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Simvastatin in acute lung injury

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Registration date 26/11/2010	**Overall study status** Completed	
Last Edited 18/05/2017	**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
9122; 10072DMcA-CS

Study information

Scientific Title
Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction (HARP 2)

Acronym
HARP 2

Study objectives
Current hypothesis as of 08/03/2011:
The aim is to test the hypothesis that treatment with enteral simvastatin 80mg once daily for a maximum of 28 days will be of therapeutic value in patients with acute lung injury (ALI). The study has two objectives:
Objective 1: To conduct a prospective randomised, double-blind, placebo-controlled phase II multi-centre trial of simvastatin for the treatment of ALI.
Objective 2: To study the biological effect of simvastatin treatment on:
(2a) systemic markers of inflammation; (2b) systemic cell-specific indices of activation and injury to the alveolar epithelium and endothelium; (2c) lung extracellular matrix degradation; (2d) assess whether response to simvastatin is determined by genetic polymorphisms.
Patient Population: Patients with ALI
Trial Setting: Adult intensive care units (ICU)
Trial Intervention: Simvastatin 80mg or identical placebo once daily administered enterally for up to 28 days Sample Size: A sample size of 524 subjects (262 in each group) will have 80% power at a two-tailed significance level of 0.05 to detect a 20% difference in ventilator-free days (VFDs). With an estimated dropout rate of 3%, this study will require a total of 540 patients (270 in each group)
Primary Outcome: The primary outcome will be VFDs
Secondary Outcomes: There are a number of secondary outcomes which include: (a) Change in oxygenation index (OI) from baseline to day, 3, 7, 14 and 28; (b) Change in sequential organ failure assessment (SOFA) score from baseline to day 3, 7, 14 and 28; (c) Non pulmonary organ failure free days (d) All cause mortality 28 days post randomisation; (e) Mortality at (first) discharge from Critical Care; (f) Mortality at (first) discharge from hospital; (g) Mortality at 12 months post randomisation; (h) Safety; (i) Biological mechanisms; (j) Health-related quality of life; (k) Cost effectiveness.

Previous hypothesis:
The aim of this study is to test the hypothesis that treatment with enteral simvastatin 80 mg once daily for a maximum of 28 days will be of therapeutic value in patients with acute lung injury (ALI).

Many different circumstances, for example severe infection or as a result of injury in a road traffic accident, may result in a person becoming critically ill. For reasons that are unclear, when people are critically ill their lungs often fail; this is termed acute lung injury (ALI). Normally the lungs are filled with air, however when lung injury occurs, the lungs fill with water. As a result, a person's breathing becomes difficult and a ventilator is needed to take over their breathing. This condition is common, can affect any age group and is often fatal. Furthermore, even after recovery from lung injury, patients frequently go on to experience a poorer quality of life, for example many are unable to return to work or look after themselves, needing considerable help from family or other carers. There is currently no effective treatment for lung injury.

The data from a proof of concept study we carried out, has suggested that simvastatin may assist patients with ALI to recover more quickly, and has informed the design and methodology of this current study.

It is planned to recruit 540 patients to this study. The study is what is called a 'randomised, placebo controlled trial'. This type of trial is widely accepted to be the best way to find out if a

treatment really works or not. In this study, there will be two groups of people; one group will be given simvastatin and the other group a dummy drug (placebo). The group (and thus the specific treatment) that a person is allocated to, is decided 'at random' using a computer programme. This ensures that the two groups of patients are the same in all ways except for that treatment. This means that any difference in the experience of patients in either of the groups should be due to the difference in treatment and not to any other difference that could influence the outcome of the treatment.

Blood and urine samples will be taken at baseline, prior to the drug being taken, and on days 3, 7, 14 and 28, to allow us to determine the ways in which ALI develops and how simvastatin might work to alleviate the condition. We will determine how long patients need assistance with their breathing on a ventilator and how fast they recover.

Patients will be followed up at 3, 6 and 12 months with a 15 minute quality of life questionnaire to measure any residual effects of their illness on their lives.

Ethics approval required
Old ethics approval format

Ethics approval(s)
ORECNI, 08/09/2010, ref: 10/NIR02/36

Study design
Randomised double-blind placebo-controlled phase II multicentre clinical study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Acute lung injury

Interventions
Simvastatin 80 mg once daily versus placebo, administered enterally via a feeding tube or orally, for up to 28 days.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)
Current primary outcome measures as of 08/03/2011:
The primary outcomes will be ventilator free days.

