The effects of interferon-gamma on sepsis-induced immunoparalysis, a randomised double-blind placebo-controlled pilot (Phase IIIb) study

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON37057

Source
ToetsingOnline

Brief title
The effects of interferon-gamma on sepsis-induced immunoparalysis

Condition

- Other condition
- Ancillary infectious topics

Synonym
blood poisoning, Sepsis

Health condition

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: Immunoparalysis, Interferon-gamma, Sepsis

Outcome measures

Primary outcome

To evaluate the (preliminary) efficacy of IFN-γ as adjunctive treatment in combination with standard therapy for the treatment of patients presenting with septic shock, by assessment of a series of surogate immunological parameters. The primary endpoint is the TNF-α secretion by ex vivo LPS-stimulated leukocytes as a marker of immunosuficiency/antimicrobial response.

Secondary outcome

- Outcome of bacterial infection (occurrence of secondary and/or opportunistic infections, duration of antibacterial treatment, microbiological evaluation)
- Hemodynamic stability (noradrenalin infusion rate, amount of infused fluids per day, amount of urine produced per day, daily fluid balance)
- Mortality (including time to death) at week 2 and week 6 after end of treatment (all causes)
- Length of stay at ICU and duration of hospitalization
- Organ function:

* Cardiovascular function: lactate level, vasopressor usage, and cardiovascular Sequential Organ Failure Assessment (SOFA) score

* Respiratory function: oxygenation index, PaO2/FiO2 (P/F) ratio, and

respiratory SOFA score

* Renal function: creatinin level, urine ouput, renal replacement

therapy usage, and renal SOFA score

* Hematologic function: hematologic SOFA score

* Hepatic function: Hepatic SOFA score

- Production of cytokines by leukocytes ex vivo stimulated with various stimuli

(including LPS, peptidoglycan, candida)

- Markers of *immune status* (including mHLA-DR and PD-1 expression, IL-6

plasma concentration)

- To determine the correlation between the level of immunoparalysis (indicated

by the commonly used marker mHLA-DR and new markers of *immune status* found),

and effectiveness of IFN-γ (indicated by TNF-α secretion by ex vivo

LPS-stimulated PBMC*s).

- Transcriptional activity of leukocytes, including microarrays with a focus on

inflammatory pathways

- Changes in phenotype or gene expression caused by mechanisms other than

changes in the underlying DNA sequence (epigenetic modifications)

Study description

Background summary

Sepsis is the leading cause of death in the ICU with an estimated 6 million victims per year worldwide. Although septic shock is traditionally viewed as an excessive systemic inflammatory reaction to invasive microbial pathogens, pharmacological suppression of the innate immune response in sepsis has proved

to be unsuccessful. An important reason for this might be that the vast majority of septic patients survive the initial pro-inflammatory hit, but die in the subsequent immunosuppressed state due to secondary/opportunistic infections. This so-called *immunoparalysis* is increasingly recognized as the overriding immune dysfunction in septic patients. Reversal of sepsis-induced immunoparalysis is therefore a promising adjunctive treatment for patients presenting with septic shock.
It was demonstrated that interferon-gamma can reverse immunoparalysis in vitro and in vivo in animals and in healthy volunteers. Moreover, in a case-series of septic patients interferon-gamma treatment leaded to reversal of immunoparalysis, reduction in mechanical ventilation time and length of stay.

Study objective

The primary aim of this pilot-study is to assess safety and the effects on immune function in patients with septic shock of adjunctive therapy with IFN-gamma, in a placebo-controlled manner. The data obtained will allow us to do a powercalculation for a subsequent larger multi-centre clinical trial. Moreover, we want to evaluate new markers that could be used to identify patients with immunoparalysis, and to monitor the patient*s immunological response to IFN-γ. In addition, mechanistic studies will be performed to further elucidate mechanisms (such as epigenetic modifications) behind immunoparalysis and the effects of IFN-γ on these mechanisms.

