European phase-II clinical trial evaluating efficacy of low dose rhIL-2 in patients with recently diagnosed type 1 diabetes

Published: 10-12-2014
Last updated: 21-04-2024

Primary objective1. To evaluate efficacy of ILT-101 for the preservation of residual pancreatic β cells function2. To select the optimal regimen of administration of ILT-101.Secondary objectivesTo assess:1. Tregs expansion after an...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON47333

Source
ToetsingOnline

Brief title
DIABIL-2

Condition

- Diabetic complications

Synonym
insulin-dependent diabetes, juvenile diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Assistance Publique - Hôpitaux de Paris (AP-HP)
Source(s) of monetary or material Support: The Research was funded by the European Commission under the Health Cooperation Programme of the Seventh Framework

Programme (Grant Agreement n°305380-2)

Intervention

Keyword: ILT-101, rhIL-2, type I diabetes

Outcome measures

Primary outcome

Primary objective

1. To evaluate efficacy of ILT-101 for the preservation of residual pancreatic

β cells function

2. To select the optimal regimen of administration of ILT-101

Secondary outcome

Secondary objectives

To assess:

1. Tregs expansion after an induction period and during maintenance therapy,

2. Safety of low-dose rhIL-2 during the treatment period (1 year) and 1 year

after its

discontinuation

3. Relation between Tregs expansion and preservation of residual pancreatic β

cells function

4. Clinical and biological responses according to (i) pubertal stage group, (i)

time from

diagnosis to treatment initiation, (iii) biomarkers of responses

Immunomonitoring:

5. Throrough evaluation of the effects of low dose rhIL-2 on disease-specific

immune

responses

6. Identification of immune biomarkers for predicting/monitoring safety and

efficacy of low

dose rhIL-2 treatment.

Study description

Background summary

The sponsor's main goal is to gain mechanistic insights on the effects of low dose rhIL-2 on diseasespecific immune responses and to identify immune biomarkers for predicting/monitoring safety and efficacy of low dose rhIL-2 treatment.
In the sponsor first clinical trial (VASCU-IL2), combining phenotyping, proteomic and transcriptome studies, the sponsor showed for the first time that low dose rhIL-2 provides clinical benefit in autoimmune diseases by leading to Tregs expansion/activation and to a global antiinflammatory effect (Saadoun, 2011).

Furthermore, in the DF-IL2 trial, sponsor also showed that rhIL-2 induced a dose-dependent increase in Tregs numbers and proportions that correlates with a decrease of B cells proportions. A NK expansion was only observed at the highest dose, e.g; 3 MIU/day
(Hartemann, 2013). Tregs enhanced levels of activation markers and of basal pSTAT5. Plasma levels of regulatory cytokines were increased in a dose-dependent manner, while cytokines linked to Teff and TH17 inflammatory cells were mostly unchanged up to the dose of 1 MIU/day. Importantly, this Tregs expansion was associated with significant dose dependent blunting of IFN-γ-secreting Teff responses against β-cell Ags (M in preparation).

Study objective

Primary objective
1. To evaluate efficacy of ILT-101 for the preservation of residual pancreatic β cells function
2. To select the optimal regimen of administration of ILT-101.

Secondary objectives
To assess:

1. Tregs expansion after an induction period and during maintenance therapy,
2. Safety of low-dose rhIL-2 during the treatment period (1 year) and 1 year after its
discontinuation
3. Relation between Tregs expansion and preservation of residual pancreatic β cells function
4. Clinical and biological responses according to (i) pubertal stage group, (i) time from
diagnosis to treatment initiation, (iii) biomarkers of responses.

Immunomonitoring:
5. Throrough evaluation of the effects of low dose rhIL-2 on disease-specific immune
responses
6. Identification of immune biomarkers for predicting/monitoring safety and efficacy of low
dose rhIL-2 treatment.

Study design

Multicentre European, sequential-group, randomized, double-blind trial evaluating ILT-101 versus placebo

Intervention

N/A

Study burden and risks

Risk: ILT-101 is a low dose formulation of IL2. Since ILT-101 is alow dose formulation of IL2 comparable to PROLEUKIN, and since
PROLEUKIN® (high-dose rhIL-2) already obtained approval for other indications, risks associated to PROLEUKIN® should be taken into consideration for assessing risk associated to ILT-101. However, PROLEUKIN*s side effects are based on adult treatment regimens at usual doses of 18 to 36 million IU/day (10 to 20 MIU/m2) with various routes of administration (IV continuous, IV bolus, SC, transnasal, intratumoral*) recommended for treatments for which the product has received marketing approval (Whittington, 1993; Jeal, 1997). These daily doses are 20 to 40 times greater than the maximum dose that we plan to use (0.5 million IU/m^2).

