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Developmental Clinical Sciences: Does GM-CSF restore effective neutrophil function in critically ill patients?

Submission date
26/06/2012

Recruitment status
No longer recruiting

Registration date
26/06/2012

Overall study status
Completed

Last Edited
11/07/2017

Condition category
Other

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Despite the introduction of multiple preventative measures, rates of hospital-acquired infection (HAI) in the intensive care unit remain high. New approaches to tackling this problem are required. A type of white blood cell called the neutrophil is the key cell fighting bacterial and fungal infection in the body. This study group has shown that the majority of patients on intensive care have neutrophils which don't eat germs effectively and are therefore less able to fight off infection. These patients, whose white blood cells don't work properly in this way, are much more likely to develop a second infection whilst in hospital (HAI). These patients can be identified by measuring the levels of a specific receptor on the surface of the neutrophils by a simple blood test. Previous work carried out by this research group has also shown that by adding a drug called granulocyte macrophage-colony stimulating factor (GM-CSF) to a sample of blood from such patients in the laboratory, it is possible to restore the ability of the neutrophils to eat bacteria and fight infection. This study, therefore, tests whether it is possible to restore the eating ability of critically ill patients' white blood cells, in real life, by giving them GM-CSF as an injection while they are on intensive care. If the study demonstrates a clear effect for GM-CSF in improving the function of patients neutrophils, the way would be paved for future studies determining whether GM-CSF can prevent HAI in future, larger studies. Currently, no good drug treatments preventing HAI in the ICU are available.

Who can participate?
Participants aged 18 or over recruited via four ICUs across North East England

What does the study involve?
The study involves two parts. The first part aims to establish the best dose of GM-CSF that should be used in order to improve the function of neutrophils in critically ill patients. Patients with faulty neutrophils who are enrolled into this part of the study are randomly allocated to receive one of two doses of GM-CSF for 4 or 7 days. The eating capacity of their neutrophils is measured before and after the injections to see which dose is the most effective in improving their function. At the same time the patients' blood tests and clinical condition are monitored to look for any unwanted side effects of treatment. The best dose (i.e., the one which produces the

greatest benefit without significant side effects) is selected for use in the second part of the study.
The second part of the study will again enroll patients on intensive care whose white blood cells don't work properly in this way. Patients who take part in this part of the study are randomly allocated to receive either an injection of the drug (GM-CSF) or an injection of a solution which has no effect (placebo or dummy drug), to see whether those patients who receive the GM-CSF injection have an improvement in the function of their neutrophils compared to those who don't. Participants are followed up for a maximum of 30 days.
As well as looking at whether or not the white blood cells work properly, the study also looks at whether there is a difference in the rates of infection picked up in hospital between the two groups and also whether there is any difference in their clinical outcomes such as length of stay in hospital, time on a ventilator and survival.

What are the possible benefits and risks of participating?
There are no definite benefits of taking part in the study. However, participants may benefit from GM-CSF injections as GM-CSF is expected to improve the function of the white blood cells during critical illness. Participants should not experience any side effects from the drawing of blood (which in the majority of cases will be from an indwelling line) other than the usual minor discomfort associated with a blood test if their line is moved prior to completion of the study. GM-CSF has been associated with potential minor side effects including mild discomfort and redness at the injection site, fever, aches and pains. All of these side effects usually resolve within a couple of days of completing the injections. GM-CSF does have some reported rare potential serious side effects including blood clots to the heart and lungs and inflammation of the lining around the heart. These side effects have only ever been reported at doses far higher than those which will be received during the study. The dose received has been associated with a good safety profile. The placebo injection should not be associated with any side effects other than mild discomfort at the injection site.

Where is the study run from?
1. Newcastle upon Tyne Hospitals Foundation Trust (UK)
2. Gateshead Foundation Trust (UK)
3. Sunderland Royal Hospital (UK)

When is the study starting and how long is it expected to run for?
July 2012 to April 2015

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

Who is the main contact?
1. Prof. John Simpson (Chief Investigator)
2. Ms Jennie Parker (Trial Manager)
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Contact information

Type(s)
Scientific

Contact name
Ms Jennie Parker

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Additional identifiers

EudraCT/CTIS number
2011-005815-10

IRAS number

ClinicalTrials.gov number
NCT01653665

Secondary identifying numbers
12337

Study information

Scientific Title
Developmental Clinical Sciences: Does GM-CSF restore effective neutrophil function in critically ill patients?

