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Can a drug with the potential to boost the immune system (interferon gamma) prevent infection in patients who are critically ill and at particularly high risk of developing new infections during their stay in an intensive care unit?

Submission date
05/08/2023

Registration date
10/11/2023

Last Edited
14/01/2025

Recruitment status
Recruiting

Overall study status
Ongoing

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Patients admitted to intensive care units (ICUs) are vulnerable to new infections while in ICU. Antibiotics are given to too many patients in the ICU and overuse leads to the emergence of "superbugs" that are resistant to antibiotics. There is a pressing need to prevent infection in the ICU using treatments other than antibiotics. Severe illnesses "stun" the immune system, leaving immune cells less able to kill bugs. A drug called interferon-gamma (IFNg) potentially restores good function to patients' immune cells. This study aims to determine whether IFNg is safe and whether it can reduce antibiotic use and infections, in patients in ICU at greatest risk of developing new infections.

Who can participate?
In UK ICUs, adult patients aged 18 years old and over on a ventilator machine, or who need support to maintain kidney function and blood pressure, and who have a low mHLA-DR (a blood test that indicates a greater risk of infection)

What does the study involve?
Each patient receives an injection under the skin (subcutaneously) once on three occasions over the next week. Patients will be allocated at random to one of four groups:
1. Placebo on all three occasions
2. IFNg - 100 microgrammes (mcg) on all three occasions
3. IFNg - 50 mcg on all three occasions
4. IFNg - first dose 100 mcg, but the next two doses are either placebo or IFNg 100 mcg, depending on whether mHLA-DR is high or low, respectively.
Once 188 patients have entered the study the study will pause and results will be analysed to

see which IFNg group had the best safety and least antibiotic use, i.e. to "pick the winner", and no more patients will be admitted to the other two IFNg groups. The study will then resume with only the placebo group and the "winner" IFNg group recruiting another 94 patients. This will assess whether antibiotic use, death, new infections, length of stay in the ICU, and side effects are significantly less in the "winner" IFNg group than in the placebo group, and whether mHLA-DR goes up more in the "winner" IFNg group.

What are the possible benefits and risks of participating?
It is not known whether the treatment will work, so we cannot say that participants will get a direct benefit. However, the information from this study may help to improve treatment and care of people in intensive care units in the future. As the aim of the study is to determine whether interferon gamma reduces infection in the intensive care unit, it is theoretically possible that participants may have a reduced risk of infection if they receive interferon gamma in the study, but we cannot know this until after the study is completed.
The clinical administration of IFNg has been associated with the following features (listed as very common or common in the Summary of Product Characteristics): fever, fatigue, nausea, vomiting, diarrhoea, elevation of hepatic enzymes, rash, injection site reaction (pain and/or rash), abdominal pain, depression, muscle aches, joint aches and back pain. In a recent trial, a potential increased risk of pneumonia was reported for IFNg - this has not been reported in clinical use of IFNg or in other clinical trials of IFNg, but the study will pay particularly close attention to whether any suggestion of increased pneumonia arises, through an independent Data Monitoring Committee.
The discomfort of blood tests will be minimised by drawing blood from existing vascular lines wherever possible (the vast majority of ICU patients have indwelling cannulae). The volume of blood taken in each blood draw will be less than 30 ml to minimise contributions to the anaemia of critical illness.
These risks are minimised in the following ways:
1. The dose used is the dose well-tolerated in long-term use in chronic granulomatous disease
2. Only three doses will be given
3. The treatment is given to patients whose clinical condition is continuously monitored in the intensive care unit (ICU). Pain is minimised as all patients are anticipated to be receiving sedation /analgesia. Liver function tests are monitored daily in the ICU, and our protocol mandates discontinuation of IMP if transaminases increase by more than 5x baseline during the study. The risk of fatigue and depression is minimised by the short-term use of the IMP.

Where is the study run from?
Newcastle University (UK)

When is the study starting and how long is it expected to run for?
August 2023 to September 2026

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Jaki Hodgson, infinit@newcastle.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1006389

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 58978, 10295, IRAS 1006389

Study information

Scientific Title
Can interferon gamma prevent infection in critically ill patients at highest risk? A phase II randomised controlled trial - INFINIT (INterFeron to reduce INfection in InTensive care units)

Acronym
INFINIT

Study objectives
The main objectives of the trial is to determine whether interferon gamma can reduce the use of antibiotics in critically ill patients at high risk of developing new infection.

