Simvastatin to reduce pulmonary dysfunction in patients with acute respiratory distress syndrome: the HARP-2 RCT

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Scientific summary

The HARP-2 trial

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Scientific summary

Background

Acute lung injury (ALI) is a common devastating clinical syndrome characterised by life-threatening respiratory failure requiring mechanical ventilation and multiple organ failure, and is a major cause of morbidity and mortality. Acute respiratory distress syndrome (ARDS) is a more severe form of ALI that is characterised by an uncontrolled inflammatory response that results in damage to the alveolar epithelial and endothelial barrier with exudation of protein-rich pulmonary oedema fluid in the alveolar space.

Acute lung injury occurs in response to a variety of insults, such as trauma and severe sepsis. It affects all age groups, has a high mortality rate of up to 30–50% and causes a long-term reduction in the quality of life for survivors. ALI has significant resource implications, as it prolongs intensive care unit (ICU) and hospital stay, and requires rehabilitation in the community. The cost per ICU bed-day exceeds £1400 and delivery of critical care to patients with ALI accounts for a significant proportion of ICU capacity. Only 54% of survivors are able to return to work 12 months after hospital discharge. The high incidence, mortality, long-term consequences and high economic costs mean that ALI is an extremely important problem.

There is a large body of evidence from in vitro and animal studies suggesting that statins may be beneficial in ALI. In summary, statins improve epithelial and endothelial function to reduce alveolar capillary permeability and reduce pulmonary oedema. In addition, they modulate the inflammatory cascade; regulate inflammatory cell recruitment, activation and apoptosis; and reduce cytokine and protease activity. This may improve outcomes, as high levels and persistence of inflammatory mediators in ALI are associated with poor outcome.

Objectives

The aim of this study was to test the hypothesis that treatment with enteral 80 mg of simvastatin once daily compared with placebo for a maximum of 28 days would be of therapeutic value in patients with ALI. The study had two distinct objectives:

- Objective 1: to conduct a prospective randomised, double-blind, placebo-controlled Phase II multitrial of simvastatin for the treatment of ALI.
- Objective 2: to study the biological effect of simvastatin treatment on mechanisms implicated in the development of ARDS.

Methods

We conducted a randomised, allocation-concealed, double-blind, clinical trial of 80 mg of enteral simvastatin or placebo once daily for a maximum of 28 days. The study was approved by a national Research Ethics Committee (REC) and research governance departments at each site in the UK and by the institutional REC at each site in Ireland. The study was also approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) and Irish Medicines Board (IMB). The Northern Ireland Clinical Trials Unit co-ordinated the overall trial, with support from the Health Research Board Galway Clinical Research Facility for centres in Ireland. The study was conducted in accordance with the protocol and the statistical analysis plan and was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The study design has been published in detail previously.

Daniel F McAuley and John G Laffey vouch for the integrity, accuracy and completeness of the data and analysis and the fidelity of the study to the protocol.

Patients were recruited from adult ICUs in 40 hospitals in the UK and Ireland. Patients' representatives provided written informed consent (assent for sites in Ireland). All surviving patients were subsequently informed about the trial after regaining competence and consent to continue in the trial was obtained.

Patients were eligible if they were intubated and mechanically ventilated and had acute onset of ALI, as defined by the presence of hypoxic respiratory failure ($PaO_2 : FiO_2$ of ≤ 40 kPa from two arterial blood gas tests taken > 1 hour apart); the presence of bilateral infiltrates on chest radiograph consistent with pulmonary oedema; and if there was no clinical evidence of left atrial hypertension or, if measured, a pulmonary arterial occlusion pressure (PAOP) of ≤ 18 mmHg. If a patient had a PAOP of > 18 mmHg, then the other criteria must have persisted for > 12 hours after the PAOP had declined to < 18 mmHg, and still be within the 48-hour enrolment window.

