The role of the CD200-CD200R pathway in human sepsis-associated immunoparalysis (SIMPA study)

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Aim of the study:To investigate the role of the CD200/CD200R axis on the responsiveness of whole blood, peripheral blood mononuclear cells (PBMCs) and neutrophils to a proinflammatory challenge in the immunoparalysed state in sepsis patients....

Ethical review	Approved WMO
Status	Pending
Health condition type	Immune disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON48977

Source
ToetsingOnline

Brief title
Sepsis-associated IMmunoPAralysis (SIMPA study)

Condition

- Immune disorders NEC
- Bacterial infectious disorders

Synonym
blood poisoning, sepsis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: immunoparalysis, inflammation, negative immune receptor, sepsis

Outcome measures

Primary outcome

- cytokine / inflammatory mediator (protein) concentrations (a.o. TNF-α, IL-1β, IL-6, IL-12, IFN-γ, IL-8, IL-10 and TFG-β) after ex vivo stimulation (with and without a CD200 axis (ant)agonist)

- mRNA cytokine / inflammatory mediator expression (a.o. TNF-α, IL-1β, IL-6, IL-12, IFN-γ, IL-8, IL-10 and TGF-β) after ex vivo stimulation (with and without a CD200 axis (ant)agonist)

Secondary outcome

1)

- cell surface expression of immune receptors as CD200R, CD200 by direct flow cytometry (protein level) (in sepsis patients VS healthy controls)

- mRNA expression of immune receptors as CD200R, CD200 (in sepsis patients VS healthy controls)

- to determine the causing or contributing factors that alter the expression (a.o. signalling pathways)

- cytokine / inflammatory mediator (protein) blood concentrations (a.o. TNF-α, IL-1β, IL-6, IL-12, IFN-γ, IL-8, IL-10 and TFG-β)

2) correlation between CD200(R) expression and SOFA score, CD200R expression

levels in survivors and non-survivors

Study description

Background summary

Sepsis is a major medical challenge with high morbidity and mortality rates. Many non-survivors from sepsis die in the later course of sepsis in a state of functional failure of cellular immunity or so called immunoparalysis (or immunosuppression or anergy). It has been proposed that this sepsis associated immunoparalysis contributes to the enhanced susceptibility to nosocomial infection and late mortality of septic patients that survive the first acute phase of sepsis. It can be considered as a marker for the immune depression that commonly follows the acute hyperinflammatory phase of sepsis.
The diminished responsiveness of blood cells involves monocytes, granulocytes and lymphocytes. Monocyte reactivity has been investigated in cultures of isolated cells and in whole blood assays. In both systems, the capacity to produce tumour necrosis factor (TNF), interleukin (IL-1) and other proinflammatory mediators was found to be markedly reduced in patients with sepsis. Interestingly, the production of IL-1 receptor antagonist (IL-1 ra) by monocytes was not attenuated during Gram-negative infection, suggesting that *immunoparalysis* is not a general downregulation of cytokine production but a purposeful adaptation of the host in favour of an anti-inflammatory phenotype. Granulocytes isolated from patients with sepsis demonstrated a similarly reduced responsiveness upon restimulation with bacterial antigens, as reflected by a diminished release of IL-1β and IL-8. Also lymphocytes have been found to secrete less proinflammatory cytokines. Furthermore, strongly reduced IFN-* production and responsiveness have been reported in experimentally induced immunoparalysis after endotoxin administration to healthy humans.

Although the mechanisms that underlie immunoparalysis have not been elucidated completely, it is conceivable that anti-inflammatory cytokines, particularly IL-10 and transforming growth factor (TGF)-β, are involved. Indeed, plasma from patients with sepsis markedly diminished the capacity of normal monocytes to secrete TNF, and IL-10 is a major denominator of this immunosuppressive effect in *septic* plasma. TGF-β was found to be the causative agent of the attenuated splenocyte reactivity in and animal model of sepsis. Other mediators released during the initial hyperinflammatory phase of sepsis that may contribute to the subsequent hyporesponsiveness of blood leukocytes include catecholamines, glucocorticoids and prostaglandines.

