Treatment of Patients with Severe Pulmonary Alveolar Proteinosis using Inhaled GM-CSF

Dr Cliff Morgan
Dr Greg Keir

Royal Brompton Hospital
London, UK
Pulmonary alveolar proteinosis

Accumulation of lipoproteinaceous surfactant material within the alveolar spaces

- Primary (90%)
- Secondary
  - haematological malignancy, inorganic dust inhalation
  - Congenital

Rare
- estimated prevalence 3-4 per 1,000,000

Median age at diagnosis: 39 years old

Male predominance
Natural History

Insidious symptom onset over several months with progressive dyspnoea and cough

Spontaneous improvement ( < 10 % )
Stable with persistent symptoms
Progressive deterioration

5 year survival 75 %
- progressive respiratory failure
- uncontrolled infection

Seymour et al. Am J Respir Crit Care Med 2002;166:215
Professor Andrew Nicholson
Professor Bryan Corrin
Pathology of the Lung (Elsevier)
Treatment

Whole lung lavage
- improved survival rate
- variable duration of benefit: 15-36 months

But
- Inpatient
- general anaesthesia
- Double lumen endotracheal tube
Alveolar surfactant

Surfactant is synthesized, stored and secreted into the alveolar space by type II pneumocytes.

Alveolar surfactant functions
- prevent alveolar collapse by reducing surface tension at the air-liquid interface
- opsonize microbial pathogens

Alveolar macrophages play a vital role in the clearance of surfactant
Pathobiology of Primary PAP:
The role of GM-CSF

Granulocyte-monocyte colony stimulating factor (GM-CSF)
- stimulation of myeloid lineage haematopoiesis
- ‘primes’ neutrophils for host defence functions
- required for the terminal differentiation of alveolar macrophages

1990’s
GM-CSF gene knock-out mice developed a disorder similar to acquired PAP in humans

*Dranoff et al Science 1994; 264*
Pathobiology of Primary PAP

Primary PAP
- high levels of neutralizing IgG autoantibodies against GM-CSF

Alveolar macrophage defects in chemotaxis, adhesion, phagocytosis, microbicidal activity and phagolysosome fusion
  Trapnell et al. *NEJM* 2003;349:2527

Recent evidence that GM-CSF replacement helps to correct the underlying macrophage dysfunction
Inhaled GM-CSF at Royal Brompton Hospital

40 year history of treating patients with PAP using whole lung lavage

November 2006
- Failure to achieve lasting remission following 6 WLL treatments

Considered for a trial of iGM-CSF
- delivered via I-neb AAD (Adaptive Aerosol Delivery) System
I-neb Adaptive Aerosol Delivery System
( Philips Respironics )

AAD technology
- delivers aerosol only during inhalation

Target inhalation mode ( TIM )
- minimizes drug impaction in upper airway

Medication chamber residual volume of 0.1 ml

Effectively doubles the delivered drug dose
Inhaled GM-CSF at Royal Brompton Hospital

Single-centre, single-arm study in patients with primary PAP

Eligibility
- proven diagnosis of PAP
- failure to achieve lasting remission following 6 WLL treatments

All cases discussed by a multi-disciplinary team prior to study inclusion

Informed consent obtained
Inhaled GM-CSF at Royal Brompton Hospital

Trained in use of I-neb AAD at day one

Commenced GM-CSF 250 µg / day ( 4 treatment days, 4 rest days )

3 monthly assessments by MDT
   - GM-CSF dose reduced as dictated by clinical response
     ( initially by omitting treatment days )
## Results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Male (m)/Female (f)</th>
<th>Age at start of inhaled GM-CSF (years)</th>
<th>Number of whole Lung Lavages before inhaled GM-CSF</th>
<th>Number of whole Lung Lavages after inhaled GM-CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>m</td>
<td>38</td>
<td>70</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>f</td>
<td>41</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>f</td>
<td>21</td>
<td>2*</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>f</td>
<td>49</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>f</td>
<td>24</td>
<td>64</td>
<td>0</td>
</tr>
</tbody>
</table>
Results

5 patients enrolled

All showed improvements in
  - lung function testing
  - dyspnoea and exercise tolerance
  - oxygen requirements

All showed a dramatic reduction in requirements for WLL

No side-effects or adverse events were observed
August 2009:
Commenced GM-CSF

November 2009:
Review
In Conclusion ...

In patients with severe pulmonary alveolar proteinosis, treatment with inhaled GM-CSF results in:
- long-lasting improvement in clinical measures
- reduced need for whole lung lavage
- reduced health care costs
In patients with severe pulmonary alveolar proteinosis, treatment with inhaled GM-CSF results in:
- long-lasting improvement in clinical measures
- reduced need for whole lung lavage
- reduced health care costs

Thank You