Risk: Risk of worsening the diabetes
An open non-controlled study using IL-2 in conjunction with rapamycin has been recently published (Long, 2012). The dose of subcutaneous rhIL-2 was 4.5 MIU 3 times weekly for 1 month and rapamycin was administered daily for three months at 2mg per day. The study showed a transient decrease in C-peptide at month 3

in all patients (n = 9 adults). The absence of control groups in this study (i.e., rapamycin alone, rhIL-2 alone or placebo) makes interpretation of this finding difficult. Nevertheless, there is now a clear explanation for this observation: (i) it has been established that rapamycin has a specific toxicity (which is reversible) for pancreatic ß cells (Lamming, 2012; Tanemura, 2012; Yang, 2011); (ii) it has been shown that rapamycin antagonizes the tolerance induced by anti-CD3 treatment in mice (Valle, 2009); (iii) it has been shown that rapamycin antagonizes the tolerance induced by IL2 treatment in mice. These effects of rapamycin likely accounted for the transient worsening of diabetes observed in this study. In our study, rapamycin will be included in the list of prohibited treatments.
In a dose-escalation study assessing immunomodulatory effects and toxicity of low-dose IL2 in patients with cancer (Meropol, 1996), one among 38 adult patients developed hyperglycaemia after 13 days of IL2 at 1.5 MIU/m2 /d sc (Soni, 1996). Glucose level dropped after withdrawal of IL2 but increased again when IL2 was reintroduced requiring insulin treatment. No risk factor was identified.

Contacts

Public
Assistance Publique - Hôpitaux de Paris (AP-HP)

Avenue Claude Vellefaux N/A
Paris 75010
FR
Scientific
Assistance Publique - Hôpitaux de Paris (AP-HP)

Avenue Claude Vellefaux N/A
Paris 75010
FR

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

- Age 6-35 years old
- Male or female both using effective methods of contraception considered as highly effective during treatment if sexually active
- Specifically; Females (if sexually active) with childbearing potential must use contraceptive methods that are considered as highly-effective (pearl index < 1). The following methods are acceptable: Oral , injectable, or implanted hormonal contraceptives (with the exception of oral minipills ie low-dose gestagens which are not acceptable (lynestrenol and norestisteron), Intrauterine device, Intrauterine system (for example, progestin-releasing toit)
-beta HCG negative at inclusion
- With type-1 diabetes:
Newly diagnosed (ADA criteria) at most three months between insulin initiation and anticipated start of experimental treatment
Positive for one or more of the autoantibodies typically associated with T1D
With a detectable peak C-peptide concentration during a standardised MMTT (>= 0.2pmol/ml)
Patients with a stable blood glucose level and seric glycaemia between 60 mg/dL and 250 mg/dL verified at MMTT visit
- Absence of clinically significant abnormal laboratory values (out of range and associated with clinical symptoms and signs) in haematology, biochemistry, thyroid, liver and kidney function;
- Voluntary, informed and written consent.
-Normal cardiac function: no documented history of heart disease and absence of family history of sudden death, normal ECG especially QTc duration within normal value (<480ms)
-Free, informed and written consent

Exclusion criteria

- Children under the age of 6 years old cannot be included
- Patient who, before inclusion, have been treated with other anti-diabetic medication than Insulin for more than 3 months consecutively
- Chronic adrenal insufficiency known or fasting ACTH >=2.5 ULN normal
at inclusion after control
- Anti TPO present at inclusion and abnormal TSH and T4

- Anti-transglutaminase positive at inclusion
- Hypersensitivity to the active substance or to any of the excipients
- Any major health problem including:any severe or evolutive auto-immune/auto-inflammatory disease (other than type 1 diabetes) present at inclusion, any significant respiratory disease (such as moderate or severe COPD or asthma) only if requiring corticosteroids (whatever route of administration) and serious digestive malfunctions.
-- Patient with existing malignancy or history of malignancy
- Major psychosocial instability with expected lack of compliance with insulin treatment, psychiatric pathology of patient or parents, or major problems of family dynamics
- Signs of active infection
- Any patient defines as BMI >= 35
- Existence of a serious malfunction of a vital organ
- History of organ allograft
- Use of treatments not allowed in the Study
- Vaccination with alive attenuated virus within 4 weeks of the first injection of the induction period and during the whole maintenance period
- Pregnant female (confirmed by laboratory testing) or lactating
- Participation in another clinical trial in the previous 3 months.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-02-2018
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	INTERLEUKIN-2
Product type:	Medicine
Brand name:	N/A
Generic name:	placebo

Ethics review

Approved WMO Date:	10-12-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-04-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	21-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	23-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	26-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	04-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	28-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	21-10-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2014-002522-12-NL
ClinicalTrials.gov	NCT02411253
CCMO	NL50014.078.14