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A placebo-controlled trial of granulocyte colony-stimulating factor in ceftazidime-treated patients in septic shock due to melioidosis

Submission date
12/09/2005

Recruitment status
No longer recruiting

Registration date
14/10/2005

Overall study status
Completed

Last Edited
21/03/2013

Condition category
Infections and Infestations

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

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
ACTRN12605000024640; 077166

Study information

Scientific Title

Granulocyte colony-stimulating factor in ceftazidime-treated patients in septic shock due to melioidosis: a placebo-controlled double-blind prospective randomised trial

Study objectives
In Darwin, Australia, the mortality in patients with melioidosis with septic shock has fallen from 95% (20 of 21 patients) to 10% (2 of 21 patients) since the adoption of granulocyte colony-stimulating factor (G-CSF). The hypothesis tested by this prospective randomised trial is that G-CSF can reduce the mortality of melioidosis-associated severe sepsis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. The Ministry of Public Health, Royal Government of Thailand
2. The Human Research Ethics Committee of the Menzies School of Health Research, Australia

Study design
Double-blind, prospective, randomised trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Septic shock due to melioidosis

Interventions
Patients will be treated with ceftazidime (the antibiotic treatment of choice), and randomised to receive either placebo or Lenograstim (recombinant human granulocyte colony stimulating factor [rhG-CSF]) (Granocyte®-Chugai Pharmaceutical, Japan). Dose: 300 µg intravenous injection, once daily for three days.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Ceftazidime, lenograstim

Primary outcome(s)
The primary outcome measures will be in-hospital mortality and 28 day mortality.

Key secondary outcome(s))
Secondary outcome measures will include the following:
1. Treatment failure: unfavourable outcome or changing the regimen using these criteria:
1.1. Obvious worsening of clinical signs and symptoms after 72 hours of treatment such as lowering of blood pressure, deterioration of shock

1.2. B. pseudomallei persistently cultured in blood after seven days of treatment
1.3. Persistent fever and no obvious improvement in any clinical signs and symptoms after ten days of treatment in the presence of other proper management such as surgical drainage of pus or fluid collection
2. Fever clearance time
3. Adverse drug reactions
4. Sequential Organ Failure Assessment (SOFA) scores at day one, three, seven and ten
5. Time to resolution of shock
6. Duration of ventilation
7. Duration of hospitalisation
8. Neutrophil function before and after treatment

Completion date
01/11/2005

Eligibility

Key inclusion criteria
1. Community acquired septic shock (must fulfil criteria for sepsis, shock and end-organ perfusion abnormalities), and melioidosis is suspected:
1.1. Sepsis: Systemic Inflammatory Response Syndrome (SIRS): two or more of the following, clinically ascribed to infection:
1.1.1. Fever: temperature more than 38°C or less than 36°C
1.1.2. Tachycardia: heart rate more than 90 beats/min
1.1.3. Tachypnoea: respiratory rate more than 20 breaths/min or arterial carbon dioxide pressure ($PaCO_2$) less than 32 mmHg or mechanical ventilation
1.1.4. White cell count more than 12,000 cells/ml or less than 4,000 cells/ml or more than 10% band forms
1.2. Shock: hypotension for more than one hour in absence of other causes of hypotension (e.g. anaesthesia or antihypertensive medication) despite adequate fluid challenge sufficient to restore circulating blood volume (systolic blood pressure less than 90 mmHg or fall of more than 40 mmHg from baseline or requirement for vasopressors/inotropes)
1.3. Septic shock: sepsis with shock with markers of perfusion abnormalities that may include one or more of:
1.3.1. Metabolic acidosis: pH less than 7.3 or base excess less than 5 or bicarbonate (HCO_3) less than 15 mmol/l or anion gap more than 20 mmol/l or lactate more than 4 mg/l
1.3.2. Respiratory dysfunction: mechanical ventilation or partial pressure of oxygen in arterial blood (PaO_2)/fraction of inspired oxygen (FiO_2) less than 300 or respiratory rate less than 5 or more than 49 breaths/min or $PaCO_2$ more than 50 mmHg or PaO_2/partial pressure of oxygen in the alveoli (PAO_2) ratio less than 0.5
1.3.3. Renal dysfunction: oliguria less than 30 ml/hour for three hours, or oliguria less than 700 ml /24 hours or creatinine more than 3 mg/dl or renal replacement therapy
1.3.4. Altered mental status Glasgow Coma Score (GCS) less than 15
1.3.5. Liver dysfunction: bilirubin more than 6 mg/dl and prothrombin time (PT) more than four seconds above normal control
1.3.6. Coagulopathy: International Normalised Ratio (INR) more than 1.4
2. Community acquired septicaemia (less than 72 hours of hospitalisation)
3. Patients who have received antibiotics prior to presentation are eligible
4. No known hypersensitivity to G-CSF
5. Aged more than 14 years, either sex
6. Need hospitalisation and intravenous antibiotic administration

7. Willingness to participate in the study and written, informed consent obtained from the patient

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Known haematological malignancy, myelodysplasia or congenital neutropaenia
2. Febrile neutropaenia
3. Pregnant or lactating women
4. Known hypersensitivity to G-CSF
5. Patients not expected to remain in hospital for treatment
6. Known objection to participation in study
7. Patients who have previously been enrolled or who have received G-CSF within the past month
8. Patients with community-acquired sepsis with cultures positive for other organisms

Date of first enrolment
01/06/2003

Date of final enrolment
01/11/2005

Locations

Countries of recruitment
Thailand

Study participating centre
C/O Wellcome Unit
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Sponsor information

Organisation

University of Oxford (UK)

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
The Wellcome Trust (UK) (grant ref: 077166)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/08/2007		Yes	No