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Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction (HARP)

Submission date 21/03/2006	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 24/04/2006	**Overall study status** Completed	
Last Edited 03/02/2014	**Condition category** Respiratory	

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
EME 08/99/08; RGHT000275

Study information

Scientific Title

Hydroxymethylglutaryl-CoA reductase inhibition in Acute lung injury to Reduce Pulmonary oedema and inflammation: a phase II, single centre, prospective, double-blind, randomised, placebo-controlled trial

Acronym
HARP

Study objectives
Treatment with hydroxymethylglutaryl-CoA (HMGCoA) reductase inhibitor, simvastatin, is safe and improves important surrogate clinical outcomes in adult patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).

Link to EME project website: http://www.eme.ac.uk/projectfiles/089908info.pdf

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. MREC approved on the 31st July 2006
2. MHRA approved on the 4th September 2006

Study design
Phase II single centre prospective double-blind randomised placebo-controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)

Interventions
Patients will be stratified for the presence of severe sepsis as a clinical risk factor for the development of acute lung injury. Stratified block randomisation using a microcomputer to simvastatin 80 mg or placebo enterally (1:1) will be performed.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)
Reduction in extravascular lung water (EVLW) in the simvastatin treated group at day 7

Key secondary outcome(s))
Current secondary outcome measure (s) as of 17/04/2012
There are a number of secondary outcomes for this clinical trial which include clinical outcomes, safety, biological mechanisms and data for the economic evaluation.
Clinical Outcomes
1. Change in oxygenation index (OI) from baseline to day 3, 7, 14 and 28
2. Change in sequential organ failure assessment (SOFA) score from baselines to days 3, 7, 14 and 28
3. Non pulmonary organ failure free days, (defined as the number of days in the first 28 days after randomisation that the patient has none of: cardiovascular support, renal support, liver support or neurological support).
4. All cause mortality 28 days post randomisation
5. Mortality at (first) discharge from critical care
6. Mortality at (first) discharge from hospital
7. Mortality at 12 months post randomisation

Safety
8. CK >10 times the upper limit of normal (measured on days 1, 3, 7, 14, 21 and 28)
9. ALT/AST >8 times the upper limit of normal (measured on days 1, 3, 7, 14, 21 and 28)
10. Need for renal replacement therapy in patients with CK elevated >10 fold
11. Serious adverse events (SAEs) and occurrence of suspected unexpected serious adverse reactions (SUSARs).
12 Biological mechanisms
13 Health-related quality of life
14. Cost effectiveness

Previous secondary outcome measure(s)
1. Physiological severity of lung injury as measured by PaO2:FiO2 ratio at day 7, respiratory compliance at day 7
2. Effects on the pulmonary circulation as measured by change in pulmonary dead space at day 7
3. Extra-pulmonary organ failure as measured by sequential organ failure assessment (SOFA) score at day 7

Completion date
04/08/2009

Eligibility

Key inclusion criteria
Mechanically ventilated adult patients admitted to the intensive care unit at the Royal Victoria Hospital, within 48 hours of the onset ALI or ARDS, will be eligible for inclusion in the study. ALI and ARDS will be defined according to the American European Consensus Conference definition.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
Current exclusion criteria as of 17/04/2012
1. Age < 16 years
2. More than 48 hours from the onset of ALI
3. Patient is known to be pregnant
4. CK >10 times the upper limit of the normal range*
5. Transaminases >8 times the upper limit of the normal range*
6. Patients currently receiving ongoing and sustained treatment with any of the following; itraconazole, ketoconazole, HIV protease inhibitors, nefazodone, cyclosporine, amiodarone, verapamil or diltiazem.
7. Patients with severe renal impairment (estimated creatinine clearance less than 30ml/minute) not receiving renal replacement therapy
8. Severe liver disease (Child's Pugh score >12; Appendix 1)
9. Current or recent treatment (within 2 weeks) with statins
10. Physician decision that a statin is required for proven indication
11. Contraindication to enteral drug administration, e.g. patients with mechanical bowel obstruction. Patients with high gastric aspirates due to an ileus are not excluded.
12. Domiciliary mechanical ventilation except for CPAP/BIPAP used for sleep-disordered breathing.
13. Known participation in other investigational medicinal product (IMP) trials within 30 days
14. Consent declined
15. Treatment withdrawal imminent within 24 hours
16. Non–english speaking patients or those who do not adequately understand verbal or written information unless an interpreter is available

* If CK, ALT and AST values are not available as part of routine care, a blood sample will be obtained after informed consent but before randomisation.
CK, ALT and AST values may be obtained up to 72 hours prior to randomisation.

Previous exclusion criteria
1. Aged under 18 years
2. Pregnancy
3. Creatinine kinase (CK) more than five times upper limit of normal range
4. Transaminases more than three times upper limit of normal range
5. Participation in other intervention trials within previous 30 days
6. Current treatment with statins
7. Contraindication to enteral nutrition
8. Unlikely to survive beyond 48 hours
9. Patients with significant end stage disease as previously defined and assent declined from the next of kin

Date of first enrolment
02/08/2006

Date of final enrolment
04/08/2009

Locations

Countries of recruitment
United Kingdom

Northern Ireland

Study participating centre
Regional Intensive Care Unit
Belfast
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BT12 6BA

Sponsor information

Organisation
The Royal Group Hospitals Trust (UK)

ROR
https://ror.org/02tdmfk69

Funder(s)

Funder type
Government

Funder Name
Research and Development Office (UK) - Doctoral Fellowship scheme from Central Services Agency, Northern Ireland

Funder Name
REVIVE (UK) - Charity for the Regional Intensive Care Unit at the Royal Group Hospitals Trust

Funder Name
Added 24/06/2010:

Funder Name
Medical Research Council (MRC)/National Institutes of Health Research (NIHR) (UK) - Efficacy and Mechanism Evaluation (EME) Programme (ref: 08/99/08)

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	01/03/2011		Yes	No
Results article	results	19/07/2013		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes