Drugs are best?

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ARDS – New treatments
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Disclosures

• Consultancy
  – SOBI
  – GSK
  – Peptinnovate
  – Bayer

• Patent; Sialic acid PLGA nanoparticles
Drugs are best?

• Current evidence
  – Statins
  – Keratinocyte growth factor

• Potential future therapies
  – Sialic acid nanoparticles
  – Aspirin
  – Interferon-beta-1a
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
Boyle et al. BMC Medicine 2013;11:166
ICS Beta Agonist Lung Injury Trial (BALTI-2)

– IV salbutamol 15 µg/kg/hr vs saline for 7 days
– Planned 1350 patients
– Current 310

Suspended

Neuromuscular blockade

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 Withdraw 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

HR 0.68 (95% CI 0.48 to 0.98; P=0.04)
Simvastatin in the Acute Respiratory Distress Syndrome

Daniel F. McAuley, M.D., John G. Laffey, M.D., Cecilia M. O’Kane, Ph.D., Gavin D. Perkins, M.D., Brian Mullan, M.B., T. John Trinder, M.D., Paul Johnston, M.B., Philip A. Hopkins, Ph.D., Andrew J. Johnston, M.D., Cliona McDowell, M.Sc., Christine McNally, B.A., and the HARP-2 Investigators, for the Irish Critical Care Trials Group*
Unassisted breathing

A Unassisted Breathing

- Simvastatin
- Placebo

Probability of Unassisted Breathing

Hazard ratio, 0.84 (95% CI, 0.68–1.03)
P=0.09

Days

No. at Risk
Simvastatin
Placebo

<table>
<thead>
<tr>
<th>Days</th>
<th>Simvastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>258</td>
<td>279</td>
</tr>
<tr>
<td>7</td>
<td>166</td>
<td>178</td>
</tr>
<tr>
<td>14</td>
<td>87</td>
<td>102</td>
</tr>
<tr>
<td>21</td>
<td>43</td>
<td>60</td>
</tr>
<tr>
<td>28</td>
<td>19</td>
<td>33</td>
</tr>
</tbody>
</table>

NEJM 2014:371;1695-703
Survival

- Probability of Survival
- Hazard ratio, 1.25 (95% CI, 0.88–1.76)
  \[ P=0.20 \]

- Days
- No. at Risk
  - Simvastatin: 259, 238, 217, 208, 202
  - Placebo: 280, 250, 231, 220, 205

NEJM 2014:371;1695-703
Rosuvastatin for Sepsis-Associated Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute
ARDS Clinical Trials Network*

ABSTRACT
Survival
# Pipeline of treatment for ARDS

<table>
<thead>
<tr>
<th>Phase</th>
<th>Monoclonal antibody</th>
<th>Proteins/peptides</th>
<th>Small molecules</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-clinical</td>
<td>Anti-IL-8 ab Anti-CD14</td>
<td>Elafin</td>
<td>NE inhibitor Imatinib</td>
<td>siRNA Sialic acid Nanoparticle</td>
</tr>
<tr>
<td>Phase 1</td>
<td></td>
<td>ACE2 Nebulised heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2</td>
<td>Anti-TNF ab Anti-TF ab</td>
<td>KGF GM-CSF</td>
<td>p38 MAPK inhibitor TRPV4 inhibitor</td>
<td>Aspirin Vitamin D Cell therapy Steroids</td>
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<tr>
<td>Phase 3</td>
<td></td>
<td></td>
<td></td>
<td>Interferon beta 1α</td>
</tr>
</tbody>
</table>
Siglec-activated immunosuppression

LPS

IL-6

TNFα

Pro-inflammatory gene activation

MyD88 dependent and independent cascades

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

Pro-inflammatory gene activation

IL-6

TNFα

LPS

CD14

TLR

MyD88 dependent and independent cascades

Siglec receptors

Pro-inflammatory gene activation
Sialic acid decorated PLGA nanoparticles (Sialic acid-NP)

