Determining the fingerprint of endotoxin tolerance

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

Summary

ID

NL-OMON48466

Source
ToetsingOnline

Brief title
100LPS study

Condition

- Immune disorders NEC
- Ancillary infectious topics

Synonym
bloodstream infection, sepsis

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Endotoxemia, endotoxin tolerance, genomics, transcriptomics

Outcome measures

Primary outcome

Single-nucleotide polymorphisms (SNPs), genome-wide differential mRNA expression of monocytes obtained before and 4 hours after the first endotoxin challenge, and plasma cytokine concentration profiles upon the first and second endotoxin challenge (including but not limited to TNF*, IL-6, IL-8, and IL-10) to determine extent of endotoxin tolerance (which is expressed as the decrease in plasma cytokine levels between the first and second endotoxin challenge). These data will be integrated to determine the SNPs/transcripts that are predictive of the extent of endotoxin tolerance developed by the subjects.

Secondary outcome

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Study description

Background summary

Sepsis remains the number one cause of death in the ICU and incident rates are rising. The focus of sepsis research has shifted away from the hyperinflammatory phase towards the detrimental role of immunosuppression, a phenomenon known as * sepsis-induced immunoparalysis* . Because to a high level of heterogeneity and a lack of appropriate biomarkers, a much-warranted precision medicine approach is not possible. The identification of novel biomarkers for sepsis-induced immunoparalysis is also hampered by the extreme heterogeneity of the patient population. Experimental human endotoxemia is a highly standardized, controlled and reproducible model, which results in the development of endotoxin tolerance, an immunologic state capturing many hallmarks of sepsis-induced immunoparalysis. This study aims to identify genomic and transcriptomics biomarkers of endotoxin tolerance. Ultimately, this

will lead to the identification of novel biomarkers for the early identification of patients who are prone to develop sepsis-induced immunoparalysis, and facilitate precision medicine for this highly vulnerable group.

Study objective

Primarily, we aim to identify SNPs and transcripts that are associated with the degree of endotoxin tolerance. To increase the chances of success, the genomic and transcriptomic data obtained in vivo will be integrated with data obtained by a previously performed in vitro study. Secondary objectives include SNPs and transcripts associated with the inflammatory response, and epigenomic changes, metabolites, and proteins associated with the inflammatory response and the degree of endotoxin tolerance. Furthermore, we will explore the role of gender and sex hormones in the inflammatory response and endotoxin tolerance, as well as the relationship between ex vivo and in vivo inflammatory responses.

Study design

An explorative, prospective study in 100 healthy volunteers who will be challenged with endotoxin twice. The study takes place at the research unit of the department of Intensive Care Medicine of the Radboud University Medical Center, Nijmegen.

Intervention

This study aims to identify the genomic and transcriptomic factors linked to the development of endotoxin tolerance in vivo. To this end, subjects will be intravenously challenged with endotoxin (1 ng/kg LPS) to evoke a transient systemic inflammatory response and subsequent development of endotoxin tolerance, which will be quantified by the response upon the second endotoxin challenge one week later. During both endotoxin challenges, the subjects will be hospitalized for 8 hours during which vital parameters are monitored carefully.

Study burden and risks

This study will yield a comprehensive insight into genomic/transcriptomic profiles underlying the in vivo inflammatory response in humans, and will improve our understanding of systemic inflammation, endotoxin tolerance, and sepsis, and possibly reveal new therapeutic targets to improve sepsis outcome. Furthermore, a unique cohort will be created, enabling extensive (future) applications and collaboration opportunities.
The burden consists of filling out several questionnaires (maximum of 45 minutes), 5 visits to the hospital (2x 10 min, 1x 30 min, 2x 8 hours) and the dis-comfort associated with endotoxemia (transient flu-like symptoms for 3-4

hours). The risks to the subjects in this study is classified as a *negligible risk* (low risk on minor harms). A subject fee is provided. Our department is highly experienced, having conducted >30 endotoxemia studies with approximately 670 volunteers over the last 15 years.

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

* Written informed consent
* Age *18 and *35 yrs
* Healthy (as confirmed by medical history, physical examination, electrocardiography, laboratory tests)

Exclusion criteria

* Pregnancy (confirmed by negative result of pregnancy tests prior to both endotoxin challenges)
* Use of any medication
* Smoking
* History or signs of atopic syndrome (asthma, rhinitis with medication and/or eczema)
* Known anaphylaxis or hypersensitivity to the non-investigational products or their excipi-ents.
* History or signs of hematological disease:
* Thrombocytopenia (<150*10^9/ml) or anemia (for males: hemoglobin < 8.0 mmol/L and for females: hemoglobin < 7.4 mmol/L)
* Abnormalities in leukocyte differential counts
* History, signs or symptoms of cardiovascular disease, in particular:
* Previous spontaneous vagal collapse
* History of atrial or ventricular arrhythmia
* Cardiac conduction abnormalities on the ECG consisting of a 2nd degree atrioventricular block or a complete left bundle branch block
* Hypertension (defined as RR systolic > 160 or RR diastolic > 90)
* Hypotension (defined as RR systolic < 100 or RR diastolic < 50)
* Renal impairment (defined as plasma creatinine >120 *mol/l)
* Liver enzyme abnormalities (above 2x the upper limit of normal)
* Medical history of any disease associated with immune deficiency
* Signs of infection (CRP > 20 mg/L, WBC > 12x109/L or < 4 x109/L)
* Clinically significant acute illness, including infections, within 1 month of the first endotoxin challenge
* Previous (participation in a study with) endotoxin (LPS) administration
* Any vaccination within 3 months within of the first endotoxin challenge
* Participation in a drug trial or donation of blood within 3 months prior to first endotoxin challenge
* Recent hospital admission or surgery with general anesthesia within 3 months prior to first endotoxin challenge
* Use of recreational drugs within 1 month of the first endotoxin challenge
* Inability to personally provide written informed consent (e.g. for linguistic or mental rea-sons) and/or take part in the study.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-05-2019
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	04-02-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-04-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-05-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-07-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-11-2019

Application type:	Amendment
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
CCMO	NL68166.091.18