

A novel method to improve the detection of cancer and metastases by peptide scanning under the protection of enzyme inhibitors: PepProtect 1

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1.To monitor the safety and tolerability of racecadotril in combination with ¹¹¹In-DOTA-MG112.To study in patients whether the neutral endopeptidase (NEP) inhibitor racecadotril improves the in vivo stability of the radiopeptide ¹¹¹In-DOTA-MG11

Ethical review	Approved WMO
Status	Pending
Health condition type	Endocrine neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON44441

Source

ToetsingOnline

Brief title

PepProtect 1

Condition

- Endocrine neoplasms malignant and unspecified

Synonym

medullary cancer of the thyroid, medullary carcinoma of the thyroid

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, Stichting Coolsingel

Intervention

Keyword: enzyme inhibitor (neutral endopeptidase), in vivo stabilization, medullary thyroid carcinoma, peptide scintigraphy (SPECT/CT)

Outcome measures

Primary outcome

1. To monitor the safety and tolerability of racecadotril in combination with ¹¹¹In-DOTA-MG11; adverse events will be monitored according to international standards, CTCAE 4.03
2. To study in patients whether the neutral endopeptidase (NEP) inhibitor racecadotril improves the in vivo stability of the radiopeptide ¹¹¹In-DOTA-MG11; percentage intact radiopeptide, 10 min. after injection, will be measured

Secondary outcome

1. To study whether the tumour uptake of ¹¹¹In-DOTA-MG11 is improved in parallel with the improved in vivo stability of ¹¹¹In-DOTAMG11 by racecadotril protection.
2. To explore the sensitivity of [racecadotril-protected] ¹¹¹In-DOTAMG11 scintigraphy (planar and SPECT/CT) to detect medullary thyroid cancer lesions

Study description

Background summary

One of the key issues for the success of using peptide-tracers in patients for

diagnosis and therapy is the stability of the compounds. Unfortunately, most labeled peptides are very unstable in the physiology of the human body, being degraded by enzymes. Peptides, including radiopeptides, can be chemically modified to improve stability against enzymatic breakdown, but subsequent evaluation to reveal candidates of choice remains challenging, as stabilization often interferes with receptor affinity.

Recently, a radically different approach has been developed; we have demonstrated a highly effective method to improve the stability of peptide-tracers in the blood stream. In mouse models this method leads to unprecedented enhancement of tumor uptake without impairing background clearance. With a single co-injection of a suitable enzyme inhibitor we stabilized circulating peptide-tracers, significantly increasing their supply and binding to receptors on the tumor cells and impressively amplifying tumor-to-background ratios. This exciting strategy exploits our recent findings that one single enzyme: neutral endopeptidase (NEP, EC 3.4.24.11, neprilysin) is a major player in the in vivo degradation of a wide array of peptide-tracers

Study objective

- 1.To monitor the safety and tolerability of racecadotril in combination with ¹¹¹In-DOTA-MG11
- 2.To study in patients whether the neutral endopeptidase (NEP) inhibitor racecadotril improves the in vivo stability of the radiopeptide ¹¹¹In-DOTA-MG11

Study design

The study is a phase I single center, open clinical trial

Intervention

Patients will twice undergo a scan with ¹¹¹In-DOTA-MG11, once at baseline without racecadotril and once with racecadotril, as intended intervention.

Study burden and risks

- Patients will undergo 2 days of investigations at *baseline-2* visit (injection, scanning and blood samples); 1 day of investigations at *baseline-1* visit (oral racecadotril, observation, 1 blood sample); 2 days of investigations at *intervention* visit (oral racecadotril, injection, scanning, blood samples). One follow-up visit is planned; in conjunction with a regular outpatient visit.
- The risk of undesirable effects is minimal; minor, self-limiting side-effects of short duration are expected ([hypotension, tachycardia, nausea, dizziness] similar to the side effects from the Pentagastrin® test)
- Radiation burden is expected to be in the range of 11 mSv for a single 200 MBq ¹¹¹In-DOTA-MG11 administration (analogous to other known hydrophilic

¹¹¹In-radiopeptides). For 2 visits, with associated low-dose CT in SPECT/CT scans, the total radiation burden for a patient in this study will be in the range of 27 mSv. This is within category IIIb, according to the recent NCRD publication *Human Exposure to Ionising Radiation for Clinical and Research Purposes: Radiation Dose & Risk Estimates*. This is justified, as the benefits of the study are aimed directly at: *directly related to saving lives or mitigating serious diseases in the future*, which is a category IIIb justification.

-Potential direct benefits: improved diagnosis/staging of MTC may lead to improved, personalized treatment strategy for some individual MTC patients, with possible better prognosis and/or less chance of unnecessary/futile surgery procedures.

-Potential future benefits: the (successful) protection of radiolabelled DOTA-MG11 may be further developed and applied for PET/CT imaging (using Ga-68), or for peptide targeted radiation therapy (e.g. using Lu-177).

-Potential future benefits: the principle of protecting naturally instable radiopeptides may aid in developing other instable radiopeptides, aimed at other forms of cancer (e.g. breast, prostate) into practice as useful clinical tools.

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

Related to the medullary cancer of the thyroid:

1. Histologically documented medullary cancer of the thyroid (MTC), or with elevated tumour marker (serum calcitonin) after previous treatment(s) for MTC

Related to the patient:

2. Life expectancy of more than 6 months.

3. WHO performance status 0 or 1

4. Male or female patients aged >18 years without upper age limit.

Exclusion criteria

1. Patients requiring treatment of the tumour urgently, before assessments required for the study can be completed.

2. Pregnancy or breast feeding. Negative pregnancy test is required in female patients with child-bearing potential.

3. Impaired renal function (eGFR <60 mL/min/1.73 m²)

4. Impaired liver function (cirrhosis, grade B of the Child-Pugh classification; or hepatic enzyme levels >3x upper limit of normal)

5. Known allergy or hypersensitivity to gastrin analogues or any of the components of the study medications.

6. Any use of NEP-inhibitors within 30 days prior to the study; any use of experimental medication or other medication that potentially interfere with racecadotril or In111-DOTA-MG11.

7. Any use of ACE inhibitors within 3 days of racecadotril administrations.

Study design

Design

Study type: Interventional

Masking: Open (masking not used)

Control: Uncontrolled

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status: Pending

Start date (anticipated): 01-11-2017

Enrollment: 12

Type: Anticipated

Medical products/devices used

Product type: Medicine

Brand name: Hidrasec

Generic name: Racecadotril

Product type: Medicine

Brand name: nvt

Generic name: 111-In-DOTA-MG11

Registration: Yes - NL outside intended use

Ethics review

Approved WMO

Date: 12-10-2017

Application type: First submission

Review commission: METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date: 04-12-2017

Application type: First submission

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	EUCTR2017-003469-93-NL
CCMO	NL63101.078.17