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 %)

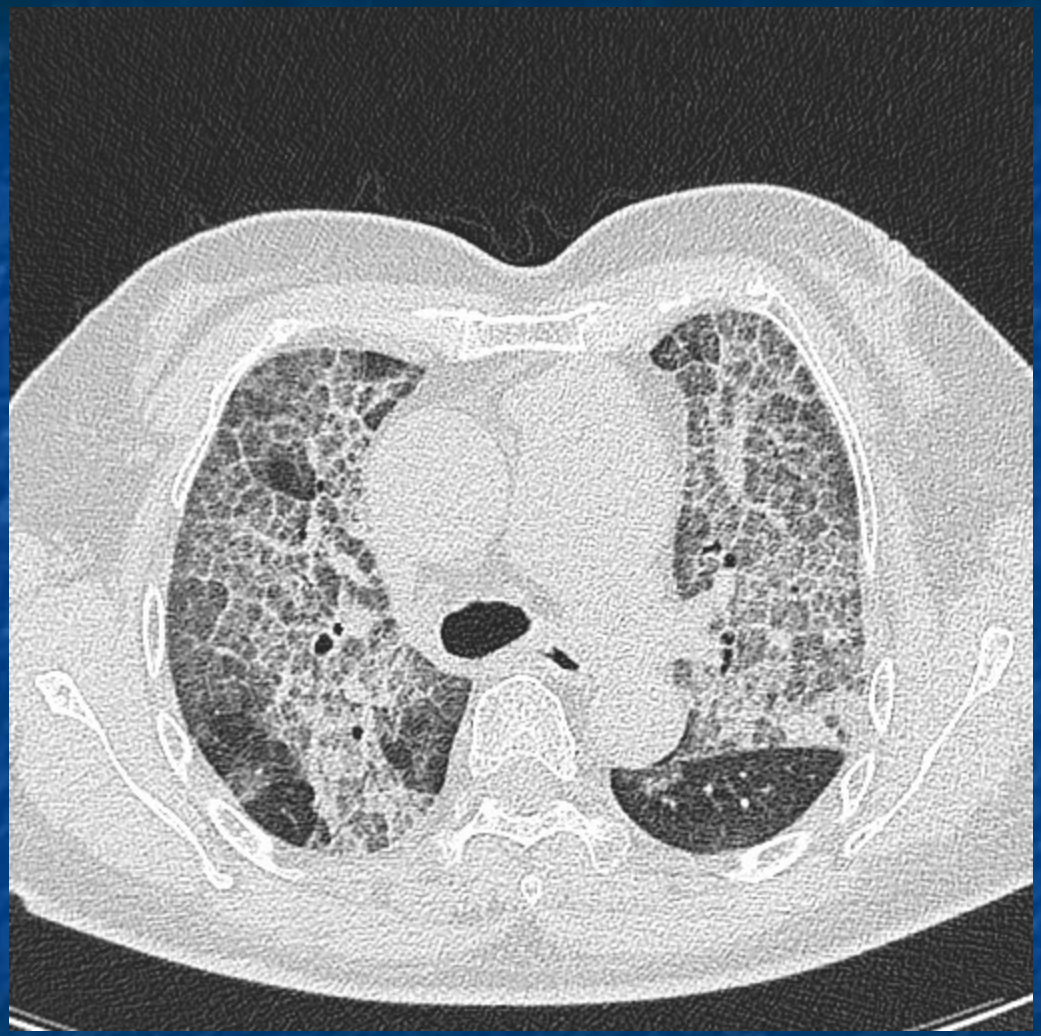
Stable with persistent symptoms

