PERSONALIZED IMMUNOTHERAPY IN SEPSIS: A MULTICENTRE AND MULTINATIONAL, DOUBLE-BLIND, DOUBLE-DUMMY RANDOMIZED CLINICAL TRIAL

Published: 03-06-2021
Last updated: 14-03-2025

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Ethical review	Approved WMO
Status	Completed
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON51161

Source
ToetsingOnline

Brief title
ImmunoSep

Condition

- Bacterial infectious disorders

Synonym
dysregulated host response to an infection, sepsis

Research involving
Human

Sponsors and support

Primary sponsor: Hellenic Institute for the Study of Sepsis
Source(s) of monetary or material Support: Horizon 2020 Grant

Intervention

Keyword: Immunotherapy, Sepsis

Outcome measures

Primary outcome

The difference in the mean total SOFA (Sequential Organ Failure Assessment)

score until day 9 after randomization.

Secondary outcome

- 28-day mortality

- 90-day mortality

- The change of mean total SOFA score on day 15 of the end of treatment

- The impact of personalized immunotherapy on the reversal of

hyper-inflammation or immunoparalysis.

- The impact of personalized immunotherapy on the resolution of infection

leading to study enrolment.

- The development of genomic, epigenomic, proteomic, metabolomic and

microbiomic surrogate biomarkers for the primary and secondary endpoints.

Study description

Background summary

Sepsis is a life-threatening organ dysfunction that results from the dysregulated host response to an infection. Accumulating knowledge suggests that there is a spectrum of dysregulation in this response. On the one end of

this spectrum there are patients whose immune response is characterized by fulminant hyper-inflammation. On the other end of this spectrum there are patients whose immune response is characterized by immunoparalysis. Ferritin and HLA-DR expression on monocytes are diagnostic biomarkers for hyper-inflammation and immunoparalysis, respectively. Personalized immunotherapy with anakinra for hyper-inflammation and recombinant human interferon gamma for immunoparalysis could be able to improve sepsis outcomes.

Study objective

The aim of ImmunoSep is to study if personalized immunotherapy targeting either fulminant hyper-inflammation or immunoparalysis is able to improve sepsis outcomes.

Study design

Prospective, multicentered, interventional, randomized, double-blind, double-dummy, placebo-controlled clinical trial

Intervention

Immunotherapy with iv anakinra 200 mg three times daily (every eight hours) or sc recombinant human interferon gamma-1b 100 µg once every other day for 15 days.

Study burden and risks

Anakinra and interferon-gamma are both licensed agents for other diseases. Therefore, the safety profile of these treatments are well-known. A similar safety profile has been reported for treatment of severely ill patients and patients with sepsis. To this end, no potential harmful risks are expected in this cohort. Potential side effect are expected to be mild and patients will recover from an occurring side effect without any expected complications.

Additional burden of blood collections and swabs are minimal and the blood collections for this study will be combined with clinically initiated blood collections where possible.

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 equal to or above 18 years.
- Both genders.
- In case of women, unwillingness to become pregnant during the study period.
- Written informed consent provided by the patient or by one first-degree relative/spouse in case of patients unable to consent.
- Community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) or primary bacteremia (BSI).
- Sepsis defined by the Sepsis-3 definitions. More precisely, sepsis is defined as the presence of total SOFA (sequential organ failure assessment score) equal to 2 or more for patients who are admitted with infection at the emergency department OR as any increase of admission SOFA by 2 or more points for patients already hospitalized.
- Patients with signs of fulminant hyper-inflammation or sepsis-associated immunoparalysis. Since the state of hyper-inflammation is considered more life-threatening than the state of immunoparalysis, patients with lab findings of both immune states are allocated to treatment targeting hyper-inflammation. It is explicitly stated that patients diagnosed with COVID-19 infection may participate only in the fulminant hyper-inflammation arm
- Time from classification into sepsis by the Sepsis-3 definitions and start of

blind intervention less than 72 hours.

Exclusion criteria

- Age below 18 years.
- Denial for written informed consent.
- Acute pyelonephritis or intraabdominal infection, meningitis or skin infection.
- Any stage IV malignancy.
- Neutropenia defined as an absolute neutrophil count lower than 1,500/mm3.
- Any *do not resuscitate* decision in the hospital.
- In the case of BSI, patients with blood cultures growing coagulase-negative staphylococci or skin commensals or catheter-related infections cannot be enrolled.
- Active tuberculosis (TB) as defined by the co-administration of drugs for the treatment of TB.
- Infection by the human immunodeficiency virus (HIV).
- Any primary immunodeficiency.
- Oral or intravenous intake of corticosteroids at a daily dose equal or greater than 0.4 mg/kg prednisone or greater the last 15 days.
- Any anti-cytokine biological treatment the last one month.
- Medical history of systemic lupus erythematosus.
- Medical history of multiple sclerosis or any other demyelinating disorder.
- Pregnancy or lactation. Women of child-bearing potential will be screened by a urine pregnancy test before inclusion in the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	29-06-2022
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Immukine
Generic name:	recombinant human interferon gamma-1b
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Kineret
Generic name:	Anakinra
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	03-06-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-10-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-09-2022
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
EudraCT	EUCTR2020-005768-74-NL
CCMO	NL76706.091.21