<table>
<thead>
<tr>
<th></th>
<th>NP non conjugated</th>
<th>NP conjugated with Sialic acid (SNP)</th>
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<tbody>
<tr>
<td>size</td>
<td>151 nm ± 10</td>
<td>152 nm ± 13</td>
</tr>
<tr>
<td>zeta potential</td>
<td>0.4 mv ± 0.4</td>
<td>0.3 mv ± 0.2</td>
</tr>
<tr>
<td>Sialic acid density</td>
<td>15 µg/mg PLGA</td>
<td></td>
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</table>
Sialic acid-NP extends survival in a caecal ligation and puncture sepsis model

n=10
p<0.0006

Spence and Greene et al. Science Translational Medicine 2015 7:303ra140
Sialic acid-NP decrease TNFα from LPS treated human macrophages
Sialic acid-NP decrease pulmonary oedema in human EVLP model of ARDS

Spence and Greene et al. Science Translational Medicine 2015 7:303ra140
TAKE TWO STEM CELLS AND CALL ME IN THE MORNING.
KGF improves alveolar fluid clearance in a human ex-vivo perfused lung model of ARDS

Lee JW et al. PNAS 2009 106:16357-62
KGF increases apoptotic epithelial cell phagocytosis

Shyamsundar et al. AJRCCM 2014 189:1520–1529
KGF in Acute lung injury to REDuce pulmonary dysfunction (KARE)

Hypothesis

• Does treatment with rhKGF improve surrogate physiological outcomes and is safe in patients with ALI?

KARE trial design

- Phase 2 trial
- 2 centres
- Randomised, double blind, placebo controlled
- Start of treatment within 72 hours of onset of ALI
- Stratified for sepsis requiring vasopressors
- rhKGF (60mcg/kg) or placebo (1:1) for up to 6 days
- Primary outcome
  - Oxygenation index (OI)
Screening, randomization and follow-up of study participants

368 assessed

60 randomized

29 were allocated to KGF
0 did not receive KGF

No patients lost to follow-up

29 were included in the analysis of the primary outcome

31 were allocated to placebo
0 did not receive placebo

No patients lost to follow-up

31 were included in the analysis of the primary outcome
## Baseline demographics

<table>
<thead>
<tr>
<th></th>
<th>KGF</th>
<th>Placebo</th>
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<tbody>
<tr>
<td><strong>Age – yr</strong></td>
<td>55.6±17.5</td>
<td>61.0±15.4</td>
</tr>
<tr>
<td><strong>Male sex – no. (%)</strong></td>
<td>17 (58.6)</td>
<td>20 (64.5)</td>
</tr>
<tr>
<td><strong>APACHE II score</strong></td>
<td>18.8±9.0</td>
<td>22.7±6.5</td>
</tr>
<tr>
<td><strong>LIS score</strong></td>
<td>2.0±0.6</td>
<td>2.2±0.6</td>
</tr>
<tr>
<td><strong>Mean arterial pressure - mmHg</strong></td>
<td>63.5±11.2</td>
<td>64.5±10.3</td>
</tr>
<tr>
<td><strong>Tidal Volume - ml/kg PBW</strong></td>
<td>7.9±2.6</td>
<td>8.3±2.1</td>
</tr>
<tr>
<td><strong>PEEP - cm H2O</strong></td>
<td>7.3±2.2</td>
<td>8.5±2.4</td>
</tr>
<tr>
<td><strong>Plateau pressure - cm H2O</strong></td>
<td>23.3±4.7</td>
<td>24.0±3.3</td>
</tr>
<tr>
<td><strong>Oxygenation index - kPa</strong></td>
<td>66.8±43.0</td>
<td>73.1±39.5</td>
</tr>
<tr>
<td><strong>PaO2/FiO2 ratio - kPa</strong></td>
<td>22.5±9.9</td>
<td>20.2±6.8</td>
</tr>
<tr>
<td><strong>Compliance - ml/cm H2O</strong></td>
<td>40.1±16.3</td>
<td>43.9±15.8</td>
</tr>
<tr>
<td><strong>SOFA score</strong></td>
<td>9.2±3.6</td>
<td>8.4±2.9</td>
</tr>
</tbody>
</table>
Ventilator Free Days

VFDs to day 28

P = 0.001 vs placebo

16.1 ± 8.6
7.9 ± 8.7
Mortality at 28 days

28-day mortality (%)

P = 0.05 vs placebo

9.7

31.0
Mortality at 60 and 90 days

P = 0.02 vs placebo

P = 0.02 vs placebo
Duration of ventilation in survivors

Duration of ICU stay (days)

Placebo
KGF

12.2±5.5
18.7±10.5

P = 0.01 vs placebo
Mechanism of action of aspirin
## Aspirin associated with reduced mortality in ARDS