Study objectives
Despite the introduction of multiple preventative measures rates of hospital acquired infection in the intensive care unit remain high. New approaches to tackling this problem are required. The neutrophil (a type of white blood cell) is the key cell fighting bacterial and fungal infection in the body. This research group has already shown that the majority of patients on intensive care have neutrophils which don't ingest germs effectively and are therefore less able to fight infection. These patients, whose white blood cells don't work properly, are much more likely to develop a second infection whilst in hospital (hospital acquired infection).

Previous work done by this group has shown that by adding a drug called granulocyte macrophagecolony stimulating factor (GM-CSF) to a sample of blood from these patients in the lab, it is possible to restore the ability of the white blood cells to ingest bacteria and fight infection.

This study will test whether it is possible to restore the capacity of patients' white blood cells to eat germs by giving them GM-CSF as an injection while they are on intensive care.

Patients taking part in the study will receive an injection, under the skin, of either the drug, GM-CSF, or a solution which will have no effect (placebo). We will compare whether those patients who have received the GM-CSF injection have an improvement in the function of the white blood cells compared to those who don't.

As well as looking at the function of the white blood cells we will also study whether there is a difference in the rates of infection picked up in hospital between the two groups.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee Yorkshire & The Humber - Leeds West, 14/02/2012, ref: 12/YH/0083

Study design
Randomised; Interventional; Design type: Treatment

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Topic: Generic Health Relevance and Cross Cutting Themes; Subtopic: Generic Health Relevance (all Subtopics); Disease: Critical Care

Interventions
Patients taking part in the study will receive an injection, under the skin, of either the drug, GM-CSF, or a placebo.

Leukine (Sargramostim), a granulocyte macrophage-colony stimulating factor, will be administered at either 3ug/kg/day or 6ug/kg/day for either 4 or 7 days; Study Entry : Registration and One or More Randomisations

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Sargramostim

Primary outcome measure

Current primary outcome measures as of 20/05/2014:
Neutrophil phagocytic capacity 2 days after administration of GM-CSF/placebo (as measured by the percentage of neutrophils ingesting ≥ 2 zymosan particles ex vivo).

Previous primary outcome measures:
Neutrophil phagocytic capacity 2 days after GM-CSF injection

Secondary outcome measures
Current secondary outcome measures as of 20/05/2014:
1. All-cause mortality 30 days post randomisation
2. Number of days of mechanical ventilation
3. Incidence of ICU acquired infections as defined by Hospitals in Europe Link for Infection Control Surveillance (HELICS) criteria
4. Length of ICU stay
5. Safety over the course of the study, during treatment and follow-up
6. Sequential neutrophil phagocytic capacity over the duration of treatment for each participant, possibly either 4 or 7 days
7. Sequential organ failure assessment score (SOFA)

Previous secondary outcome measures:
1. 30 day mortality, for up to 30 day post-injection follow up
2. Duration of mechanical ventilation during the course of the study, for treatment and follow-up
3. Incidence of ICU acquired infections for the duration of time the participant is on the study (treatment and follow-up)
4. Length of ICU stay for the duration of time the participant remains in follow-up; other measures of neutrophil function
5. Safety over the course of the study, during treatment and follow-up
6. Sequential neutrophil phagocytic capacity over the duration of treatment for each participant, possibly either 4 or 7 days
7. Sequential organ failure assessment score (SOFA) for the duration of time the participant remains on study (treatment and follow-up)

Overall study start date
02/07/2012

Completion date
30/04/2015

Eligibility

Key inclusion criteria
Current inclusion criteria as of 20/05/2014:
1. Male and female, aged >= 18 years
2. Patients admitted to intensive care unit within the last 72 hours
3. Fulfill criteria for systemic inflammatory response syndrome (SIRS)
4. Has required support of one or more organ systems (invasive ventilation, inotropes or haemofiltration) during current ICU stay
5. Survival over next 48 hours deemed most likely outcome by responsible ICU clinician
6. Neutrophil phagocytic capacity <50%