The exclusion criteria were:

- aged < 16 years
- presence of ALI for > 48 hours
- pregnancy
- creatine kinase (CK) levels of > 10 times the upper limit of the normal range
- alanine transaminase (ALT) and/or aspartate aminotransferase (AST) levels of > 8 times the upper limit of the normal range
- receiving ongoing and sustained treatment with concomitant drugs
- severe renal impairment and not receiving renal replacement therapy
- severe liver disease
- current or recent treatment with a statin (within 2 weeks)
- physician decision that a statin is required for proven indication
- contraindication to enteral drug administration
- domiciliary mechanical ventilation except for continuous positive airway pressure/bilevel positive airway pressure used for sleep-disordered breathing
- known participation in another clinical trial of an investigational medicinal product within the previous 30 days
- consent declined
- treatment withdrawal imminent within 24 hours
- non-English speaking without the presence of an interpreter.

On examination of the screening data submitted by sites, it became apparent that the inclusion of clarithromycin and erythromycin in the exclusion criteria had a significant effect on recruitment, with 10% of patients excluded because they were receiving these drugs. To address this situation, a substantial amendment was submitted and authorised in August 2011, allowing the removal of clarithromycin and erythromycin from the exclusion criteria. A further amendment was also approved to increase the eligibility level of ALT and/or AST from more than five times the upper limit of normal to more than eight times the upper limit of the normal range; this amendment was approved in March 2012. Both of these amendments allowed for a significant improvement in recruitment.

A total of 40 mg of simvastatin or identical placebo (95% lactose) tablets were packaged identically and identified only by the unique trial identifier. A computer-generated randomisation sequence was used. Patients were randomised in a 1 : 1 ratio using an automated centralised 24-hour telephone or web-based randomisation service (Centre for Healthcare Randomised Trials, University of Aberdeen, UK). Randomisation was by permuted block stratified by site and by vasopressor requirement (defined as any inotropic requirement except dopamine < 6 µg per kg per minute).

Patients received 80 mg of simvastatin once daily (as two 40-mg tablets) or two identical placebo tablets administered enterally via a feeding tube or orally for up to 28 days. The first dose of study drug was administered as soon as possible, ideally within 4 hours of randomisation, and subsequent doses were given each morning starting on the following calendar day.

The trial drug was terminated if any one of the following conditions was met, prior to the maximum treatment period (28 days from randomisation): study drug-related AE; CK level of > 10 times the upper limit of normal; ALT/AST level of > 8 times the upper limit of normal; development of a clinical condition requiring immediate treatment with a statin; discharge from critical care environment; death; discontinuation of active medical treatment; patient or relative request for withdrawal of patient from the study; decision by the attending clinician that the study drug should be discontinued on safety grounds.

Patient health-related quality of life and resource use was measured by the EuroQol-5 Dimensions, three-level version questionnaire, completed at hospital discharge, and a follow-up questionnaire that was posted out to all patients 3, 6 and 12 months after the date of patient randomisation.

Neutrophil activation was measured by plasma matrix metalloproteinase (MMP)-8. Systemic inflammation and acute phase responses were measured by interleukin 6 (IL-6), C-reactive protein (CRP) and 25-hydroxyvitamin D (vitamin D). Alveolar epithelial and endothelial activation/injury were measured by plasma receptor for advanced glycation end-products (RAGE) and angiopoietin 2 (Ang2) levels respectively. Plasma concentrations were measured at recruitment (baseline) and day 3 (except vitamin D, which was measured to day 14). Plasma concentrations of MMP-8, IL-6, Ang2 and RAGE were measured by enzyme-linked immunosorbent assay. CRP was measured by immunoturbidimetric assay performed by Randox Laboratories (Crumlin, Northern Ireland). Plasma vitamin D was measured by liquid chromatography mass spectrometry by colleagues in the laboratory of Barbara Obemayer-Pietsch, Heidelberg, Germany.

Results

Patients were recruited from 21 December 2010 until 13 March 2014. Out of the 5926 patients who were assessed for eligibility, 540 (9%) underwent randomisation. Four patients who did not fulfil the eligibility criteria were randomised in each group and are included in the analysis. Five patients allocated to the simvastatin group and three patients in the placebo group did not receive study drug. One patient in the simvastatin group was lost to follow-up. No data on the primary outcome were available for one patient in the simvastatin group and two patients in the placebo group.