Previous primary outcome measures:
Ventilator free days (VFDs) to day 28 defined as the number of days from the time of initiating unassisted breathing, to day 28 after randomisation, assuming survival for at least two consecutive calendar days after initiating unassisted breathing and continued unassisted breathing to day 28.

If a patient returns to assisted breathing and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation. If a patient was receiving assisted breathing at day 27 or dies prior to day 28, without initiating unassisted breathing or before 48 consecutive hours of unassisted breathing, VFDs will be 0. Patients transferred to another hospital or other health care facility will be followed to day 28 to assess this endpoint.

For example, if a subject initiates unassisted breathing on day 16 and survives to day 28, he/she will be assigned a value of 12 VFDs. If a similar subject begins unassisted breathing on day 16 but dies on day 25, the VFDs is 9. In keeping with previous trials unassisted breathing is defined as:
1. Extubated with supplemental oxygen or room air
2. Open T-tube breathing
3. Tracheostomy mask breathing
4. CPAP less than or equal to 5 cm H20 without pressure support

Patients receiving pressure support via non-invasive ventilation will be defined as receiving assisted ventilation.

Key secondary outcome(s))

Current secondary outcome measures as of 07/09/2012:
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 day 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
1. CK >10 times the upper limit of normal (measured on days 1, 3, 7, 14, 21 and 28)
2. ALT/AST >8 times the upper limit of normal (measured on days 1, 3, 7, 14, 21 and 28)
3. Need for renal replacement therapy in patients with CK elevated >10 fold
4. Serious adverse events (SAEs) and occurrence of suspected unexpected serious adverse reactions (SUSARs) as defined in section 7.4.2

Biological mechanisms
1. Neutrophil activation biomarkers which may include but are not limited to measurement of plasma MPO and MMP-8

2. Plasma inflammatory response biomarkers which may include but are not limited to measurement of CRP, cytokines (including but not limited to TNF-alpha, IL-1 aplha, IL-6, IL-8), proteases and anti-proteases, HO-1, adhesion and activation molecule expression (including but not limited to sICAM-1), coagulation factors (including but not limited to thrombin-anti-thrombin complex, tissue factor, protein C, thrombomodulin and plasminogen activator inhibitor-1), RAGE ligands and vitamin D status
3. Alveolar epithelial and endothelial injury biomarkers which may include but are not limited to measurement of plasma cell specific biomarkers such as RAGE, SP-D, Ang I/II and vWF)
4. Systemic endothelial function biomarkers which may include but is not limited to measurement of spot urine albumin:creatinine ratio (ACR)
5. Pulmonary extracellular matrix (ECM) degradation and turnover biomarkers which may include but are not limited to measurement of urinary desmosine indexed to urine creatinine and procollagen peptide III
6. Assess whether response to simvastatin is determined by genetic polymorphisms as well as link genotypic information to the phenotypic information recorded as part of this study
7. Peripheral blood NF-êB activation

Data for Economic Evaluation
1 Health related quality of life (HRQoL)
1.1EQ-5D at discharge 3, 6 and 12 months post randomisation
2. Resource use:
2.1 Length of ICU stay (level 3 care)
2.2 Length of HDU stay (level 2 care)
2.3 Length of hospital stay
2.4 Health service contacts up to 12 months post randomisation

Previous secondary outcome measures from 14/09/2011, until 07/09/2012:
There are a number of secondary outcomes which include:
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 day 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
8. Safety:
8.1 CK >10 times the upper limit of normal (measured on days 1, 3, 7, 14, 21 and 28)
8.2 ALT/AST >5 times the upper limit of normal (measured on days 1, 3, 7, 14, 21 and 28)
8.3 Need for renal replacement therapy in patients with CK elevated >10 fold
8.4 Serious adverse events (SAEs) and occurrence of suspected unexpected serious adverse reactions (SUSARs) as defined in section 7.4.2
9. Biological mechanisms
10. Health-related quality of life
11. Cost effectiveness

Previous secondary outcome measures from time of registration:
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 day 3, 7, 14 and

28
3. All cause mortality 28 days post-randomisation
4. Mortality at (first) discharge from ICU
5. Mortality at (first) discharge from hospital
6. Mortality at 12 months post randomisation

Safety:
1. CK greater than 10 times the upper limit of normal (measured on days 1, 3, 7, 14 and 28)
2. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) greater than 5 times the upper limit of normal (measured on days 1, 3, 7, 14 and 28)
3. Need for renal replacement therapy in patients with CK elevated greater than 10-fold
4. Serious adverse events (SAEs) and occurrence of suspected unexpected serious adverse reactions (SUSARs)

