Safety and Efficacy of Recombinant Interferon-Gamma 1b (rIFN-Gamma 1b) Given With Standard Therapy in Patients With Candidemia

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This study has been transitioned to CTIS with ID 2024-510816-55-00 check the CTIS register for the current data. The primary objective of the study is to evaluate the efficacy and safety and rIFN-γ as adjunctive treatment in combination…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Fungal infectious disorders
Study type	Interventional

Summary

ID

NL-OMON52806

Source
ToetsingOnline

Brief title
rIFN-Gamma 1b in Candidemia

Condition

- Fungal infectious disorders

Synonym
candidemia, fungal infection

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: Horizon2020

Intervention

Keyword: Candidemia, Interferon-Gamma

Outcome measures

Primary outcome

The primary study endpoint is the time to first negative blood culture.

Secondary outcome

- 1. The time to treatment success (resolution of infection). To achieve this endpoint of resolution of infection, the following criteria are to be met: microbiological eradication of Candida from the blood and any other site of infection; resolution of fever; resolution of other diagnostic variables, such as imaging results, where applicable; and no new signs of infection. The time at which all the variables are met is defined as the date of resolution of infection. Treatment is considered to have failed if new signs of disease have emerged, when none of the other criteria of resolution have been met, when antifungal treatment is changed for any reason, or when a patient withdraws from the study before resolution of infection has been documented. Cases are scored to have improved if no new signs of disease are present and at least one of the other criteria of resolution has been met.

- 2. Percentage of patients with Mycological Outcomes at end of study treatment (EOST), end of treatment (EOT), and 2 and 4 weeks after end of treatment (EOT).

- 3. Percentage of patients with Treatment Success at end of treatment (EOT), and 14 and 28 days after end of treatment (EOT).

- 4. Overall survival at Study Day 28.

- 5. Number of patients with Treatment Emergent Adverse Events (TEAEs). (Time frame 49 days)

- 6. Evaluation of patient status at end of rIFN-γ treatment including organ (dys)function (Sequential Organ Failure Assessment [SOFA] score), and adverse events. (Time frame 14 days)

- 7. Nutritional status (body weight, BMI), nutritional blood parameters (prealbumin, total lymphocytes, cholesterol). (Time frame 49 days)

- 8. Genetics and transcriptomics

- 9. Gut microbiota composition and Candida genomics and metabolomics.

- 10. Changes in circulating cytokines, biomarkers, LAP activation, inflammasome, immunoprofiling.

Study description

Background summary

General introduction
Fungal infections are commonly described in the general population. Most of these infections are superficial and easily treated. However, the incidence of invasive fungal infections is increasing as a result of the use of invasive medical interventions, immunosuppressive treatment for autoimmune diseases and cancer, and the HIV pandemic. These invasive infections are associated with a high morbidity and mortality in the general population and hospitalized and intensive care unit patients. Despite development of novel therapeutic strategies, the burden and death due to fungal infections remains unacceptably high. Candida is one of the most common causes of these invasive fungal infections.

Antifungal immunity
Candida is considered an opportunistic pathogen, so an inadequate host defence, rather than the virulence of the fungus, is associated with the intensity of Candida infection. It is widely adopted that phagocytic cells play a crucial role in immunity to fungal infections. This is supported by the high prevalence of invasive fungal infections in patients with neutropenia or an defect in

phagocyte NADPH oxidase (chronic granulomatous disease). Phagocytes are activated to kill fungi by pro-inflammatory cytokines as interferon gamma (IFN-γ) and interleukin 17 (IL-17) produced by Th1 and Th17 lymphocytes. Also CD4 T-lymphocyte immunodeficiencies are associated with invasive fungal infections(6). Interventions to stimulate the host defence against fungi have been proposed consisting of colony-stimulating factors based on the conclusion that neutrophils play a central role in the host defence against Candida and recombinant IFN-γ since the Th1 and Th17 responses are essential in antifungal immunity.

Interferon-gamma
IFN-γ is a cytokine that is critical for innate and adaptive immunity against infection since it activates monocytes that increases their antigen presenting capacity by upregulation of co-stimulatory and HLA molecules and primes for pro-inflammatory cytokine responses. Recombinant IFN-γ (rIFN-γ) as an adjuvant immunotherapy has been studied the last decades. It has been shown that rIFN-γ activates macrophages and polymorphonuclear neutrophils against Candida infection, and reduces fungal burden in mice with disseminated candidiasis(7). In a trial with patients with chronic granulomatous disease the use of rIFN-γ was shown successfully protect against aspergillosis(8). Therefore, the IDSA Guideline state administration of rIFN-γ could be considered as an escape medicine in patients with severe or refractory invasive fungal infections. The addition of rIFN-γ to standard treatment in HIV-positive patients with cryptococcal meningitis was shown to be safe to use and showed faster fungal clearance. Combining the results with the knowledge on antifungal host defence, a potential benefit of rIFN-γ immunotherapy can be suggested in patients with invasive fungal infections as candidemia.

Study objective

This study has been transitioned to CTIS with ID 2024-510816-55-00 check the CTIS register for the current data.

The primary objective of the study is to evaluate the efficacy and safety and rIFN-γ as adjunctive treatment in combination with standard therapy for the treatment of patients with candidemia. Efficacy is defined as clearance of candidemia within the first 7 days of treatment, taking into account mortality.

The secondary objectives of this study are:
• To evaluate new markers that could be used to identify patients that respond to immunotherapy with rIFN-γ.
• To identify markers that can monitor the patient*s immunological and clinical response to rIFN-γ immunotherapy.
• To perform mechanistic studies to further elucidate mechanisms that are important for host defence against candidemia and the effects of rIFN-γ on these mechanisms.

