A study to characterize the humoral and cellular response following simultaneous immunization with a neo-antigen (KLH) and a recall antigen (tetanus) in healthy volunteers

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Investigation of the immune response following immunization with Immucothel/Alhydrogel with or without tetanus. Per efficacy endpoint, the following parameters will be explored:(a) Response size;(b) Inter-individual variability of the response;(c)...

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

Summary

ID

NL-OMON45727

Source
ToetsingOnline

Brief title
KLH and tetanus toxoid immunization in healthy volunteers

Condition

- Autoimmune disorders

Synonym
Autoimmune disorders

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Kymab ltd

Intervention

Keyword: cellular response, KLH antigen, tetanus antigen

Outcome measures

Primary outcome

Efficacy endpoints

* KLH-specific and tetanus toxoid-specific IgG and IgM titers (ELISA);

* OX40 and OX40L expression by flow cytometric analysis, on T-cells, B-cells

and monocytes;

* Ex vivo lymphocyte proliferation upon Immucothel challenge of isolated PBMCs.

Response quantification by flow cytometry (OX40, OX40L), proliferation (by

CellTrace Violet), and (optionally) cytokine release (e.g. IL-2, IL-6, IL10,

IL-17 and IFNy);

* mRNA analysis of lymphocyte populations (T-helper cells, cytotoxic T-cells

and T-regulatory cells) sorted by immunomagnetic selection. Readouts may entail

OX40, OX40L, and optionally other cell activation markers;

* Erythema, swelling and redness at the sites of intradermal KLH (Delayed Type

Hypersensitivity [DTH] upon intradermal injection of 1 *g Immucothel in 10*L,

on the flexor aspect of the forearm).

Tolerability / safety endpoints

- Treatment-emergent (serious) adverse events ((S)AEs).

- Concomitant medication

- Clinical laboratory tests

o Haematology

o Chemistry

o Urinalysis

- Vital signs

o Pulse Rate (bpm)

o Systolic blood pressure (mmHg)

o Diastolic blood pressure (mmHg)

- Electrocardiogram (ECG)

o Heart Rate (HR) (bpm), PR, QRS, QT, QTcF

- Immucothel intramuscular injection site responses.

Secondary outcome

Not applicable

Study description

Background summary

Keyhole limpet hemocyanin (KLH) is derived from the keyhole limpet, a type of mollusc. KLH is regarded as an ideal immunization antigen for studying T-cell dependent immune response to a neoantigen. KLH is available as a pure homogeneous substance, as a clinical grade product (KLH subunits), it has been used widely in patients and the injected form appears to be associated with mild local reactions and perhaps mild pyrexia (Immucothel SmPC). It appears to be immunogenic for the entire population, it has no cross-reacting antibody, and it elicits predictable primary T-cell dependent immune responses following one or two administrations.
For a future FIH trial investigating the effects of OX40/OX40L interaction blocking, a model that allows direct pharmacodynamics (PD) assessment of the compound is desirable. In this future study, both the influence of the compound

on the immune response following presentation of a novel antigen and of a recall antigen needs to be assessed. KLH will be the novel antigen that will be administered. Tetanus toxoid will be the recall antigen that is presented, since the entire population of the Netherlands born after 1957 has been vaccinated against tetanus.
The aim of the present study is to characterize the humoral and cellular response after novel antigen presentation (KLH) and recall antigen presentation (tetanus), and evaluate if the T cell response to one antigen is substantially modulated by the response to the other antigen. Characterization and quantification of the immune response to these immunizations will allow rational design of the future OX40/OX40L blocking study, and allow application of KLH and tetanus immunizations in other future clinical studies.

Study objective

Investigation of the immune response following immunization with Immucothel/Alhydrogel with or without tetanus. Per efficacy endpoint, the following parameters will be explored:
(a) Response size;
(b) Inter-individual variability of the response;
(c) Time course of the response.
Moreover, for each efficacy endpoint, it will be confirmed that a simultaneous administration of tetanus toxoid does not interfere (or only minimally) with the KLH response. This is valuable information to support simultaneous KLH/tetanus toxoid immunizations in the future intervention trial targeting OX40/OX40L. The data generated in the current study will allow selection of the most robust readout measures for quantification of the Immucothel/Alhydrogel-induced immune response in the future OX40/OX40L study and allow for a power analysis of studies using this model

Study design

A randomized, double-blind, placebo-controlled study investigating the effects of immunization with Immucothel, adsorbed to Alhydrogel, administered to healthy male volunteers on its own or administered simultaneously with tetanus toxoid into the contralateral deltoid muscle. Each participant will receive two KLH injections in the deltoid muscle, separated by one week and a single tetanus immunization at day 0.

Intervention

Six volunteers will receive Immucothel/Alhydrogel, six will receive Immucothel/Alhydrogel and tetanus toxoid, and three volunteers will receive placebo (saline).

Study burden and risks

Burden: measurements, blood and urine sampling, lifestyle restrictions and time investment.
Risks: potential adverse events caused by the vaccin

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

Eligible subjects must meet all of the following inclusion criteria at screening:
1. Healthy male subjects, 18 to 45 years of age (inclusive). The health status is verified by absence of evidence of any clinical significant active or uncontrolled chronic disease following a detailed medical history and a complete physical examination including vital signs, laboratory measurements and 12-lead ECG;
2. Body mass index (BMI) between 18 and 30 kg/m2, inclusive, and with a minimum bodyweight of 50 kg;

3. Previous immunization with tetanus toxoid as reported by the subject;
4. Willing to give written informed consent and willing and able to comply with the study protocol.

Exclusion criteria

Eligible subjects must meet none of the following exclusion criteria at screening:
1. Any disease associated with immune system impairment, including auto-immune diseases, HIV, any confirmed history of severe allergic reaction and transplantation patients;
2. Known infection requiring antibiotic therapy within the last three months prior to the study
3. Previous known exposure to Immucothel® or KLH;
4. Any adverse immune reaction following immunization with tetanus toxoid;
5. Known allergy against Thiomersal®, which is a stabilizer in the tetanus toxoid immunization;
6. Received immunosuppressive or immunomodulatory medication within 30 days prior to enrollment or planned to use during the course of the study;
7. Use of medication (prescription or over-the-counter) within 21 days of the first study day, or less than 5 half-lives (whichever is longer), and during the course of the study;
8. Participation in an investigational drug or device study within 3 months prior to screening or more than 4 times a year;
9. Previous participation in an investigational drug or device study involving the dosing of a biological targeted at any immune pathway within one year prior to screening;
10. Loss or donation of blood over 500 mL within three months prior to screening;
11. Any (medical) condition that would, in the opinion of the investigator, potentially compromise the safety or compliance of the subject or may preclude the subjects* successful completion of the clinical trial.
12. History of Schistosomiasis (infection with Schistosoma parasite).
13. History or current nicotine use in access of 5 cigarettes per day, or unable not to smoke during the course of the study, defined as between the screening visit and the final visit.
14. Tetanus toxoid immunization within the last 10 years before study participation

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-03-2017
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	IMMUCOTHEL
Product type:	Medicine
Brand name:	Tetanus vaccin

Ethics review

Approved WMO Date:	30-01-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-02-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2017-000084-32-NL
CCMO	NL60489.056.17