Bevacizumab and endothelium dependent vasodilation

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To determine the effect of bevacizumab on the vasodilator response of acetylcholine in humans by using plethysmography.To determine the effect of bevacizumab on the vasodilator respons of nitroprusside in humans by using plethysmography

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vascular hypertensive disorders
Study type	Interventional

Summary

ID

NL-OMON32503

Source
ToetsingOnline

Brief title
BVZach

Condition

- Vascular hypertensive disorders

Synonym
high blood pressure, Hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: KWF/ NFCVE

Intervention

Keyword: Bevacizumab, Fore arm vascular tone, Hypertensie, VEGF-inhibitor

Outcome measures

Primary outcome

The forearm vasomotor response to increasing doses of intra-arterially administered acetylcholine (two doses each) before and during administration of bevacizumab, expressed as percentage change in forearm blood flow ratio (flow infused arm/flow control arm) from baseline.

Secondary outcome

na

Study description

Background summary

The introduction of angiogenesis inhibitors has remarkably improved treatment of patients with several types of cancer. One of the most reported side effects of angiogenesis inhibitors is hypertension. In patients treated with bevacizumab, a monoclonal antibody against vascular endothelial growth factor, hypertension had an overall incidence up to 32%. The increase in blood pressure occurs early in treatment. The etiology of hypertension caused by treatment with angiogenesis inhibitors is unclear. Understanding the pathogenesis of this side effect is essential for optimal treatment with this class of drugs.
One of the main targets of angiogenesis-inhibitors is vascular endothelial growth factor and its receptors. Animal and human studies show that VEGF induces vasodilation and hypotension by stimulation of NO production. Furthermore animal studies suggest that endogenous VEGF may play a role in maintaining normal vascular tone in blood vessels.
Theoretically inhibition of VEGF or VEGFr in humans would decrease NO production causing vasoconstriction and thereby induce hypertension.
As shown in previous studies(11;12) endothelial function (NO-dependent respons) is diminished by treatment with a VEGF-inhibitor. However these studies do not allow a conclusion on the direct causal relationship between VEGF inhibition and alteration in endothelial function. In this study we will infuse bevacizumab in the brachial artery and measure its effect on the

vasodilator response to acetylcholine. This allows us to separate local direct effects of bevacizumab on the endothelium from systemic actions such as blood pressure that could indicrectly interfere with endothelial function. If appropriate, we will also study the interaction between bevacizumab and nitroprusside to explore specificity of the interaction between Ach and bevacizumab

Study objective

To determine the effect of bevacizumab on the vasodilator response of acetylcholine in humans by using plethysmography.
To determine the effect of bevacizumab on the vasodilator respons of nitroprusside in humans by using plethysmography

Study design

This is a single center, interventional controlled trial.
The brachial artery will be cannulated (20 gauge catheter) for infusion of bevacizumab, acetylcholine or nitrprusside and measurement of arterial blood pressure. Forearm blood flow will be assessed by venous occlusion strain gauge plethysmography.
If the vasodilation caused by infusion of acetylcholine is diminished by simultaneous infusion of bevacizumab twelve new healthy subjects will be recruited in the same way for the second part of this study. In the second group the forearm blood flow response to nitroprusside alone and during simultaneous infusion of bevacizumab will be assessed using strain gauge plethysmography to study if the effect of the diminished vasodilator respons to acetylcholine during bevacizumab infusion is endothelium dependent.If there is no effect of bevacizumab on the vasomotor response to acetylcholine the second part of the study will not be conducted and the total number of subjects will stay twelve.

Intervention

The brachial artery will be cannulated (20 gauge catheter) for infusion of bevacizumab 144 microgram/dl forearm volume (15 minutes).

Study burden and risks

Intra-arterial infusion of bevacizumab allows the use of very low cumulative doses that reach local concentrations in the infused forearm that are sufficient to induce a local effect with very low systemic concentrations. In a study to evaluate the short-term safety of systemic bevacizumab (5mg/kg) in patients with age-related macular degeneration no adverse events were reported except hypertension. In our previous experiment infusion of the same concentration of bevacizumab during the same amount of time no side effects

were reported.
During plethysmography, wrist cuffs are inflated to exclude the hand (mainly skin) circulation from the experimental preparation. This will cause rapidly reversible numbness and discomfort in both hands due to inflation of the wrist-cuffs. The subjects will not benefit directly from participating in this study.

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. Age 18-50 years old
2. Male
3. Results of serum glucose, lipids and creatinine should be within the laboratory's reference ranges.

4. Subject is able and willing to sign the Informed Consent Form prior to screening evaluations.

Exclusion criteria

1. Documented history of sensitivity/idiosyncrasy to medicinal products or excipients.
2. History of or current abuse of drugs, alcohol or solvents.
3. History of malignant disease.
4. First degree relatives with a history of cancer before the age of 50
5. First degree relatives with a history of premature cardiovascular disease before the age of 50
6. Current use of medication.
7. Hypertension (systole >140mmHG, diastole >90mmHg)
8. Diabetes mellitus
9. Smoking
10. Any clinically relevant abnormality on ECG.
11. A history of thrombosis or first degree family members with a history of recurrent thrombosis
12. Inability to understand the nature and extent of the trial and the procedures required.
14. Previous participation in a study with bevacizumab.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-06-2010
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	Bevacizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-12-2009
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-04-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2009-017970-18-NL
CCMO	NL31012.091.09