Secondary objectives of the trial are:
1. To determine whether interferon gamma is safe in critically ill patients at high risk of developing new infection
2. To determine whether interferon gamma reduces new infections in critically ill patients at high risk of developing such infections

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 20/10/2023, South Central - Hampshire B Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8088; hampshireb.rec@hra.nhs.uk), ref: 23/SC/0295

Study design
Randomized placebo-controlled double-blind parallel-group study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Critically ill patients in intensive care units who are at particularly high risk of secondary (hospital-acquired) infection

Interventions
After informed consent has been received and eligibility confirmed, patients will be randomised into the trial. Randomisation will be performed using the Sealed Envelope system, a secure, 24-hour web-based randomisation system.

The intervention is three subcutaneous injections over a week (three times in a week) of either interferon-gamma (IFNg) or sterile water for injection (WFI) as a placebo. Prior to the interim analysis, there are four treatment groups, interferon-gamma treatment at three different doses and a placebo treatment. After an interim analysis, the best interferon-gamma treatment dose will be chosen and patients will be recruited into one of two groups, the best interferon-gamma treatment dose and placebo. The four treatment groups are:
1. IFNg 100 mcg
2. IFNg 50 mcg
3. IFNg/placebo where the first dose is 100 mcg IFNg sc, the second dose is 100 mcg sc if the mHLA-DR is <8000 mAb/cell (if it is ≥8000 mAb/cell placebo is given sc), and the third dose is 100 mcg sc if the mHLA-DR is <8000 mAb/cell (if it is ≥8000 mAb/cell placebo is given sc)
4. Placebo (sterile WFI)

The preparations will be administered in a syringe on the basis of the randomisation allocation. The first administration is expected to be on the same day as randomisation (day 0). The second dose will be given at least 48 hours later. The third dose will be given at least 48 hours after the 2nd dose. The IMP is to be administered three times over 7 days.

Intervention Type
Drug

Pharmaceutical study type(s)
Dose response, Pharmacoeconomic, Prophylaxis

Phase

Phase II

Drug/device/biological/vaccine name(s)
Interferon gamma 1b

Primary outcome measure
Antibiotic-free days over a 14-day period (AFD-14). AFD-14 is defined as the number of 24-hour periods in which participants were alive and in which intravenous/enteral antibiotics were not used to treat active infection. AFD-14 is measured from days 3-16 inclusive.

Secondary outcome measures
1. Infection-free survival (IFS). IFS is a composite measure that takes into account the development of new infection or death. The unit of infection-free survival is a day. If a participant is alive and has not developed a new infection for a given day, this counts as one day of infection-free survival. IFS is counted from randomisation (i.e. day 0) to day 16 inclusive.
2. Antibiotic days. The number of days on which an antibiotic, including antimicrobial agents and anti-fungal agents used intravenously or enterally to treat active infection, was taken from days 3-16 inclusive.
3. New infections. A new infection is defined as a new episode of sepsis, pneumonia, abdominal infection, blood-stream infection, catheter/line-associated infection, urinary tract infection, central nervous system infection, surgical site infection, cellulitis, new Clostridium difficile infection, or any other acute infection. New infections from days 0-16 will be recorded.
4. New antibiotic prescriptions. The number of new antibiotic prescriptions started on days 3-16 inclusive will be recorded.
5. Sequential Organ Failure Assessment (SOFA) score. The SOFA score will be recorded on the day of randomisation (counted as day 0) and on the days on which the 2nd and 3rd doses of IFNg /placebo are given, if the participant is still in the ICU.
6. Change in mHLA-DR. For each participant the difference in mAb/cell will be calculated for the intervals between the 1st and 2nd mHLA-DR results; the 1st and 3rd mHLA-DR results; and the 2nd and 3rd mHLA-DR results.
7. Time on intubation and mechanical ventilation, defined as days intubated and mechanically ventilated from randomisation to day 30 post-randomisation.
8. Length of ICU stay, defined as the time from admission to ICU to discharge from the ICU, and measured up to day 30 from randomisation.
9. Safety of IFNg assessed by comparing the frequency of SARs in the arms
10. Potential toxicity: routinely collected data will be reviewed to assess possible signals of toxicity from the IMP. The main recordings used to assess potential toxicity will be blood neutrophil count, serum liver transaminases, serum creatinine and serum amylase.
11. 30-day all-cause mortality, defined as death from any cause within 30 days of randomisation.
12. 1-year all-cause mortality, defined as death from any cause in the year from randomisation.

