Effect of Interleukin-1 receptor antagonist on insulin sensitivity in subjects with type 1 diabetes mellitus.

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Determine whether blockade of IL-1 had positive effects on insulin sensitivity in type 1 diabetic subjects without residual beta cel function

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON34115

Source
ToetsingOnline

Brief title
Effect of IL-1RA on insulin sensitivity

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: European Association for the Study of Diabetes (EASD)

Intervention

Keyword: Inflammation, Insulin sensitivity, Interleukin-1 receptor antagonist, Type 1 diabetes mellitus

Outcome measures

Primary outcome

insulin sensitivity as determined by the euglycemic hyperinsulinemic clamp

technique

Secondary outcome

glycemic control

adipocyte insulin sensitivity

changes in circulating hormonal and inflammatory factors and lipid profile.

Study description

Background summary

Deminished insulin sensitivity is the primary defect in type 2 diabetes mellitus and does also play an important role in the pathophysiology of type 1 diabetes mellitus. Obesity induced inflammation appears to be an important factor in the origination of insulin resistance. Once diabetes has emerged chronically elevated glucose levels are another factor in the induction of insulin resistance.

TNFalpha and IL-6 are the best known pro-inflammatory cytokines which are involved in the induction of insulin resistance. However there are multiple studies which find a positive association between IL-1 and obesity too. Furthermore IL-1 leads to insulin resistance in human adipocytes.

It has been shown before that blocking IL-1, using anakinra, in type 2 diabetic patients results in better glycemic control. Another trial showed that an anti-IL-1 antibody improved the glycemic control in mice.

Alltogether these results suggest that blocking of IL-1 should improve glucose control. When this would be tested in type 2 diabetic subjects the blockade of IL-1 would potentially have possitive effects on the beta-cell as well as on

the insulin sensitivity. A direct effect on one of these two mechanistic possibilities could theoratically lead to an indirect improvement of the other possibility by inhibition of glucose toxicity. In type 1 diabetics without residual beta-cell function the effect of IL-1 blockade on glycemic control can only be the direct effect of deminished insulin resistance.

Study objective

Determine whether blockade of IL-1 had positive effects on insulin sensitivity in type 1 diabetic subjects without residual beta cel function

Study design

Open label research project. 15 Patients with type I diabetes mellitus are treated during 1 week with interleukin-1 receptor antagonist (anakinra) 100 mg subcutaneous once daily. Before, directly after and after 4 weeks insulin sensitivity is determined using a clamp technique. At the same time points as the clamp a fatbiopsy is taken.

Intervention

anakinra 100 mg subcutaneous once daily during 8 days.

Study burden and risks

There is a very low chance on serious side effects of the study medication, evenmore because of the short treatment period. Furthermore the study medication and the used dose is approved by EMA. Subjects are requested to contact the researchers in case of fever or other complaints which might be caused by the study.

In respect to the diagnostic procedures (euglycemic hyperinsulinemic clamp and fatbiopsy) there is much experience in our research group and complications are very uncommon.

The participating subjects are required to keep a diary and to visit the hospital three times. This implies a reasonable time investment for the subjects. At the other side the trial does not run for a long time interval. Furthermore blood collection is planned on three time points, fatbiopsy is taken on two occasions.

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

Type 1 diabetes with absence of residual Beta-cell function
Age 18-65 yrs
Body mass index of > 25 kg/m2
Insulin requirement > 0.5 U/kg bodyweight
HbA1c > 8.5% for the last 6 months

Exclusion criteria

Inability to give informed consent
Presence of any medical condition that might interfere with the current study protocol.
Immunodeficiency or immunosuppressive treatment (including TNFα blocking agents and corticosteroids)
Anti-inflammatory drugs (including nonsteroidal anti-inflammatory drugs, 100 mg or less of aspirin per day is allowed)
Signs of current infection (fever, C-reactive protein (CRP) > 30 mmol/l, treatment with

antibiotics, previous or current diagnosis of tuberculosis.
A history of recurrent infections
Pregnancy or breast-feeding (contraception of at least 3 months before inclusion is required for fertile women)
Liver disease (aspartate aminotransferase or alanine aminotransferase level of more than three times the upper limit of normal range)
Renal disease (creatinine > 130 µmol/l
Neutropenia < 2 x 109/l

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-03-2011
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kineret
Generic name:	anakinra
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	18-01-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-02-2011
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	EUCTR2010-023479-24-NL
CCMO	NL34377.091.10