Biological mechanisms:
1. Neutrophil activation as measured by plasma MPO and MMP-8
2. Plasma inflammatory response as measured plasma CRP, TNF-alpha, IL-1-alpha, IL-6, IL-8 and sICAM-1
3. Alveolar epithelial and endothelial injury as measured by plasma RAGE, SP-D and vWF
4. Systemic endothelial function as measured by spot urine albumin:creatinine ratio (ACR)
5. Lung extracellular matrix (ECM) degradation as measured by urinary desmosine indexed to urine creatinine
6. Assess whether response to simvastatin is determined by genetic polymorphisms as well as link genotypic information to the phenotypic information recorded as part of this study
7. Peripheral blood NF-kappa-B activation

Data for economic evaluation:
1. Health related quality of life (HRQoL) EQ-5D at discharge 3, 6 and 12 months after randomisation
2. Resource use:
2.1. Length of ICU stay (level 3 care)
2.2. Length of HDU stay (level 2 care)
2.3. Length of hospital stay
2.4. Health service contacts up to 12 months after randomisation
2.5. Patient out-of-pocket expenditure and loss of earnings up to 12 months after randomisation
2.6. Carer out-of-pocket expenditure and loss of earnings up to 12 months after randomisation

Completion date
01/09/2015

Eligibility

Key inclusion criteria
Current inclusion criteria as of 14/09/2011:
1. Patient must be receiving invasive mechanical ventilation
2. Patient must have ALI [34] as defined by acute onset of:
2.1 Hypoxic respiratory failure ($PaO_2/FiO_2 \leq 40$ kPa from 2 blood gases >1 hour apart).
2.2 Bilateral infiltrates on chest X-ray consistent with pulmonary oedema.
2.3 No clinical evidence of left atrial hypertension or if measured, a pulmonary arterial occlusion

pressure (PAOP) less than or equal to 18 mmHg. If a patient has a PAOP > 18 mmHg, then the other criteria must persist for more than 12 hours after the PAOP has declined to < 18 mmHg, and still be within the 48-hour enrolment window

Acute onset is defined as follows: the duration of the hypoxia criterion (a) and the chest X-ray criterion (b) must be <28 days at the time of randomisation.

Infiltrates considered consistent with pulmonary oedema ± include any patchy or diffuse infiltrates not fully explained by mass, atelectasis, or effusion or opacities known to be chronic (>28 days). The findings of vascular redistribution, indistinct vessels, and indistinct cardiac borders are not considered consistent with pulmonary oedema ±.

All ALI criteria (a-c above) must occur within the same 24 hour period. The time of onset of ALI is when the last ALI criterion is met. Patients must be enrolled within 48 hours of ALI onset

Previous inclusion crieteria:

1. Patient must be receiving invasive mechanical ventilation
2. Patient must have ALI as defined by acute onset of:

a) hypoxic respiratory failure ($PaO_2/FiO_2 \leq 40$ kPa from 2 blood gases >1 hour apart).
b) bilateral infiltrates on chest X-ray consistent with pulmonary oedema.
c) No clinical evidence of left atrial hypertension or if measured, a pulmonary arterial occlusion pressure (PAOP) less than or equal to 18 mmHg. If a patient has a PAOP ≤ 18 mmHg.

All ALI criteria (a-c above) must occur within the same 24 hour period. The time of onset of ALI is when the last ALI criterion is met. Patients must be enrolled within 48 hours of ALI onset.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 07/09/2012:
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 until 07/09/2012:
6. Patients currently receiving ongoing and sustained treatment with any of the following; itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, cyclosporine, amiodarone, verapamil or diltiazem. Patients receiving low dose erythromycin as a prokinetic will not be excluded.
12. Domiciliary mechanical ventilation
Added 08/03/2011:
16. Non–english speaking patients or those who do not adequately understand verbal or written information unless an interpreter is available

Date of first enrolment
01/12/2010

Date of final enrolment
01/09/2015

Locations

Countries of recruitment
United Kingdom

Northern Ireland

Ireland

Study participating centre

Royal Hospitals
Belfast
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BT12 6BA

Sponsor information

Organisation
Belfast Health and Social Care Trust (UK)

ROR
https://ror.org/02tdmfk69

Funder(s)

Funder type
Charity

Funder Name
National Institute for Health Research (NIHR) (UK) - Efficacy and Mechanism Evaluation Programme (EME)

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	30/10/2014		Yes	No
Results article	long-term outcomes and cost-effectiveness results	17/05/2017		Yes	No
Protocol article	protocol	17/09/2012		Yes	No
HRA research summary			28/06/2023	No	No
Participant information	Participant information sheet	11/11	11/11		

sheet	/2025	/2025	No	Yes