

Project Title:	Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction (HARP).
Project Ref:	08-99-08
Cost:	£964,437
Lead Applicant & Institution:	Dr Danny McAuley Respiratory Medicine Research Cluster The Queen's University Belfast
Start Date:	Anticipated 1 September 2010
Plain English Summary:	<p>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, which is termed "acute lung injury".</p> <p>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" which is a machine to assist breathing, 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.</p> <p>The aim of this study is to investigate if a drug called simvastatin, a drug commonly used to treat high cholesterol, is safe and effective in the treatment of lung injury. The study will take place over 4 years in 14 large intensive care units throughout Ireland.</p> <p>Our 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 treatment.</p> <p>We will determine how long patients need assistance with their breathing on a ventilator and how fast they recover, as well as measuring any residual effects of their illness on their lives for one year after they leave hospital. We will also take blood samples to allow us to determine the ways</p>

	<p>by which lung injury develops and by which simvastatin might work to alleviate the condition.</p> <p>Ethical issues: critically ill patients are often unconscious or sedated and so cannot give their consent to take part in medical research. However, in order to develop new therapies to improve outcomes for critically ill patients we need to be able to carry out clinical trials involving patients who are not able to give consent. In these circumstances a relative or other person who is close to the patient and who can assess whether the patient would have been likely to agree, can give or withhold consent. These arrangements for research on patients unable to give their own consent are considered to be best practice and are governed by law.</p> <p>If simvastatin is effective, the potential benefits of this treatment would be considerable. It may contribute towards saving lives and reducing time spent in ICU. Demand for ICU care exceeds supply and a treatment which reduced use of ICU resources would result in increased capacity and improved access to appropriate facilities for critically ill patients.</p>
<p>Abstract:</p>	<p><u>Objective 1:</u> (The plan for undertaking a phase 2 randomised trial to test the effectiveness and safety of simvastatin in ALI/ARDS)</p> <p><u>Design:</u> This will be a prospective, randomised, double-blind, placebo-controlled phase 2 multi-centre, clinical study of simvastatin in patients with ALI/ARDS.</p> <p><u>Setting:</u> Fourteen adult general ICUs.</p> <p><u>Target population:</u> Mechanically ventilated, intubated adult patients with ALI/ARDS defined according to the American-European Consensus Conference definition.</p> <p><u>Interventions:</u> Patients will be randomised to receive once daily simvastatin 80mg or identical placebo tablet administered enterally via a feeding tube or orally for up to 28 days.</p> <p><u>Outcomes and duration of follow-up:</u> The primary clinical efficacy outcome will be ventilator free days (VFDs). VFDs are the number of days after initiating unassisted breathing to day 28 after randomisation, assuming a subject survives for at least 48 hours after initiating unassisted breathing. VFDs represent a validated outcome measure which quantifies the number of days alive and free from mechanical ventilation. It remains the most useful and validated clinical outcome measure in phase 2 clinical trials in ALI/ARDS. Patient data will be recorded in the case record form daily by the research nurse until day 28. Follow-up at 3, 6 and 12 months will use a postal questionnaire containing the EQ-5D and resource use questions for the health economic analysis.</p> <p><u>Objective 2:</u> (the studies of biological markers of inflammation and lung injury to provide insight into the mechanism of action of simvastatin in ALI/ARDS)</p> <p>We will test the hypothesis that simvastatin decreases neutrophil activation, pro-inflammatory cytokines and adhesion molecule expression, and will explore whether this occurs by reduced NFkB activation. Furthermore, we will investigate whether simvastatin reduces plasma levels of cell-specific indices of activation and injury to the alveolar epithelium and the endothelium. We shall also assess simvastatin's effect on lung extracellular</p>

	<p>matrix destruction. Blood and urine will be taken on days 0, 3, 7, 14 and 28.</p> <p><u>Sample size:</u> The mean (standard deviation; SD) VFDs in 432 patients with ALI/ARDS was 12.7 (10.6) days. On the basis of published data, a conservative treatment effect of 20% has been estimated for this study. A 20% treatment effect represents a 2.6 day increase in VFDs. A 2.6 day increase in VFDs either as a result of improved mortality and/or decreased duration of ventilation would be of major importance. 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 VFDs. If a dropout rate of 3% is estimated this study will require a total of 540 patients (270 in each group).</p> <p><u>Statistical analysis:</u> A statistical analysis plan will be submitted to the DMEC for approval. Analyses will be on an intention-to-treat basis. As VFDs are unlikely to be normally distributed, the groups will be analyzed by comparing the medians and 95% confidence intervals (CI). The comparison of other continuous outcomes will be by analysis of variance, including covariates where appropriate. Statistical diagnostic methods will be used to check for violations of the assumptions, and transformations will be performed where required. For binary outcome measures risk ratios and associated 95% CI will be calculated. Binary variables assessed daily will be analysed using logistic regression analysis corrected for days at risk. Time-to-event outcomes will be analysed by survival methods and reported as hazard ratios with 95% CI. The analysis plan for the statistical evaluation of the biomarkers is given in the protocol.</p> <p><u>Project timetable and milestones:</u> The trial will be carried out over 4 years. Prior to funding for this study commencing, all the regulatory approvals will be in place which will avoid any delay to recruitment. There will be a 3 month run-in period to allow set-up and training. Patient recruitment has conservatively been estimated at 1.3 patients/centre/month over 31 months.</p> <p>There will be 12 months of follow up to collect health-related QoL outcomes. Data cleaning and validation, analysis of the primary and other physiological outcomes, laboratory assays and analyses, and publication of these results will also be undertaken during this 12 month period. A final 2-month period is required for analysis and publication of the follow-up results.</p>
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