transplant
- Uncontrolled hypertension (diastolic > 100 mmHg, systolic > 160 mmHg) despite drug treatment
- Arrhythmia or angina pectoris (may participate if stable ischemic heart disease but without symptoms
- Chronic infection (clinical)
- Pregnancy or women who do not want to use safe contraception. Breastfeeding
- BMI > 40
- Diabetes with HbA1C>10%
- Immunosuppressive treatment (within 12 months)
- Chronic cough
- Allergy to study medicine
- Proteinuria above 10 g/day
- History of obstructive urinary tract disease (untreated)
- Abnormal calcium (ionized >1.40 mmol/l) or phosphate (serum < 0.8 mmol/l)
- Participates in other experimental intervention studies

Design

Prospective, randomized study with runin period (8 weeks) with ACE inhibitor (ramipril) monotherapy. At study start randomization to either ACE-treatment or combination therapy with angiotensin II antagonist (telmisartan) and ACE (ramipril) treatment. By randomizing, lanthanum carbonate is added in 50% in each group. The study has two orthogonal dimensions and is further

stratified for diabetes mellitus. The one dimension regarding comparison between ACE therapy versus combination treatment with ATII antagonist and ACE treatment. The second dimension regarding supplementation with lanthanum carbonate. Using block randomization, one treatment dimension is balanced in relation to the other and a balanced design is achieved (see statistics). The study period for the individual patient is 2 years from randomization. The trial ends at the last visit (corresponding to 24 months after the last patient´s randomization) and the patient is sought to be transferred to DUAL blockade and relevant treatment for secondary hyperparathyroidism according to usual guidelines.

Methods

Laboratory analyzes
a) Basic parameters measured at the start of the study and every 3 months: see appendix I and II. 24-hour urine proteinuria and albuminuria, urine albumin:creatinine ratio. CRP, fibrinogen, albumin, hemoglobin, leukocytes, platelets, Na, K, carbamide, creatinine, Ca++, phosphate, PTH, HCO3, HBA1C, LDH, ALAT, alkaline phosphatase, bilirubin.
24-hour urine clearance (1 measurement in run-in period). Estimated GFR (MDRD formula) ml/min/m^2 used for inclusion.
Every 6. months, the following additional measurements are made:
b) Fasting lipid profile, fasting glucose, vitamin D status.
c) Cr-EDTA clearance
d) Insulin sensitivity is assessed by fasting insulin.
e) The degree of calcification is measured by pulsewave analysis in the form of both pulsewave velocity (PWV) and pulsewave amplitude (PWA), Sphygmocor, AtCor Medical, Australien. Non-invasive method that can detect the intraarterial pulse pressure. The investigation takes approx. 10 minutes and takes place in a supine position. Measured every 6. months.
f) Blood pressure is measured both in the outpatient clinic (sitting position after 5 min. rest) and also during a 24-hour period (see flow chart).
g) Biobank; some blood- and urine samples are analyzed immediately and some blood- and urine samples are frozen for later analysis when all study samples are available (calcification inhibitors including CRP, PTH, Fetuin-A, lipids, insulin, FGF-23).
At randomization and completion of the study, the following are measured:

a) Coronary arterial calcification (CAC) is measured by multislice CT.
b) Aortic calcification is measured by chest X-ray (AP-billede).

Study medicine

ACE inhibitor and ATII antagonist
Starting dose of ramipril 5 mg x 1 and telmisartan 40 mg x 1 (Micardis®) with the expected maximum dose of ramipril 10 mg x 1 and telmisartan 80 mg x 1 (appendix III). Treatment target for blood pressure is <130/80 mmHg, where other antihypertensive treatment is intended to be reduced. In diabetes, BT target is <125/75 mmHg.

Lanthanum
Lanthanum (Fosrenol®) starting dose is 250 mg x 3 and is changed according to the flowchart.

Statistics

STATA version 9.0 is used. The primary study objectives are change in GFR as well as proteinuria. Calculated number of patients in each group with the following criteria: 2alfa = 0.05 (two-sided), beta =0.1.
GFR (Cr EDTA clearance): MEREDIF 0.1 ml/min/month, and SD = 3 ml/min with a strength of 80% for a significant effect after two years, n=33 in each group. The strength is increased to >0.90 with GFR MEREDIF = 1.0 ml/min/year and 50 patients in each group. Due to the expected dropout during the 2-year study period, 50 patients are included in each group.

Proteinuria: expected 30% reduction (approx. 0.3-0.6 g/l/year). With SD 30% and 50 patients in each group, the strength is >0.98. With a 20% reduction, the strength is >0.90.

Coronary arterial calcification (CAC) score: strength >0.80 to detect a difference of 250 units in CAC with a SD of 400 and 40 patients in each group. With a SD of 400 and 50 patients in each group, a strength of >0.85 is obtained to detect a difference of 250 Units.

By block randomization it is achieved that we can analyze data as two separate studies and by assessing one dimension can be adjusted for the treatment in the other dimension (see design). It will be corrected for drop-out patients (after 3 months) with intention to treat analysis (clearance and proteinuria) and data will be calculated with t-test for delta values and for non-normally distributed data (MSCT) logarithmic conversion is performed. Drop-out patients within 3 months are sought to be replaced.
All data will be described, including data completeness as well as reason for lack of observations. Any deviation from the statistical plan will be described in the final publication.

Recruitment

Patients with renal impairment (CKD stage II-IV) in out-patient clinics in treatment at one of the participating centers. Recruitment by the center´s investigator (letter is sent if the patient want to participate and is followed up by telephone contact).
Participants may receive travel imbursement and lost earnings on visits in addition to the usual 3-month outpatient visits.

Randomzation

Each center receives a set of envelopes where stratification has been performed in relation to diabetes (40%), DUAL versus ACE treatment and 50/50 % distribution with respect to +/- Lanthanum treatment.
Envelopes are therefore divided into 2 piles (+/- diabetes), where each group´s envelopes hence is divided regarding treatment. Patients are included consecutively, but medication is unblinded. Randomization list and packing of envelopes are performed by statisticians who do not participate in the recruitment of patients for the study. Randomization list is kept by statisticians until the study is completed.

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