Study design

A randomised double-blind placebo-controlled pilot (Phase IIIb) study: 20 non-neutropenic patients with documented bacterial septic shock fulfilling the enrollment criteria (shown in paragraph 5 of the study protocol) will be randomized to receive either interferon-gamma or placebo in a ratio 1:1. Interferon gamma will be administered subcutaneous at a dose of 100 µg/day on days 0-2-4-7-9-11(thrice weekly). Administration of interferon-gamma is to be discontinued after 12 days in all patients, or earlier if antibacterial drugs are discontinued earlier. interferon-gamma treatment will be initiated when the noradrenalin dose is reduced to 50% of maximum dose, ensuring that the sepsis-induced pro-inflammatory phase has passed. The first day of study drug administration is denoted as day 1. Once entered, the patient remains in the study for 28 days (4 weeks). This time, from first study drug administration to week 4 is defined as the *study period*. All patients will be assessed according to clinical, microbiological and immunological criteria at regular intervals during and at the end of the study period. Mortality will be assessed at 2 and 4 weeks. Blood sampling will be collected at different time points during the follow-up. They will include 3 x 10 ml blood collected in EDTA tubes and 2.5 ml blood collected in Paxgene tubes for identification of host response biomarkers. A baseline assessment will be conducted prior to randomization into the study and initiation of study drug therapy.

Intervention

Interferon gamma will be administered subcutaneous at a dose of 100 µg/day on days 1-3-5-8-10-12 (thrice weekly). Administration of IFN-* is to be discontinued after 12 days in all patients, or earlier if antibacterial drugs are discontinued earlier. IFN-* treatment will be initiated when the noradrenalin dose is reduced to 50% of maximum dose, ensuring that the sepsis-induced pro-inflammatory phase has passed.

Study burden and risks

Blood sampling will be collected at 7 different time points during the follow-up. They will include 3 x 10 ml blood collected in EDTA tubes and 2.5 ml blood collected in Paxgene tubes for identification of host response biomarkers.

Adverse reactions to systemic IFN-* include fever, chills, fatigue, myalgias and headache. These influenza-like symptoms are typically mild, decrease over time, and can usually be managed with prophylactic antipyretics. Other common adverse reactions include rash and depression. Reversible neutropenia can occur. Data from clinical trials, however, indicate that clinically significant hematologic abnormalities and other serious adverse reactions are infrequent even when patients are treated for years. Exacerbation of multiple sclerosis has been described. IFN-γ treatment in septic patients and healthy volunteers was tolerated well

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

1. Written informed consent from patient of legal representative
2. Age >18 years
3. Presence of septic shock of bacterial origin (A-C required):
A. Evidence of bacterial infection (last 96 hours), at least one: pathogenic microorganism in blood, sputum, urine, normally sterile body fluid, or on central venous catheter; Focus of infection identified (e.g. ruptured bowel, purulent drainage/sputum); or leukocytes in normally sterile body fluid
B. Two SIRS criteria (last 24 hours): fever (>38.3 *C), hypothermia (<35.6 *C), tachycardia (>90bpm), tachypnea (>20/min), or PaCO2 <32 mmHg, or mechanical ventilation, leukocytosis (>12,000/µl), leucopenia (<4,0000/µl), or >10% immature forms.
C. Presence of shock with need for vasopressor therapy to maintain SBP >= 90 mmHg.

Exclusion criteria

1. Pregnancy or lactating
2. Subjects with a history of allergy or intolerance to IFN-*
3. Systemic autoimmune disease, hematologic disease (neoplasma, acute leukemia), transplant patients, or patients on steroid medication receiving a prednisolon equivalent of > 5 mg per day
4. Human immunodeficiency virus positivity
5. Presence of an advanced directive to withhold or to withdraw life sustaining treatment
6. Underlying disease with a prognosis for survival < 3 months, or moribund patient highly likely to die within 24 hours.
7. Cardiopulmonary resuscitation (<72 hours) before enrolment
8. Acute myocardial infarction or pulmonary embolisation (<72 hours)
9. Participation in a clinical trial until 30 days prior to inclusion
10. Subjects with a history of documented epileptic seizures
11. Subjects with severe renal impairment (creatinine clearance less than 30 mL/min)
12. Subjects with severe liver failure (impaired synthesis of proteins such as coagulation factors manifested by increased prothrombine time)

13. Subjects with an absolute neutrophil count of less than 500/mm3 at study entry

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:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-11-2012
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Immukine
Generic name:	Recombinant human interferon-gamma
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	19-07-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	08-11-2012
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
Other	ClinicalTrials.gov nr volgt
EudraCT	EUCTR2012-002491-14-NL
CCMO	NL40914.091.12