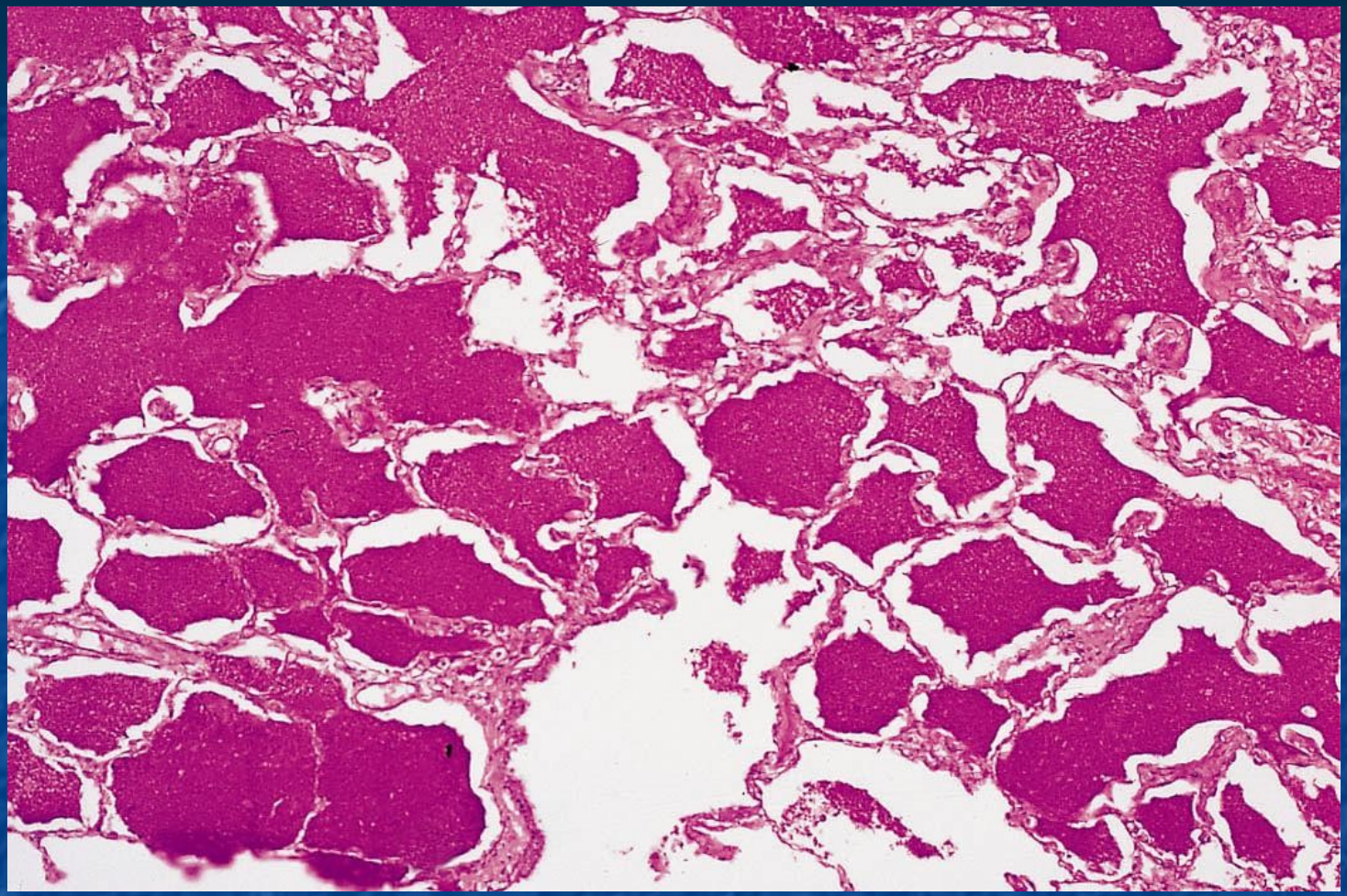
Progressive deterioration

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)

