The effects of immunostimulation with GM-CSF or IFN-γ on immunoparalysis following human endotoxemia. A parallel randomised double-blind placebo-controlled study

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Primary objective: The primary objective of the study is to determine the effects of GM-CSF/IFN-γ on the in vivo immunoparalysis induced by human endotoxemia. This will be determined by measuring plasma levels of various pro and anti-...

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

Summary

ID

NL-OMON35765

Source
ToetsingOnline

Brief title
Effects of GMCSF/IFN-γ on immunoparalysis

Condition

- Immune disorders NEC
- Hepatobiliary neoplasms malignant and unspecified

Synonym
Blood poisoning, sepsis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Endotoxemia, GM-CSF, IFN-&gamma, immunoparalysis, LPS

Outcome measures

Primary outcome

The main study parameter is the difference in the LPS-induced increase in plasma TNF-α concentration between day 1 and day 7.

Secondary outcome

Secondary study parameters include plasma levels of other inflammatory mediators, ex vivo production of inflammatory mediators by stimulated leukocytes, monocyte HLA-DR expression, NF*B activation by ROS/RNS, transcriptional activity of leukocytes, changes in phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence (epigenetics), urinary markers of tubular injury, twitch transdiaphragmatic pressure, illness score, mean arterial pressure, heart rate and temperature.

Study description

Background summary

Sepsis is a major medical challenge associated with a high mortality rate. Release of pro-inflammatory mediators can result in hemodynamic instability, coagulation abnormalities and end-organ dysfunction. Previous strategies have aimed to treat sepsis by inhibition of pro-inflammatory mediators, however,

most of these approaches have failed. This might be due to the fact that the majority of septic patients do not succumb to the initial pro-inflammatory *hit*, but die at a later time-point in a pronounced immunosuppressive state. This so-called *immunoparalysis*, which renders patients extremely vulnerable to secondary infections, results from the triggering of counter-regulatory anti-inflammatory pathways in response to initial pro-inflammation response. Interferon-gamma (IFN-γ) and granulocyte macrophage colony-stimulating factor (GM-CSF) are known for their immunostimulatory effects. GM-CSF has been demonstrated to increase monocyte HLA-DR expression and endotoxin-induced pro-inflammatory cytokine production ex vivo in whole blood of patients with severe sepsis. Moreover, recent pilot trials in septic patients indicate that long-lasting monocyte deactivation in sepsis can be reversed by treatment of sepsis patients with immunostimulants, such as GM-CSF and IFN-y. Controlled, biomarker-guided studies focused on the mechanism of action of immunostimulatory therapies in a standardized setting have not been performed yet.
We have previously shown that endotoxin administration in healthy volunteers leads to pronounced immunosupression. Consequently, human endotoxemia can serve as a model for sepsis-induced immunoparalysis. Furthermore, to date, all studies on the subject have analyzed the *immune status* of the patients using ex vivo stimulation of leukocytes or flow cytometry analysis of circulating leukocytes obtained from the immunocompromised host. We have recently demonstrated that, following endotoxin administration, ex vivo leukocyte hyporesponsiveness returns to normal within one day while the in vivo response to endotoxin is impaired for 2 weeks. These data indicate that ex vivo measurements do not accurately reflect the in vivo situation. In the present project, we wish to study the effects of IFN-γ and GM-CSF in a parallel double-blind placebo-controlled randomized manner on the immunoparalysis following human endotoxemia, both in vivo and ex vivo.

Study objective

Primary objective: The primary objective of the study is to determine the effects of GM-CSF/IFN-γ on the in vivo immunoparalysis induced by human endotoxemia. This will be determined by measuring plasma levels of various pro and anti-inflammatory cytokines and assessing the difference in the LPS-induced cytokine response between day 1 and 7. The primary outcome measure is the difference in the LPS-induced increase in plasma TNF-α concentration between day 1 and day 7 during experimental endotoxemia.

Secondary Objective(s): There are 8 secondary objectives:

1. To determine the effects of GM-CSF/IFN-γ on ex vivo responsiveness of leukocytes to various inflammatory stimuli.

2. To determine the effects of GM-CSF/IFN-γ on monocyte HLA-DR expression.

3. To determine the effects of GM-CSF/IFN-γ on activation of nuclear factor-*B (NF-*B) by reactive oxygen and nitrogen species (ROS and RNS).