Exploratory outcome measures:
Health economics:
To determine the cost of each treatment arm and to estimate the short-term cost-effectiveness of the “winning” treatment arm:
1. Hospital service use data and length of hospital stay: hospital costs will be estimated for each treatment arm using hospital service use data including length of ICU stay and length of hospital stay up to 30 days.
2. Health-related quality of life: participant-reported score on the EQ-5D-5L at 30 days and 1 year after randomisation.

Biological assays:
To determine the effect of IFNg on innate immune function, in a subset of participants exploratory analyses will be conducted on blood samples collected pre-treatment. Analyses may include, but will not be confined to:
1. Phagocytosis by neutrophils
2. Bacterial killing by neutrophils
3. Reactive oxygen species generation by neutrophils
4. Phagocytosis by monocytes
5. Bacterial killing by monocytes
6. Reactive oxygen species generation by monocytes
7. Quantification of cytokines in serum

Overall study start date
03/08/2023

Completion date
30/09/2026

Eligibility

Key inclusion criteria
1. Patient has been managed in ICU for ≥2 days
2. Either (a) intubated and receiving mechanical ventilation or/and (b) on both vasopressors (to control blood pressure) and renal replacement therapy
3. Age ≥18 years old
4. Informed, written consent obtained from a personal legal representative or professional legal representative
5. Blood monocyte HLA-DR level of <8000 anti-monocyte HLA-DR antibodies per cell
6. Negative pregnancy test in women of child bearing potential

Participant type(s)
Patient

Age group
Mixed

Lower age limit
18 Years

Sex
Both

Target number of participants
282

Key exclusion criteria
1. Breast-feeding or pregnancy
2. Known history of seizures
3. Chronic liver disease with Child-Pugh score C or worse
4. Known allergy to interferons or latex

5. Concomitant enrolment in another interventional trial, except where a co-enrolment agreement exists
6. Solid organ or bone marrow transplantation
7. Patient is under active haematological malignancy surveillance
8. Current active systemic chemotherapy or immunotherapy for cancer (hormonal treatment will not exclude patients) known human immunodeficiency virus (HIV) with a documented CD4 count of <300 cells per cubic millilitre in the last 6 months in those not on renal replacement therapy, an estimated glomerular filtration rate <15 ml/min/1.73 metres squared
9. Blood neutrophil count < 0.5x10^9/L
10. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 4 times the upper limit of normal according to the recruiting hospital's clinical reference range
11. Known 2nd or 3rd degree heart block
12. History of severe heart failure or history of New York Heart Association (NYHA) heart failure score of 3 or 4
13. Proposed use of vaccines in the 10 days from randomisation
14. Known receipt of a vaccination in the 28 days prior to admission to the ICU
15. Consultant in charge of the patient's care considers the patient's participation inappropriate

Date of first enrolment
29/04/2024

Date of final enrolment
30/09/2026

Locations

Countries of recruitment
England

Northern Ireland

United Kingdom

Study participating centre
Sunderland Royal Hospital
Kayll Road
Sunderland
United Kingdom
SR4 7TP

Study participating centre
Freeman Hospital
Freeman Road
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NE7 7DN

Study participating centre
Addenbrookes
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Study participating centre
The Royal Victoria Hospital
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Study participating centre
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L9 7AL

Study participating centre
Royal Liverpool University Hospital
Prescot Street
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L7 8XP

Study participating centre
The James Cook University Hospital
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Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

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None provided
tnu-tr.sponsormanagement@nhs.net

Sponsor type
Hospital/treatment centre

Website
http://www.newcastle-hospitals.org.uk/

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Conference presentation
3. Publication on website

Intention to publish date
30/09/2027

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request by bona fide teams at the end of the trial from Newcastle University. Requests will

be considered by a Data Access Committee, and subject to presenting a clear plan of what the data will be used for, how the data will be analysed, how the results will be disseminated, and who the authors will be. Data transfer will be subject to the completion of a Data Sharing Agreement between Newcastle University and the end users.

IPD sharing plan summary

Available on request