It has been proposed that *immunoparalysis* may contribute to the enhanced susceptibility to nosocomial infections and late mortality of patients who survive the initial acute phase of sepsis syndrome. As a consequence,

strategies aiming to restore immune function have been developed and in part tested in patients with sepsis. Cytokines that were able to reverse monocyte deactivation in vitro and in animals are interferon-γ (IFN-y) and granulocyte macrophage colony stimulating factor (GM-CSF). One pilot study was conducted with recombinant IFN-γ in patients with sepsis and evidence for *immunoparalysis* defined as the presence of < 30% human leukocyte antigen - antigen d related (HLA-DR) positive monocytes for at least two days. Nine patients were treated with daily subcutaneous injection of IFN-γ until > 50% of their monocytes were HLA-DR positive for three consecutive days. IFN-γ treatment restored the TNF production capacity of monocytes and was not associated with adverse effects. Although in this small uncontrolled study the efficacy of IFN-γ could not be determined, it was encouraging that eight patients recovered from sepsis shortly after treatment. In a small controlled study involving 60 infants with neutropenia and clinical signs of sepsis, daily subcutaneous injection of recombinant human GM-CSF for seven consecutive days was associated with an increase in neutrophil counts and a reduced mortality (3 of 30 in the GM-CSF group versus 9 of 30 in the control group).

The CD200 receptor (CD200R) is an inhibitory receptor that contributes to control the immune response. CD200R is expressed on myeloid cells such as monocytes, macrophages, granulocytes, as well as on lymphocytes. In myeloid cells, it has been shown that binding of CD200 to CD200R induces CD200R intracellular signaling leading to inhibition of inflammation via a unique inhibitory pathway involving a direct interaction with the adaptor protein downstream of tyrosine kinase 2 and the subsequent recruitment and activation of Ras GTPase-activating protein (20). Splenocytes from CD200R knockout (KO) mice show diminished LPS induced TNF-α and IL-12 supernatant levels compared to those of wild-type mice (21). Also, addition of CD200Fc did not suppress TNF-α and IL-12 supernatant concentrations of LPS stimulated splenocytes from the KO mice, in contrast to those of the wild-type mice. Furthermore, in in vivo experiments, blockade of this immune inhibitory ligand-receptor pair (CD200/CD200R) - either pharmacologically or genetically - leads to an enhanced susceptibility to chronic (sterile) inflammatory diseases (e.g. collagen-induced arthritis, autoimmune encephalomyelitis) (22-25), suggesting an immunosuppressive effect of this receptor pair pathway in vivo. In a Gram-negative (meningitis) infection model, CD200 protects the host by limiting inflammation (26). In that study, mice lacking CD200 have an increased mortality associated with more inflammation, compared to wild-type mice. Interestingly, Van der Vlist et al. from our (LTI) research group found that the signal transduction machinery of CD200R can switch from inhibitory to stimulatory signaling depending on the environment (submitted). Presently, the role of CD200-CD200R pathway in the phenomenon of sepsis associated immunoparalysis is unknown. We here hypothesize that the CD200-CD200R pathway underlies sepsis induced immunodepression by inhibiting the responsiveness of leukocytes.

Study objective

Aim of the study:
To investigate the role of the CD200/CD200R axis on the responsiveness of whole blood, peripheral blood mononuclear cells (PBMCs) and neutrophils to a proinflammatory challenge in the immunoparalysed state in sepsis patients.

Primary objective:
To determine the effect of the inhibition or stimulation of the CD200/CD200R axis on the hyporesponsiveness of whole blood, PBMCs and neutrophils to a proinflammatory challenge in the immunoparalysed state in patients with sepsis (with other words: can we restore the hyporesponsiveness by targeting the CD200/CD200R axis?)

Secondary objectives:
- To establish the extent of CD200(R) expression on the surface of monocytes, lymphocytes and neutrophils during immunoparalysis and to investigate the underlying mechanisms.
- To evaluate whether CD200 (R) expression is correlated with disease severity (Sequential sepsis-related Organ Failure Assessment; SOFA score) and whether there is a difference in expression levels between survivors and non-survivors.

Study design

Observational study

Study burden and risks

The burden from blood sampling from a line thas has already been inserted is minimally invasive and has a neglectable risk for damage/deleterious effects for the study subjects.

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

- newly diagnosed sepsis as defined in the protocol
- 18 years or older
- able to understand the study information and sign an informed consent (as an alternative, the presence of a representative that is able to understand the study information and sign an informed consent)
- willing and according to the investigator able to follow the study procedures

Exclusion criteria

- immunosuppressive therapy before admission to the ICU and thus before blood can
be drawn
- pregnancy
- lactation
- known active HIV, HBV or HCV infection
- continuous venovenous hemofiltration (CVVH)
- coagulation disorder
- mechanical ventilation at home
- inclusion in a clinical intervention trial in which the intervention may reasonably interfere with the outcomes of this study
- admission for more than two weeks on the wards prior to IC admission

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2019
Enrollment:	35
Type:	Anticipated

Ethics review

Approved WMO

Date:	07-08-2019
Application type:	First submission
Review commission:	METC NedMec

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	NL65412.041.19