4. To determine the effects of GM-CSF/IFN-γ on inflammatory transcriptional pathways (by use of microarrays).

5. To determine the effects of GM-CSF/IFN-γ on changes in phenotype and gene expression caused by mechanisms other than changes in the underlying DNA sequence (by use of epigenetics).

6. To determine the effects of GM-CSF/IFN-γ on (subclinical) tubular injury known to occur during human endotoxemia.

7. To determine the effects of GM-CSF/IFN-γ on LPS-induced clinical symptoms (illness score) and hemodynamic/temperature changes.

8. To determine the effects of endotoxin on (subclinical) diaphragm function and the effects of GM-CSF/IFN-γ on endotoxin-induced diaphragm dysfunction.

Study design

Parallel, randomized double-blind placebo-controlled intervention pilot study in healthy human volunteers during repeated experimental endotoxemia. Both the mechanism and the extent of restoration of the immunoparalysis may be different between GM-CSF and IFN-y. Use of a parallel study design enables us to evaluate the effects of GM-CSF and IFN-y against a placebo group and head-to-head against each other.

Intervention

All subjects (n=18) will receive an intravenous bolus of endotoxin (LPS derived from E coli O:113, 2 ng/kg) twice, with an interval of 6 days (LPS administration on day 1 and 7). Subjects will receive either GM-CSF (4 µg/kg/day subcutaneously, n=6), IFN-γ (100 µg/day subcutaneously, n=6) or placebo (NaCl 0.9% subcutaneously, n=6) in a randomized, double-blind manner on day 2, 4 and 6.

Study burden and risks

A medical interview and physical examination are part of this study. During endotoxemia, volunteers will be monitored on the research unit of our intensive care and receive an arterial line to facilitate blood pressure monitoring and blood sampling. The arterial line will be placed under local anaesthesia using 2% lidocaine. Furthermore, a venous cannula will be placed for the administration of fluids and LPS and an esophageal catheter will be placed for measurement of twitch transdiaphragmatic pressure. To elicit twitch

transdiaphragmatic pressure, cervical magnetic stimulation will be performed. The administration of LPS induces flu-like symptoms for approximately 4-6 hrs. This model of systemic inflammation has been applied for many years in various research centres in the world. Endotoxin administration is considered safe and no long-term effects have ever been documented.
At the Radboud University Medical Centre, over a 150 volunteers have received more than 250 injections of lipopolysaccharide. Therefore, there is sufficient experience with this model at this centre. Administration of GM-CSF and IFN-γ is well-tolerated in healthy volunteers. In total, approximately 600 ml blood will be drawn during the 8 days of the study and urine will be collected. Subjects will not benefit directly from participation to the study. A subject fee is provided.

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

- Age >=18 and <=35
- Male
- Healthy

Exclusion criteria

- Use of any medication
- History of allergic reaction to GM-CSF/ IFN-γ.
- Smoking.
- Previous spontaneous vagal collapse.
- History, signs or symptoms of cardiovascular disease.
- (Family) history of myocardial infarction or stroke under the age of 65 years.
- Cardiac conduction abnormalities on the ECG consisting of a 2nd degree atrioventricular block or a
complex 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 creatinin >120 µmol/l).
- Liver enzyme abnormalities or positive hepatitis serology.
- Positive HIV serology or medical history of any other obvious disease associated with immune deficiency.
- Febrile illness during the week before the LPS challenge.
- Participation in a drug trial or donation of blood 3 months prior to the LPS challenge.
- Chronic hiccups (defined as hiccups longer than 15 minutes in the past 6 months)
- Pre-existent muscle disease (congenital or acquired) or diseases / disorders know to be associated with myopathy including diabetes and auto-immune diseases.
- Pre-existent lung disease
- Upper airway / esophageal pathology
- Recent (< 1 month) nasal bleeding
- Phrenic nerve lesions
- Any metals in body (pacemaker, splinters, metal stitches)

Study design

Design

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):	24-05-2011
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Immukine
Generic name:	Interferon-gamma
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Leukine
Generic name:	Recombinant GM-CSF
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

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	EUCTR2011-001126-20-NL
CCMO	NL36068.091.11
Other	volgt