Effect of aminobisphosphonates and statins on circulating Vgamma9Vdelta2-T cells

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To study (in patients who have an indication for treatment with an intravenous aminobisphosponate because of bone metastases of a malignant tumor) the effects of aminobisphophonate treatment on the phenotype and function on circulating Vy9Vd2-T...

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

Summary

ID

NL-OMON36478

Source
ToetsingOnline

Brief title
ABP statins study

Condition

- Metastases

Synonym
cancer, tumor

Research involving
Human

Sponsors and support

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

Intervention

Keyword: aminobisphosponates, statins, Vgamma9Vdelta2 T cells

Outcome measures

Primary outcome

1. Phenotypic (APC markers: CD1d, CD40, CD80, CD83, CD86, HLA-DR;

activation/memory markers: CD25, CD27, CD45RA, CD45RO, CCR7)and functional

(IFN-*, TNF-*, granzyme B) changes in the circulating pool of Vy9Vd2-T cells.

2. Occurrence of a febrile response.

Secondary outcome

not applicable

Study description

Background summary

Vy9Vd2-T cells are lymphocytes that play an important role in antitumor immunity. They can be activated by phosphoantigens, which has recently been shown to result in their acquisition of antigen presenting call properties. Aminobisphosphonates are administered 3-4 weekly to patients with bone metastases from various malignancies in order to reduce the number of skeletal events. By inhibiting mevalonate metabolism (resulting in the accumulation of endogenous phosphoantigens) aminobisphosphonates can also result in the activation of Vy9Vd2-T cells. Since preclinical data indicate that statins inhibit endogenous phosphoantigen accumulation and Vy9Vd2-T cell activation, one can envision that statins can similarly inhibit the aminobisphosphonate-induced activation of Vy9Vd2-T cells in vivo. In this study the effects of aminobisphosphonate treatment and the inhibitory effects of the simultaneous use of statins on Vy9Vd2-T cells will be evaluated. This is relevant as data from e.g. breast cancer and prostate cancer patients indicate that aminobisphosphonates, via the activation of Vy9Vd2-T cells, can induce clinically relevant antitumor responses. Inhibition of this activation by the simultaneous use of statins could be detrimental in such circumstances.

Study objective

To study (in patients who have an indication for treatment with an intravenous aminobisphosponate because of bone metastases of a malignant tumor) the effects of aminobisphophonate treatment on the phenotype and function on circulating Vy9Vd2-T cells and to determine whether these effects are inhibited by simultaneous treatment with statins.

Study design

A total of 40 patients will be entered in this study. Half of the patients will receive standard intravenous treatment with aminobsiphosphonates, the other half will be additionally be treated with a statin. Patients already receiving statin treatment will continue this treatment, other patients will be asked whether they are willing to be treated with a statin for a maximum of 5 weeks. Consenting patients will be randomized to receive i.v. aminobisphosponates plus or minus simvastatin 40 mg once daily. Simvastatin will be started one week prior to the first administration of aminobisphosphonates and continued for a maximum of 5 weeks.

In each patient 20 ml peripheral blood will be drawn (t=0, t=24 hr, t=1 week, t=3-4 weken (prior to the 2nd aminobisphosphonate administration). In addition, patients will be requested to measure their temperature thrice daily during the 2 days following the first aminobisphosponate administration. This, because a relation between the occurrence of a febrile response upon aminobisphosponate administration and an activation and expansion of Vy9Vd2-T cells has been suggested.

Peripheral blood mononuclear cells will be isolated from the drawn peripheral blood. Using intra- and extracellular flowcytometry Vy9Vd2-T cells will be characterized phenotypically (APC markers: CD1d, CD40, CD80, CD83, CD86, HLA-DR; activation/memory markers: CD25, CD27, CD45RA, CD45RO, CCR7) and functionally (IFN-*, TNF-*, granzyme B). In addition, the frequency of CD3+, CD4+, CD8+ T cells, NK cells, B cells, iNKT cells, CD4+CD25+ regulatory T cells, and circulating dendritic cells will be assessed.

Intervention

Treatment with simvastatin in patients with malignant bone metastases with an indication for treatment with aminobisphosphonates.

Study burden and risks

This study exerts a minimal burden on patients (blood withdrawel on 4 occasions, thrice daily temperature assessment for 2 days). Part of the patients will be treated with simvastatin (1 tablet daily) for 4-5 weeks. Simvastatin has been administered to enormous amounts of patients facing hypercholesterolemia world-wide. From this clinical experience it is known that

it can be safely administered to patients with a relatively small chance of (serious) side-effects.

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

-patients with an indication for intravenous treatment with an aminobisphosphonate because of bone metastases of a malignant tumor.
-WHO 0, 1, 2 performance score

Exclusion criteria

-WHO 3, 4 performance score
-prior or current use of aminobisphosphonates
-immunosuppressive medication (NSAID allowed)
-chemotherapy and/or radiotherapy in 4 weeks prior to start of aminobisphosphonate administration
-renal insufficiency (creatinin clearance < 30 ml/min)
-liver enzyme abnormalities: -bilirubin > 1.5 times ULN (upper limit of normal)
-ASAT or ALAT > 2.5 times ULN (in absence of livermetastases)
-ASAT or ALAT > 5 times ULN (in presence of livermetastases)
-concomitant use of strong inhibitors of CYP3A4, such as itraconazol, ketoconazol, erytromycin, claritromycin, hiv-protease inhibitors or grapefruit juice is contra-indicated.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-11-2010
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Simvastatine
Generic name:	simvastatine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	26-03-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-08-2011
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
EudraCT	EUCTR2010-018491-24-NL
CCMO	NL31295.029.10