The baseline characteristics of the patients at randomisation were similar in the two study groups. The main causes of ARDS were pneumonia and sepsis.

Patients received study drug for a mean of 10.2 days [standard deviation (SD) 7.1 days] in the simvastatin group and 11 days (SD 7.9 days) in the placebo group ($p = 0.23$). The most common reasons for discontinuation of study drug were discharge from critical care, death and a study drug-related adverse event (AE). Five patients allocated to the simvastatin group and three patients allocated to the placebo group received treatment with non-trial statins.

Outcomes

The number of ventilator-free days (VFDs) was not significantly different between the study groups [12.6 days (SD 9.9 days) in the simvastatin group and 11.5 days (SD 10.4 days) in the placebo group; $p = 0.21$]. There was no significant difference in the number of VFDs after adjusting for the baseline $PaO_2 : FiO_2$ ratio {mean difference 1.4 [95% confidence interval (CI) –0.3 to 3.2; $p = 0.10$]}.

There was a larger improvement in the oxygenation index (OI) from baseline in the simvastatin group at day 3 but there were no significant differences in the change in OI or sequential organ failure assessment (SOFA) score from baseline between the groups. There was no significant difference in the number of non-pulmonary organ failure-free days between the groups. There was also no significant difference between the study groups in 28-day mortality.

Mortality at critical care discharge, hospital discharge or 12 months post randomisation were also not significantly different between the groups. For survivors only, the mean duration of ICU stay was 13.9 days (SD 14.4 days) in the simvastatin group and 14.4 days (SD 13.3 days) in the placebo group ($p = 0.71$); and the mean duration of hospital stay was 37.7 days (SD 64.5 days) and 35.4 days (SD 311 days), respectively ($p = 0.66$). There was no significant difference in the probability of breathing without assistance to day 28 or survival. Hazard ratios reported are for the comparison of the placebo group with the simvastatin group.

Prior subgroup analyses did not suggest that the effects of simvastatin were modified by any of the variables investigated. There was no statistically significant interaction between treatment and age ($p = 0.62$), vasopressor requirement ($p = 0.17$) or presence of sepsis ($p = 0.50$).

Simvastatin had no effect on systemic markers of neutrophil activation, systemic inflammation and acute phase response, nor on markers of alveolar epithelial or endothelial activation and injury. Stratifying patients according to their relative baseline degree of cell-specific injury or systemic inflammation did not identify a subgroup that benefited from simvastatin in terms of improving VFDs or 28-day mortality.

Overall AEs related to the study drug were significantly more common in the simvastatin group. The majority were related to elevated levels of CK and hepatic transaminases. Serious adverse events (SAEs) (other than those reported as trial outcomes, e.g. death) were reported in 25 patients (11 patients in the simvastatin group and 14 patients in the placebo group). In total, 28 SAEs were reported (12 in the simvastatin group and 16 in the placebo group), with one patient in the simvastatin group having two SAEs and two patients in the placebo group each having two SAEs.

The return rate of the follow-up questionnaires was 60% for the 3-month questionnaires, 59% for the 6-month questionnaires and 53% for the 12-month questionnaires.

Simvastatin was cost-effective at 1 year compared with placebo for the treatment of ARDS, and was associated with both a small quality-adjusted life-year (QALY) gain (0.064, 95% CI 0.002 to 0.127) and a cost saving (£3601, 95% CI –£8061.10 to £859.28).

Conclusion

Simvastatin, although safe and generally well tolerated, did not increase the number of VFDs or improve mortality in patients with ARDS. However, it was found to be highly cost-effective at 1 year compared with placebo, and was associated with both a small QALY gain and a cost saving.

However, given the small impact on QALYs, as well as the health economics analysis being a secondary outcome of this study, and that the assumptions underpinning the economic benefit are based on the analysis of a subgroup of responders, there is insufficient evidence to support the treatment of patients with ARDS with simvastatin in the NHS. There is a need to confirm if ARDS endotypes that are more likely to benefit from targeted treatment with simvastatin exist. The potential role of simvastatin in the prevention of ARDS in patients at a high risk of developing ARDS has not yet been evaluated.

Trial registration

This trial is registered as ISRCTN88244364.

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This report

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