Novel pharmacotherapy in ARDS

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Disclosures

• GSK; consultancy and participate in research funded by GSK
Novel pharmacotherapy in ARDS

- Current therapies
- Potential future therapies
  - Statins
  - Keratinocyte Growth Factor (KGF)
  - Sialic acid nanoparticles
No pharmacological treatment for ARDS

Ashbaugh et al. described using “a clinical trial of a variety of drugs, respirators and fluid regimens” with limited success

Ashbaugh et al. Lancet 1967
Beta agonists in ARDS

- Increase surfactant release
- Reduce endothelial permeability
- Increase alveolar fluid clearance
- Reduce PMN recruitment and cytokine production
- Enhance epithelial repair

Perkins GD et al. Critical Care 2004;8:25
Salmeterol attenuates acid-induced experimental lung injury

Excess lung water (μl)

![Bar chart showing the comparison between Saline and Salmeterol (10^{-6} M) groups at 2 hours and 4 hours.](chart.png)

- **2 hours**
  - Saline: [Value]
  - Salmeterol (10^{-6} M): [Value]

- **4 hours**
  - Saline: [Value]
  - Salmeterol (10^{-6} M): [Value]

*Significant difference indicated by asterisk.*

McAuley et al. CCM 2004;32:1470
IV salbutamol reduced extravascular lung water

EVLWI  ml kg\(^{-1}\)

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>Salbutamol</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

P=0.7

P=0.04

Perkins et al. AJRCCM 2006;173: 281
Beta agonists in ARDS

• ARDSnet Acute Lung injury Treatment with Albuterol (ALTA)
  – Nebulised salbutamol 5mg vs saline 4 hourly for 10 days

• ICS Beta Agonist Lung Injury Trial (BALTI-2)
  – IV salbutamol 15µg/kg/hr vs saline for 7 days
ALTA
Ventilator free days to day 28

Control: 16.6 days
ALTA: 14.4 days

P=0.13

Matthay et al. AJRCCM 2011
ALTA
Survival to 60 days

Placebo, overall survival
Albuterol, overall survival

Days after Randomization
Probability

Matthay et al. AJRCCM 2011
BALTI-2
Ventilator free days to day 28

Difference -2.7 (-4.7, -0.7)
P<0.001

Gao et al. Lancet 2012
BALTII-2
Survival to 28 days

Kaplan-Meier survival estimates

Survival

Days

Placebo
Salbutamol

P = 0.033

Gao et al. Lancet 2012
Beta blockers in acute respiratory failure

Noveanu at al. Critical Care 2010, 14:R198
Pharmacologic therapies for ARDS

- Glucocorticoids
- Surfactant therapy
- Lisofylline
- Ketoconazole
- Inhaled nitric oxide
- Procysteine
- Neutrophil elastase inhibitor
- Activated protein C
- Omega-3 antioxidants
Neuromuscular blockade

The NEW ENGLAND JOURNAL of MEDICINE

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

Neuromuscular blockade

1326 Patients were assessed for eligibility

→ 986 Were excluded

340 Underwent randomization

→ 178 Were assigned to receive cisatracurium

→ 1 withdrew consent

→ 177 received cisatracurium

→ 177 were included in the analysis

→ 162 were assigned to receive placebo

→ 162 received placebo

→ 162 were included in the analysis
Neuromuscular blockade
Cellular effects of statins
Simvastatin attenuates LPS-induced experimental lung injury

Jacobson et al. AJP Lung 2005;288:L1026
Observational data to support a role for statins in ARDS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Sample Size</th>
<th>Mortality (%)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No statin</td>
<td>n = 164</td>
<td>34%</td>
<td>OR 0.27 (0.06 - 1.21)</td>
<td>0.09</td>
</tr>
<tr>
<td>Statin</td>
<td>n = 24</td>
<td>21%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Irish Critical Care Trials Group. Critical Care 2008;12:R30
Simvastatin in the inhaled LPS model of lung injury

Treatment with a clinically relevant dose of simvastatin will reduce pulmonary inflammation induced by LPS inhalation in humans

Shyamsundar et al. AJRCCM 2009 179:1107-1114
Simvastatin decreases pulmonary neutrophilic activity following LPS inhalation

\[ \* p < 0.05 \text{ vs placebo} \]
Simvastatin pre-treatment reduces systemic inflammation following LPS inhalation

* p < 0.05 vs placebo
HMGCoA reductase inhibition in ALI to Reduce Pulmonary oedema (HARP)

