PaRatHyroidectomy versus cInacalcet for the correctioN of secondary hyperparathyrOidism in end-stage renal disease patients (RHINO-trial), a pilot-study

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Parathyroid gland disorders
Study type	Interventional

Summary

ID

NL-OMON42882

Source
ToetsingOnline

Brief title
RHINO-trial pilot

Condition

- Parathyroid gland disorders

Synonym
overactive parathyroids due to chronic renal failure, parathyroid hyperplasie

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: cinacalcet, Parathyroidectomy, secondary hyperparathyroidism

Outcome measures

Primary outcome

Of this pilot study: inclusion rate

Of the RHINO trial: Quality of Life, measured by the KDQOL-36 questionnaire

Secondary outcome

- VAS scores of 13 HPT related symptoms

- PTH levels

- Costs

- cardiovascular events

- QALY (measured by the EQ-5D vragenlijst)

- Adverse events (cinacalcet group) c.q. complications (PTx group)

- renal function (eGFR)

- Biochemical parameters for mineral metabolism (calcium, phosphate, albumin,

alkaline phosphatase, FGF-23)

- All-cause mortality

Study description

Background summary

Hyperparathyroidism (HPT) is one of the most common abnormalities of mineral metabolism in patients with end stage renal disease (ESRD), with a prevalence up to 25-30%.1 It is characterized by parathyroid gland hyperplasia and increased plasma levels of parathyroid hormone (PTH). This condition results in disturbances in vitamin D, phosphorus, calcium and PTH metabolism. In end stage renal disease, HPT leads to severe bone disorders.2,3 HPT is associated with an increased cardiovascular morbidity and mortality risk.1 Currently, for treatment of patients with HPT the (KDIGO) guidelines advise to perform parathyroidectomy (PTx) only after initiation of pharmacological therapy such as vitamin D analogues, phosphate binders or calcimimetics.4
The global prescription patterns have dramatically shifted from surgery to predominantly medical treatment. However, calcimimetics have never been directly compared with (sub-)total parathyroidectomy (PTx). Currently, calcimimetics form the largest single drug cost for dialysis patients in the USA and EU (>260 million dollars per year).5 The hypothesis is that calcimimetics lower PTH levels in ESRD. However, the long-term benefits and harms on patient-level are uncertain. Brunaud et al. showing no significant difference in PTH levels after two years of follow-up in patients treated with cinacalcet versus standard care.6 In addition, the EVOLVE trial clearly showed cinacalcet not to significantly reduce the risk of death or major cardiovascular events in patients with moderate-to-severe HPT who were undergoing dialysis.7 More importantly, an impressive rate of cinacalcet related adverse effects such as vomiting and nausea was reported (45,9% versus 18,9 in placebo group) compromising treatment compliance. A large multicenter randomized control trial comparing PTx and cinacalcet with long term follow-up would ultimately define the treatment of choice in patients with chronic renal failure.

Study objective

The aim of the RHINO trial is to compare the effect of parathyroidectomy and cinacalcet treatment on quality of life in end-stage renal disease patients with hyperparathyroidism and to evaluate cost-effectiveness.

The aim of this pilot study is to establish the rate of inclusion of ESRD patients with sHPT in this trial, and to evaluate logistic challenges in including and treating patients in this multidisciplinary and multicentre trial.

Study design

Multicenter randomized controlled superiority trial.

Intervention

(sub-)total parathyroidectomy versus cinacalcet

Study burden and risks

Interventions
Both treatments, PTX and cinacalcet are recognized medical treatments for the indication sHPT.
Parathyroidectomy:
Overall, the strong association between high PTH levels and increased mortality support (sub-)total PTx as valuable treatment option to acquire immediate and durable adjustment of PTH levels. Multiple studies showed that PTx is very effective in lowering PTH levels.1,2 Although PTx has improved in quality in the last decades it remains an invasive procedure executed in a fragile population with cause-specific morbidity (i.e. hypocalcaemia, emergency admissions) and hospital readmissions (myocardial dysrhythmias, cerebrovascular events). However, in our previous study, we showed that PTx is a very safe procedure with low complication rates.3 Moreover, several studies conclude that patients experience an improved quality of life after they underwent PTx.4-6

Cinacalcet:
Cinacalcet is a drug that acts as a calcimimetic (i.e. it mimics the action of calcium on tissues) by allosteric activation of the calcium-sensing receptor that is expressed in various human organ tissues. It is sold by Amgen under the trade name Sensipar in North America and Australia and as Mimpara in Europe. Cinacalcet is used to treat secondary hyperparathyroidism as a consequence of end-stage renal disease.16 Cinacalcet was FDA approved in March 2004 and was the first allosteric G protein-coupled receptor modulator to enter the pharmaceutical market.17 Since its introduction in 2004, the calcimimetic agent cinacalcet has become a common first-line therapy for HPT patients insufficiently responsive to vitamin D and phosphate binders. Since this policy change several questions have been raised about the efficacy, side effect profile and costs of cinacalcet.7,8 The EVOLVE trial reported an impressive rate of cinacalcet related adverse events (AE) such as vomiting and nausa (45.9% versus 18.9%).9 Moreover, studies evaluating the effect of cinacalcet on lowering PTH levels show contradictory results 7,9,10 Consequently, cinacalcet is no longer subsidized by the Australian Government.11

Overall, no extra hospital days / visits are required. Required biochemical tests are part of routine follow-up, of which patients will not experience additional burden. We do not expect additional physical and/or physiological discomfort. No investigational treatment with possible risks is being used. The additional burden consist of a quality of life questionnaire that needs to be filled in. We expect patients to fill in these surveys in approximately 30 minutes.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700RB
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700RB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Diagnosed end-stage renal disease
- PTH * 9 ULN
- Calcium * 2.2 mmol/L
- Female or male aged at least 18 years
- *3 months of chronic dialysis
- The patient must speak the Dutch language
- The patient understands the purpose and risk of the study and has given written informed consent to participate in the study
- On cinacalcet therapy with PTH * 9 ULN when commencing therapy
- Patients have been treated with standard medical care, comprising of vitamin D and/or phosphate binders

Exclusion criteria

* Calcium levels <2.2 mmol/L
* History of renal transplantation
* History of parathyroidectomy
* Head/neck radiation in history

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	mimpara
Generic name:	cinacalcet
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	06-02-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	17-07-2017
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	EUCTR2016-002174-12-NL
CCMO	NL57928.042.16