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02 (1.00 – 1.05)</td>
<td>0.08</td>
</tr>
<tr>
<td>APACHE II Score</td>
<td>1.07 (1.02 – 1.13)</td>
<td>0.01</td>
</tr>
<tr>
<td>Aspirin Use</td>
<td>0.42 (0.18 – 0.96)</td>
<td>0.04</td>
</tr>
<tr>
<td>PaO2 / FiO2 ratio</td>
<td>0.97 (0.93 – 1.00)</td>
<td>0.09</td>
</tr>
<tr>
<td>Vasopressor Use</td>
<td>2.09 (1.05 – 4.16)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Effect of Aspirin on REDucing INflammation in an in vivo model of Acute lung injury - ARENA

Double-blind Randomised Placebo controlled Aspirin 75/1200mg

FEV1 Bronchoscopy & BAL Plasma

FEV1 Plasma

6 hours 18 hours

Day 7 FEV1 Plasma
LPS inhalation using a breath activated nebulizer
Aspirin in human EVLP model

1 hr

- Re-warm CPAP

4 hrs

- Add 100 ml fresh whole blood
- Randomised to aspirin or placebo
- Instill 6mg LPS

BAL (Baseline)

Surgical preparation of lung
Aspirin reduces BAL neutrophilia

**ARENA**

- **Placebo**
- **Aspirin**

**EVLP model**

- **Placebo**
- **Aspirin**

*p*=0.03

*p*=0.02
Aspirin reduces BAL inflammatory cytokines

**BAL TNFα (pg/ml)**

- Placebo: Lower TNFα levels
- Aspirin: Higher TNFα levels

**p=0.04**

**BAL IL-6 (pg/ml)**

- Placebo: Lower IL-6 levels
- Aspirin: Higher IL-6 levels

**p=0.03**
Aspirin reduces histological injury

(i) (ii) (iii) (iv)

Histological injury score (AU)

Placebo

Aspirin
Aspirin to prevent ARDS

Lung Injury Prevention with Aspirin (LIPS-A): a protocol for a multicentre randomised clinical trial in medical patients at high risk of acute lung injury

Salicylic acid as a Treatment for ARDS
STAR Study

Daily screening in ICU of mechanical ventilated patients
Does the patient have a diagnosis of ARDS?
(Onset < 7 days AND PaO₂/FiO₂ ratio ≤ 40kPa on PEEP ≥ 5 cmH₂O and bilateral infiltrates on CXR and not due to cardiac disease)

Patients with ARDS assessed for eligibility

Consent obtained from the Per LR or Prof LR

Randomised
N=60

Placebo
N=30

Aspirin
N=30

Data collection
Pulmonary and non-pulmonary organ function
ICU and hospital outcomes
Safety
BAL, blood and urine samples
The effect of intravenous interferon-beta-1a (FP-1201) on lung CD73 expression and on acute respiratory distress syndrome mortality: an open-label study


Interferon-beta-1a

Conclusions

- Currently no effective therapy
- Novel therapies
- Prevention versus treatment
Acknowledgements

- C Scott
- J Laffey
- G Curley
- M Matthay
- G Perkins
- D Thickett

Efficacy and Mechanism Evaluation programme

MRC Medical Research Council
National Institute for Health Research

Department for Employment and Learning
www.delni.gov.uk

The Intensive Care Society

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BJA British Journal of Anaesthesia

Northern Ireland CHEST HEART & STROKE
Critical Care Reviews Meeting 2016
Titanic Centre, Belfast
Friday January 29th 2016
Discussing the Biggest Critical Care Studies of 2015
with their Chief Investigators

The Great Debate
Vincent vs Gattinoni: RCTs are Killing Critical Care

2016’s Big Trials
Holcomb: PROPRR
Young: HEAT
SPLIT
Walsh: ABLE (UK)
RECOVER
Gordon: VANISH
Mac Sweeney: The Best of the Rest

How I Manage.....
Holcomb: Traumatic Haemorrhage
Young: Pyrexia in ICU
Walsh: Anaemia in ICU
Vincent: Septic Shock
Gattinoni: Hypoxaemic Respiratory Failure

John Hinds’ Trauma Lecture
Burns: Trauma Care - Back to the Future

An Informal Chat with........
Holcomb | Vincent | Walsh | McAuley
Burns | Gordon | Young | Mac Sweeney | You

Speakers
Young
Gattinoni
Walsh
Burns
Vincent
McAuley
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