Study design

This study will be a randomized open label interventional phase 2 pilot study of the safety and efficacy of rIFN-γ in patients with candidemia. All patients with candidemia will be randomized between adjunctive rIFN-γ immunotherapy (100microgram subcutaneous three times a week for two weeks) in combination with standard therapy or only standard therapy according to ESCMID/EFISG (Europe) or IDSA (US) guidelines. We will assess the effect on clinical outcome and investigate relevant biomarkers that can guide this immunotherapeutic approach.

Intervention

In this study, patients with documented candidemia fulfilling the enrolment criteria will be randomized in a ratio 1:1 to receive either human rIFN-γ or standard therapy. rIFN-γ will be administered subcutaneous at a dose of 100 µg/ day on days 0-2-4-7-9-11 (thrice weekly). Administration of rIFN-γ is to be discontinued after twelve days in all patients

Study burden and risks

Many clinical trials pose only a minimal additional risk to subject safety compared to normal clinical practice. According to the EU clinical trial regulation 536/2014(15), these low-intervention clinical trials are of crucial importance for assessing standard treatments and diagnoses, thereby optimizing the use of medicinal products and thus contributing to a high level of public health. Trials like these should be subject to less stringent rules, as regards monitoring, requirements for the contents of the master file and traceability of investigational medicinal products. The published scientific evidence supporting the safety and efficacy of an investigational medicinal product not used in accordance with the terms of the marketing authorization could include high quality data published in scientific journal articles, as well as national, regional or institutional treatment protocols, health technology assessment reports or other appropriate evidence.

We consider the current study a low intervention clinical trial in line with the definition from the EU clinical trial regulation 536/2014(15) for the following reasons:
• rIFN-γ as investigational medicinal product is authorised. Also, the use and dose are supported by the EMA. Therefore, the additional risk for participation is reduced to minimum compared to standard treatment.
• rIFN-γ therapy has been used in clinics for a long time in the fields of rheumatology and oncology and has a well-known safety profile. Moreover, rIFN-γ is already licensed as a prophylactic agent for patients with chronic granulomatous disease based on a randomized trial in which the number and severity of infections was reduced by rIFN-γ therapy(16).

• The IDSA Guideline state that adjunctive treatment with rIFN-γ can be considered for severe and refractory aspergillosis(9).
• rIFN-γ is proposed to be safe as a treatment for invasive fungal infections in a high risk population (after allogeneic hematopoietic stem cell transplantation)(17).
• We already performed a pilot study which provided evidence that immunotherapy with rIFN-γ is of potential benefit in patients with fungal sepsis(11).
• The additional diagnostic and monitoring procedures besides the treatment with the investigational product do not pose more than minimal risk and burden. This is fully in line with EU clinical trial regulation 536/2014 definition of a low intervention clinical trial.

Given the vulnerable population, we set the risk at moderate according to NFU guidelines.

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

Males or non-pregnant females (who must agree to use barrier methods of contraception during the study therapy period, women of childbearing age must have a negative urine pregnancy or serum test at baseline).
Subjects who are 18 years of age or older.
Subjects with at least one positive blood culture isolation of Candida species from a specimen drawn within 120 hours prior to study entry.
Subjects who have clinical evidence of infection sometime within 120 hours prior to enrolment, including at least one of the following:
-Temperature >37.8 *C on two occasions at least four hours apart or one measurement > 38.2 *C
-Systolic blood pressure <90 or a >30 mmHg decrease in systolic blood pressure from the subject's normal baseline or the need for vassopressive therapy.
-Signs of inflammation (swelling, heat, erythema, purulent drainage) from a site infected with Candida (e.g. joint, skin, eye, bone, oesophagus).
-Radiologic findings of invasive candidiasis.
Subject or their legal representative must sign a written informed consent form.
- In case a patient eligible to participate in this study is incapacitated and as such unable to personally provide informed consent, a written consent form must be signed by their legal representative.
- Only incapacitated patients that can be expected to regain the capability to consent will be included in this study. In this case, informed consent will be discussed personally with the study participant after recovery.
- The inclusion of incapacitated subjects will only be performed under the above conditions in a country in which such an approach is legal and deemed ethically acceptable.

Exclusion criteria

Subjects with a history of allergy or intolerance to rIFN-γ or any other IMP ingredient or with a history of immediate type hypersensitivity to latex/rubber.
Subjects with a history of documented epileptic seizures.
Subjects with severe liver failure (>5x upper limit AST or ALT or impaired synthesis of proteins such as coagulation factors manifested by increased prothrombin time).
Treatment with heterologous serum proteins, or immunological preparations such as vaccines, toxins, serums and allergens within three days before trial enrolment.
Women who are pregnant or lactating.
Subjects who are unlikely to survive more than 24 hours.
Subjects who have failed previous systemic antifungal therapy for the Candida spp. infection which is being studied.

Subjects who have received more than 120 hours of systemic antifungal therapy for the current episode, within 120 hours prior to study entry.
With respect to incapacitated subjects:
- Any patient that is deemed incapable of personally providing informed consent due to a neurodegenerative disease, genetic syndrome, and/or perinatal asphyxia, will not be eligible for inclusion in this trial.
- Any incapacitated subject that is not expected to recover to a point where they will personally be able to provide informed consent will not be eligible for inclusion in this trial.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-03-2023
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Recombinant Interferon-Gamma 1b
Generic name:	Immukin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-08-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-11-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-12-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-12-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-01-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-01-2023
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
EU-CTR	CTIS2024-510816-55-00
EudraCT	EUCTR2020-003204-13-NL
ClinicalTrials.gov	NCT04979052
CCMO	NL74527.091.21