Defining phenotypes and treatment effect heterogeneity to inform acute respiratory distress syndrome and sepsis trials: secondary analyses of three RCTs

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Scientific summary

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Background

Sepsis and acute respiratory distress syndrome are two heterogeneous acute illnesses associated with a high risk of death. Heterogeneity in this case means inter-individual variation in susceptibility to illness, illness manifestation (phenotype), response to treatment and outcomes, or combinations thereof.

Objectives

We hypothesised that negative randomised controlled trials in sepsis and acute respiratory distress syndrome are due to heterogeneity. A negative trial is one in which differences between the intervention and control arms are statistically non-significant. This hypothesis could be tested in two different ways: first, by assessing heterogeneity of treatment effect, that is whether or not treatment effect varies according to patients' pre-randomisation risk of outcome, and, second, by assessing whether or not distinct patient subgroups (subphenotypes) in which treatment effect differs can be identified in trial populations using clinical and biomarker data.

Methods

We tested our hypothesis using data from three recent randomised controlled trials: two sepsis trials [i.e. the Vasopressin vs Noradrenaline as Initial Therapy in Septic Shock (VANISH) trial and the Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis (LeoPARDS) trial] and one acute respiratory distress syndrome trial [i.e. the Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction (HARP-2) trial]. To test for heterogeneity of the effect on 28-day mortality of vasopressin (Pressyn AR®; Ferring Pharmaceuticals, Saint-Prex, Switzerland), hydrocortisone sodium phosphate (hereafter referred to as hydrocortisone) (Efcortesol™; Amdipharm plc, St Helier, Jersey) and levosimendan (Simdax®; Orion Pharma, Espoo, Finland) in patients with sepsis, and simvastatin in patients with acute respiratory distress syndrome, we used the total Acute Physiology And Chronic Health Evaluation II (APACHE II) score as the baseline risk measurement, comparing treatment effects in patients with baseline APACHE II scores above (high) and below (low) the median using regression models with an interaction between treatment and baseline risk.

Results

When we assessed heterogeneity of treatment effect using multivariable baseline risk of death models, we observed considerable within-trial variation in the baseline risk of death. We observed potential heterogeneity of the treatment effect of simvastatin in acute respiratory distress syndrome, but no evidence of heterogeneity of the treatment effect of vasopressin, hydrocortisone or levosimendan in the two sepsis trials. Our findings could be explained either by true lack of heterogeneity of treatment effect (i.e. no benefit of vasopressin, hydrocortisone or levosimendan relative to comparator in any patient subgroups) or by lack of power to detect heterogeneity of treatment effect.

To assess whether or not distinct phenotypes exist within sepsis and acute respiratory distress syndrome trial populations, we performed latent class analysis using clinical, laboratory and biomarker data. In the VANISH trial we identified two sepsis subphenotypes and found that subphenotype 2 individuals had more inflammation (higher concentrations of interleukin 1 beta, interleukin 6, interleukin 8, interleukin 10,

myeloperoxidase, angiotensin II, troponin, B-type natriuretic peptide and soluble tumour necrosis factor receptor 1) and shorter survival. There were no significant treatment effect differences between the two subphenotypes. In the LeoPARDS trial, we identified three sepsis subphenotypes and found that subphenotype 3 individuals had more inflammation (higher concentrations of interleukin 1 beta, interleukin 6, interleukin 8, interleukin 10, interleukin 17, angiotensin II, troponin, B-type natriuretic peptide, C–C motif chemokine ligand 2 and soluble tumour necrosis factor receptor 1) and were less likely to survive to 90 days. There were no significant between-class differences in the treatment effect of levosimendan, but among all subphenotypes survival was lower in the levosimendan group. A multinomial logit model with interleukin 6, interleukin 8, interleukin 10 and C–C motif chemokine ligand 2 as predictors gave a sensitivity of around 0.9 and a specificity of $\geq$ 0.9 for all subphenotypes. In the HARP-2 trial we again identified two subphenotypes of acute respiratory distress syndrome, and mortality was higher among those with the hyperinflammatory subphenotype than those with the hypoinflammatory subphenotype. Among those with the hyperinflammatory subphenotype, patients treated with simvastatin were more likely than those treated with a placebo to survive to 28 days.

Conclusions

We present a hypothesis-driven secondary analyses of three recent negative randomised controlled trials in sepsis and acute respiratory distress syndrome. Pre-randomisation risk of death varied in all three trial populations, and this variation was associated with differences in the treatment effect of simvastatin. We report three subphenotypes of sepsis and two subphenotypes of acute respiratory distress syndrome, with an association between an inflammatory phenotype and greater risk of death being a consistent finding. These phenotypes have discriminant markers that could form the basis point-of-care tests for future studies. A minimum set of markers to characterise phenotypes in sepsis and acute respiratory distress syndrome should be confirmed with an observational cohort study. Our analysis highlights the value of identifying sepsis and acute respiratory distress syndrome patients with similar marker profiles and the value of stratified medicine in these populations.

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