PET-CT of biodistribution of rituximab in relation to therapeutic outcome and histological response of lymphoid tissue in rheumatoid arthritis patients

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1. To image tissue biodistribution (joints, lymph nodes and internal organs) of rituximab in RA patients by [89Zr]rituximab PET-CT in RA patients with clinically active disease that will start rituximab treatment.2. To investigate whether…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Observational invasive

Summary

ID

NL-OMON38399

Source
ToetsingOnline

Brief title
Rituximab PET-CT of rheumatoid arthritis

Condition

- Autoimmune disorders

Synonym
rheumatic disease of the joints, Rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Farmaceutisch bedrijf Hofmann-La Roche,Hoffmann-La Roche

Intervention

Keyword: Lymphoid tissue, PET-CT, Rheumatoid arthritis, Rituximab

Outcome measures

Primary outcome

Visualized tissue biodistribution patterns of RA patients by [89Zr]rituximab

PET-CT at initiation of treatment.

Secondary outcome

1. [89Zr]rituximab PET-CT images of RA responders and non-responders to

rituximab treatment.

2. Analysed lymphoid tissue response to rituximab treatment in relation to

clinical outcome and imaging data.

Study description

Background summary

There is cumulative evidence that B-cells play an important role in the pathophysiological process of rheumatoid arthritis (RA). Targeted depletion of B cells with a monoclonal antibody such as rituximab appears to be highly effective in RA patients (1), also in RA patients refractory to disease modifying anti-rheumatic drugs (DMARDS) and anti-tumor necrosis factor *alpha therapy (2). Nevertheless, 30-50% of RA patients does not respond to rituximab treatment. Treatment could be more effective if potential responders to anti-B cell therapy could be selected before treatment. Knowledge about tissue biodistribution in responders / non-responders may help to develop predictive markers for therapeutic response.
Positron emission tomography (PET) imaging may provide such information. Information about effects of anti-B cell treatment on lymphoid tissue in RA is lacking. Therefore, in the current study immunohistochemical staining of aspirated lymphoid tissue will be performed similar to our previous studies on

synovial tissue (9,10). Histological data will be compared to imaging.

Study objective

1. To image tissue biodistribution (joints, lymph nodes and internal organs) of rituximab in RA patients by [89Zr]rituximab PET-CT in RA patients with clinically active disease that will start rituximab treatment.
2. To investigate whether therapeutic outcome of rituximab treatment is related to a difference in tissue biodistribution at initiation of treatment by [89Zr]rituximab and PET-CT.
3. To investigate the relationship between histological response of lymphoid tissue to rituximab treatment and clinical response as well as PET imaging results.

Study design

Twenty anti-B cell therapy naive RA patients who have a clinical indication for initiation of anti-B cell treatment will be included. Patients will be treated with rituximab by the standard clinical infusion schedule (at inclusion (t=0) and at day 14), followed by infusion of [89Zr]Rituximab at initiation of the treatment (t=0). PET-CT images will be performed at day 3. In addition, before rituximab treatment and 4 weeks later, lymphoid tissue will be obtained by ultrasound-guided inguinal lymph node histological biopsy for immunohistochemical analysis. Clinical follow-up will be performed up to 24 weeks. PET-CT data will be compared to clinical response and immunohistochemical data.
Inclusion of patients, infusion of (radiolabeled) rituximab and PET-CT imaging procedure (including withdrawal of blood samples) as well as clinical follow-up will be performed at the VU Medical Center (VUMC). The lymph node biopsy and immunohistochemical investigation of lymphoid tissue will be performed at the Academic Medical Center (AMC).

Study burden and risks

1. Radiation exposure
Based on preliminary data of [89Zr]rituximab and other labelled Mabs such as [89Zr]U36 cMab (effective dose = 0.53 ± 0.03 mSv/MBq (8)), an effective dose of 10 mSv is expected. CT scans used for attenuation correction will give an additional dose of 2 mSv per patient. The total effective dose is expected to be around 12 mSv per patient, or about 6 times the yearly natural background radiation dose in the Netherlands. According to the ICRP-62 model, the risk level corresponds to *moderate*, while the social benefit is regarded as *substantial*.

2. Idiosyncratic reaction to the tracer
A low dose of [89Zr]rituximab will be administered. [89Zr]rituximab has been

safely administered to oncology patients. In general, 89Zr-labeled antibodies have been administered to >100 patients without adverse side-effects.

3. Vena puncture and withdrawal of blood samples
[89Zr]rituximab will be administered intravenously. The necessary vena puncture is similar to that applied for blood withdrawal in clinical practise. An venous infusion needle will be placed for withdrawal of blood samples at various time points, which prevents repeated puncturing of the veins.

4. Discomfort during scanning
It may be uncomfortable to lie motionless on the scanning bed of the PET-CT. For some patients, the scanning may be anxious. To reduce anxiety and discomfort as much as possible, patients will be made acquainted with the surroundings beforehand. In addition, the staff will be present during scanning and can remove the patient from the scanner if requested.

5. Discomfort during biopsy of lymphoid tissue
After local anesthesia, a small incision will be made in the left or right inguinal region to perform the biopsy. This leaves a scar of approximately 0.5 cm. There is a small risk of development of a local haematoma, which heals spontaneously. The whole procedure will take not more than 45 minutes. Prof. Tak*s group has extensive experience with this approach, which is well tolerated by the patients and which has been previously approved by AMC*s IRB.

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

1.Men and women, * 18 years of age
2.Diagnosis of rheumatoid arthritis according to the ACR criteria (Arnett et al 1988)
3.Treatment with disease modifying anti-rheumatic drugs (DMARDS) and in addition, corticosteroids up to 10 mg daily and non-steroidal anti-inflammatory drugs (NSAIDs) is permitted, provided that there is a stable dose for at least 2 weeks. Patients should have been treated previously with at least one anti-tumour necrosis factor (anti-TNF) medication with inadequate response or intolerance. Anti-TNF should be discontinued at least 4 weeks before initiation of rituximab treatment.
4.Patients must be able to adhere to the study appointments and other protocol requirements.
5. Patients must be capable of giving informed consent and the consent must have been obtained prior to the study related procedures.

Exclusion criteria

1.Treatment with any investigational drug within the previous 3 months.
2.Pregnancy or breast-feeding.
3.Previous exposure to radioactivity (nuclear imaging) in the year preceding inclusion in this study.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-10-2010
Enrollment:	15
Type:	Actual

Ethics review

Approved WMO

Date:	05-07-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	02-08-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	05-11-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
CCMO	NL31575.029.10