Previous inclusion criteria:
1. Male and female, aged >= 18 years
2. Patients admitted to intensive care unit within the last 48 hours
3. Fulfill criteria for systemic inflammatory response syndrome (SIRS)
4. Require exogenous support of one or more organ systems (invasive ventilation, inotropes or haemofiltration)
5. Predicted to require organ support for further 48 hours or more
6. Survival is considered to be the most likely outcome by the attending clinician at the time of enrolment
7. Neutrophil CD88 expression is low (i.e. corresponding to < 50% neutrophil phagocytic capacity)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 70; UK Sample Size: 70

Key exclusion criteria
Current exclusion criteria as of 20/05/2014:
1. Absence/refusal of informed consent
2. Current prescription of a colony stimulating factor
3. Any history of adverse reaction/allergy to GMCSF
4. Total white cell count >30x109/litre at the time of screening
5. Haemoglobin < 7.5g/dl at the time of screening
6. Age < 18 years
7. Pregnancy or lactation
8. Known in-born errors of neutrophil metabolism
9. Known haematological malignancy and/or known to have > 10% peripheral blood blast cells
10. Known aplastic anaemia or pancytopaenia
11. Platelet count <50x10^9/litre
12. Chemotherapy or radiotherapy within the last 24 hours
13. Solid organ or bone marrow transplantation
14. Use of maintenance immunosuppressive drugs other than maintenance corticosteroids (allowed up to prednisolone 10mg/day or equivalent)
15. Known human immunodeficiency virus (HIV) infection
16. Active connective tissue disease (eg rheumatoid disease, systemic lupus erythematosus) requiring active pharmacological treatment
17. ST segment elevation myocardial infarction, acute pericarditis (by ECG criteria) or pulmonary embolism (radiologically confirmed) in the previous week
18. Involvement in any study involving an investigational medicinal product in the previous 30 days

Previous exclusion criteria:
1. Absence/refusal of informed consent
2. Current prescription of a colony stimulating factor
3. Any history of adverse reaction/allergy to GMCSF
4. Total white cell count > 20x10^9/litre at the time of screening
5. Haemoglobin <8.5g/dl at the time of screening
6. Age < 18 years
7. Pregnancy or lactation
8. Known in-born errors of neutrophil metabolism
9. Known haematological malignancy and/or known to have > 10% peripheral blood blast cells
10. Known aplastic anaemia or pancytopaenia
11. Platelet count <50x10^9/litre
12. Known history of cancer (unless undergone curative resection or treatment)
13. Solid organ or bone marrow transplantation
14. Use of maintenance immunosuppressive drugs other than maintenance corticosteroids (allowed up to prednisolone 10mg/day or equivalent)
15. Known human immunodeficiency virus (HIV) infection
16. Active connective tissue disease (eg rheumatoid disease, systemic lupus erythematosus) requiring active pharmacological treatment
17. ST segment elevation myocardial infarction, acute pericarditis (by ECG criteria) or pulmonary embolism (radiologically confirmed) in the previous week
18. Involvement in any study involving an investigational medicinal product in the previous 30 days

Date of first enrolment
02/07/2012

Date of final enrolment
30/04/2015

Locations

Countries of recruitment
United Kingdom

Study participating centre
Newcastle upon Tyne Hospitals Foundation Trust
NE7 7DN

Study participating centre
Gateshead Foundation Trust
NE9 9SX

Study participating centre

Sunderland Royal Hospital
SR4 7TP

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Trust (UK)

Sponsor details
Freeman Road
High Heaton
Newcastle upon Tyne
England
United Kingdom
NE7 7DN

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council (MRC) (UK)

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
A full article is currently being reviewed, estimated publication in December 2017.

Intention to publish date
01/12/2017

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to the use of anonymous participant level data being made available not being specified in the participant information sheet or consent form during the trial.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Abstract results	results	15/05/2016		No	No
HRA research summary			28/06/2023	No	No