(Methyl)prednisolone and diazoxide in type 1 diabetes at onset

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To examine the effects and safety of methylprednisolone combined with diazoxide on the progression of type 1 diabetes at the onset of disease

Ethical review	Approved WMO
Status	Will not start
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON48794

Source
ToetsingOnline

Brief title
PREDIDM1

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Autoimmune disorders
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes mellitus type 1, Type 1 diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Sanofi;Tjanka foundation,Sanofi-aventis

Intervention

Keyword: Beta-cells, Corticosteroids, Diazoxide, Type 1 diabetes

Outcome measures

Primary outcome

The difference of the 2 hour MMTT mean C-peptide AUC between the treatment and placebo group after 24 months. The MMTT is also performed at baseline, 17 days, 6 weeks, 14 weeks, 12 months and at 24 months.

Secondary outcome

• The proinsulin and glucose concentration before and during the MMTT at baseline, 2 weeks, 6 weeks, 14 weeks, 26 weeks, 12 months and 24 months.

• Insulin use (assessed as the average IU/kg/day during the last week) and HbA1c at baseline, 6 weeks, 14 weeks, 26 weeks, 28 months, 12 months and 24 months.

• Time spent with interstitial glucose in hypoglycemic range (<3.9), target range (4.0-10) and hyperglycemic range (>10.0), standard deviation, coefficient of variance and mean amplitude of glucose excursions (MAGE), as determined by open continuous glucose measurement (CGM) during the treatment period and a blinded CGM at 12 and 24 months

• General and diabetes specific quality of life, diabetes self-management, hypoglycaemic distress and hyperglycaemic distress assessed by questionnaire at baseline, after 14 weeks, 8, 12 months and 24 months.

• Occurrence of adverse events and severe adverse events (specifically infections)

• Pancreas inflammation as determined by FDG-PET scan, before and 3 months

after methylprednisolone or placebo

• Effect on β-cell auto-immunity and β-cell stress measured by

o Number of immune cells determined by FACS analysis

o T cell responsiveness to diabetes specific antigens (including

Insulin-defective ribosomal products (DRiPs)) as determined by LST, compared to

other antigens

o Number of CD8+ autoreactive T cells as determined by tetramer using the Q-DOT

assay

o Level or quality of beta-cell autoantibodies (eligible autoantibodies: anti

GADA or IA-2A) by commercial ELISA.

Study description

Background summary

: Type 1 diabetes is an auto-immune disease that leads to destruction of beta cells and thereby inadequate endogenous insulin secretory capacity. Currently, treatment consists of intensive insulin therapy. Despite medical and technological advances, many challenges remain. Treatment with intensive insulin therapy is a trade-off between long-term complications and hypoglycaemia. Therefore, type 1 diabetes is associated with increased mortality, even when glycaemic regulation is optimal1. In contrast, endogenous insulin production has been shown to improve both glycaemic regulation, beyond the limits of insulin treatment, and reduce the risk of hypoglycaemia2. Many patients with type 1 diabetes have a large β-cell reserve at diagnosis, sometimes characterised by a *honeymoon phase*. During this period no or little exogenous insulin therapy is required3. This β-cell reserve quickly depletes during the course of the disease. If these residual β-cells can be retained, patients will have improved glycaemic control and fewer hypoglycaemic events. The combination of intensive anti-inflammatory (high dose steroid) treatment and β-cell protective (diazoxide) treatment might effectively stop or significantly reduce the auto-inflammatory process while preventing the steroid-associated β-cell detrimental side effects in patients with new onset type 1 diabetes mellitus. Therefore, we expect that the combination of these

two therapies will potentiate each other.

Study objective

To examine the effects and safety of methylprednisolone combined with diazoxide on the progression of type 1 diabetes at the onset of disease

Study design

This is a double-blind randomized placebo-controlled trial.

Intervention

The 21 participants in the treatment group will receive a three-day intravenous methylprednisolone 1000mg course followed by 12 weeks prednisolone in a taper dose, combined with diazoxide 2dd 200mg from three days before the methylprednisolone. At the first of methylprednisolon the dose will be raised when there are no signs of (orthostatic) hypotension to 2dd400mg until week 2 and diazoxide 2dd 200mg from the third week until one week after cessation of the prednisolone. The placebo group will receive placebo in an identical schedule.

Study burden and risks

Since corticosteroids cause insulin resistance and diazoxide inhibits insulin secretion, more exogenous insulin will be needed to control glucose variation in the treatment group during the first three months. After the treatment, less exogenous insulin requirement is expected. High dose corticosteroids and diazoxide have side effects, but these are manageable and safety parameters will be monitored intensively during the treatment period.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Age 16 - 40 years
• Diagnosis of type 1 diabetes in the last eight weeks
• Presence of β-cell autoantibodies (eligible autoantibodies: anti-GAD and anti-IA-2)
• Of Caucasian ethnicity
• Mixed meal test stimulated C-peptide AUC0-120min >0.2 nmol/L

Exclusion criteria

• Unmanageable metabolic instability (ketoacidosis)
• Current use of other immunosuppressive or immunomodulatory therapy
• Current acute infection
• Current parasitic infections
• Heart failure
• Hyperuricemia
• History of malignancy
• (Possible) previous tuberculosis infection
• Active ulcus ventriculi or duodeni
• Use of CYP3A4 inhibitors of inducers
• Known hypersensitivity or intolerability to one of the investigational products
• Female patients who are pregnant or breastfeeding
• Female patients who are fertile and unwilling to use adequate contraception

during the 12 month study period
• Recent patient*s involvement in other studies which in the opinion of the investigators could affect the safety of the patient or the result of the study
• Any condition which, in the opinion of the Investigator might jeopardise the subject*s safety or compliance with the protocol

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	42
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Prednison
Generic name:	Prednisolone
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Proglicem
Generic name:	Diazoxide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Solu-Medrol

Generic name:	Methylprednisolone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-07-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	16-08-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2018-000686-37-NL
CCMO	NL65374.058.18
Other	Volgt

Study results

Summary results
Trial never started