- Proof of concept single centre trial
- Prospective double blind
- Within 48 hours of onset of ALI
- Randomised to simvastatin 80mg or placebo for up to 14 days
- Outcomes:
  - Extra-vascular lung water
  - Pulmonary function and systemic organ failure
  - Safety
  - Biological markers in plasma and BAL
Simvastatin improves oxygenation index
Simvastatin improves sequential organ failure assessment (SOFA) score.
Simvastatin decreases bronchoalveolar lavage IL-8

![Graph showing the decrease in IL-8 levels with Simvastatin compared to Placebo.](image)

- **p = 0.89**
- **p = 0.05**
HARP-2

Patients with ALI assessed for eligibility
N=2500 (approx)

Excluded
Failure to fulfil inclusion and exclusion criteria
Consent declined

Within 48 hours of onset of ALI

Randomised to HARP study
N=540

Placebo
N=270

Simvastatin 80mg
N=270

Loss to follow-up for primary outcome and withdrawal of consent after recruitment
Estimated 3%

28 days

Analysis
N=524
Primary outcome
Ventilator free days
Repair phase in ARDS

 Ware and Matthay. NEJM 2001;50:204
Mesenchymal stem cells (MSCs) decrease pulmonary inflammation

Lee JW et al. PNAS 2009 106:16357-62

<table>
<thead>
<tr>
<th>Condition</th>
<th>Absolute Neutrophil Counts</th>
<th>Absolute Neutrophil Counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Lung Lobe</td>
<td>$9 \pm 6 \times 10^6$ cells</td>
<td>$25 \pm 25 \times 10^6$ cells</td>
</tr>
<tr>
<td>LPS Lung Lobe</td>
<td>$13 \pm 11 \times 10^6$ cells</td>
<td></td>
</tr>
<tr>
<td>LPS + MSC Lung Lobe</td>
<td>$6 \pm 5 \times 10^6$ cells</td>
<td></td>
</tr>
<tr>
<td>LPS + MSC conditioned media Lung Lobe</td>
<td>$13 \pm 11 \times 10^6$ cells</td>
<td></td>
</tr>
</tbody>
</table>

* $P = 0.1017$

$P = 0.0171$
rhKGF restores the protective effect of conditioned medium treated with siRNA for KGF.

* P<0.001 vs. Control
√ P<0.03 vs. LPS (0.1 mg/kg)
# P<0.01 vs. LPS + CM MSC (KGF siRNA)
KGF improves alveolar fluid clearance

![Bar chart showing the effect of KGF on alveolar fluid clearance (in %/h) with error bars for control and + rhKGF conditions. The chart indicates a significant improvement with a * symbol.]
KGF in the inhaled LPS model of lung injury

Treatment with a clinically relevant dose of KGF will induce pro-epithelial repair factors in a human \textit{in vivo} model of acute lung injury.

- Day 1-3: KGF 60µg/kg or Placebo
- Day 3: FEV1 Plasma LPS inhalation
- 6 hr after KGF: FEV1 BAL/Plasma
- 18 hrs: FEV1 Plasma
KGF increases alveolar surfactant protein D

\[ p = 0.003 \]
KGF increases apoptotic epithelial cell phagocytosis

\[ p = 0.02 \]
KGF in Acute lung injury to REduce pulmonary dysfunction (KARE)

Patients with ALI assessed for eligibility

Excluded
Failure to fulfil inclusion and exclusion criteria
Consent declined

Randomised
N=60

Within 48 hours of onset of ALI

Placebo

KGF 60mcg/kg for up to 7 days

Loss to follow-up for primary outcome and withdrawal of consent after recruitment
Estimated 3%

Primary outcome
Oxygenation index

Secondary outcomes
Pulmonary and non-pulmonary organ function
Safety

Mechanistic studies
Siglec-activated immunosuppression

Pro-inflammatory gene activation

TLR

CD14

MyD88 dependent and independent cascades

IL-6

TNFα

LPS

Siglec receptors

Boyd and al, Journal of Immunology 2009
Siglec-activated immunosuppression

- **LPS**
- **TLR**
- **CD14**
- **IL-6**
- **TNFα**
- **Siglec receptors**

MyD88 dependent and independent cascades

Pro-inflammatory gene activation
NANA-NP decreases TNFα from LPS treated human macrophages
NANA-NP extends survival in a caecal ligation and puncture model

\[ n=10 \]
\[ p<0.0006 \]
Conclusions

• Salbutamol harmful
• Potential role of neuromuscular blockade
• Simvastatin improves pulmonary and non-pulmonary organ dysfunction and inflammation and is well tolerated
  – Large clinical studies now ongoing
• Potential novel therapies
Acknowledgements

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