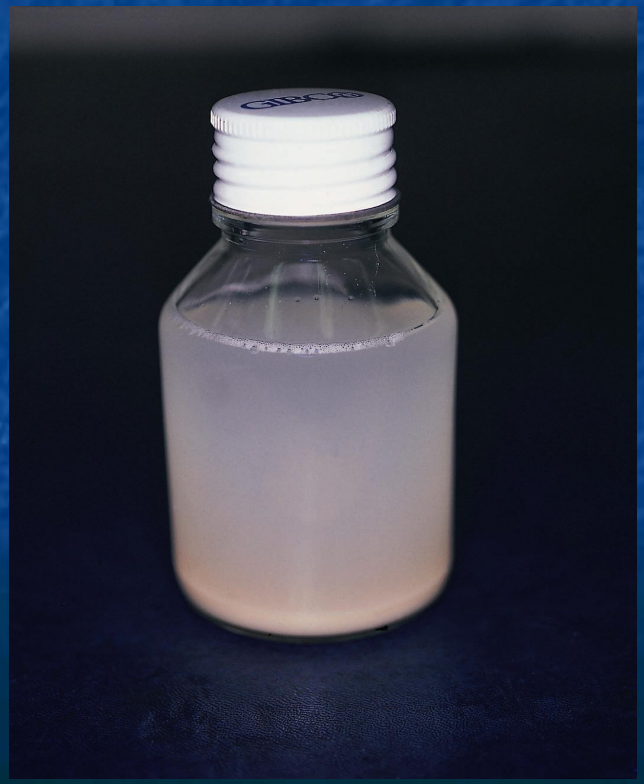
Treatment

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

Kitamura et al . *J Exp Med 1999;190:875*

Alveolar macrophage defects in chemotaxis, adhesion, phagocytosis, microbicidal activity and phagolyosome 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

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

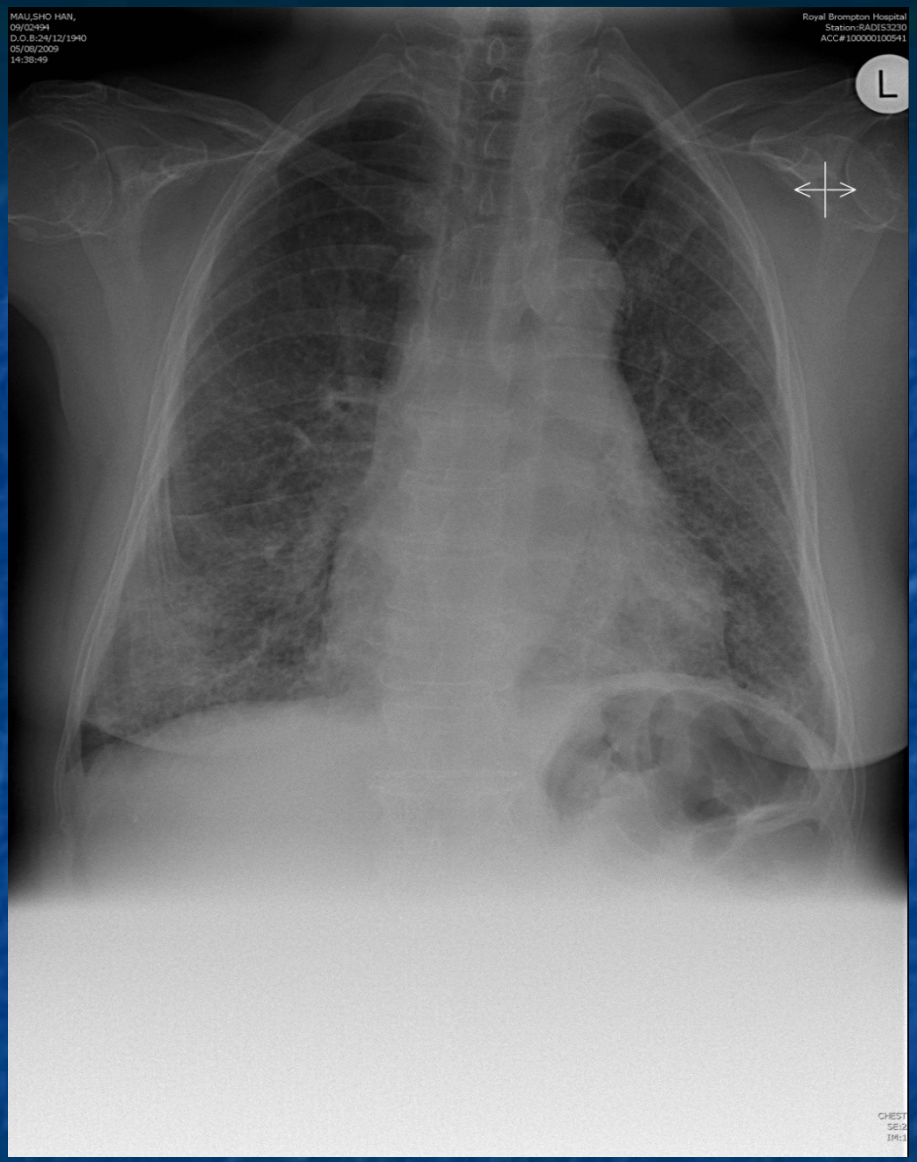
Results

5 patients enrolled

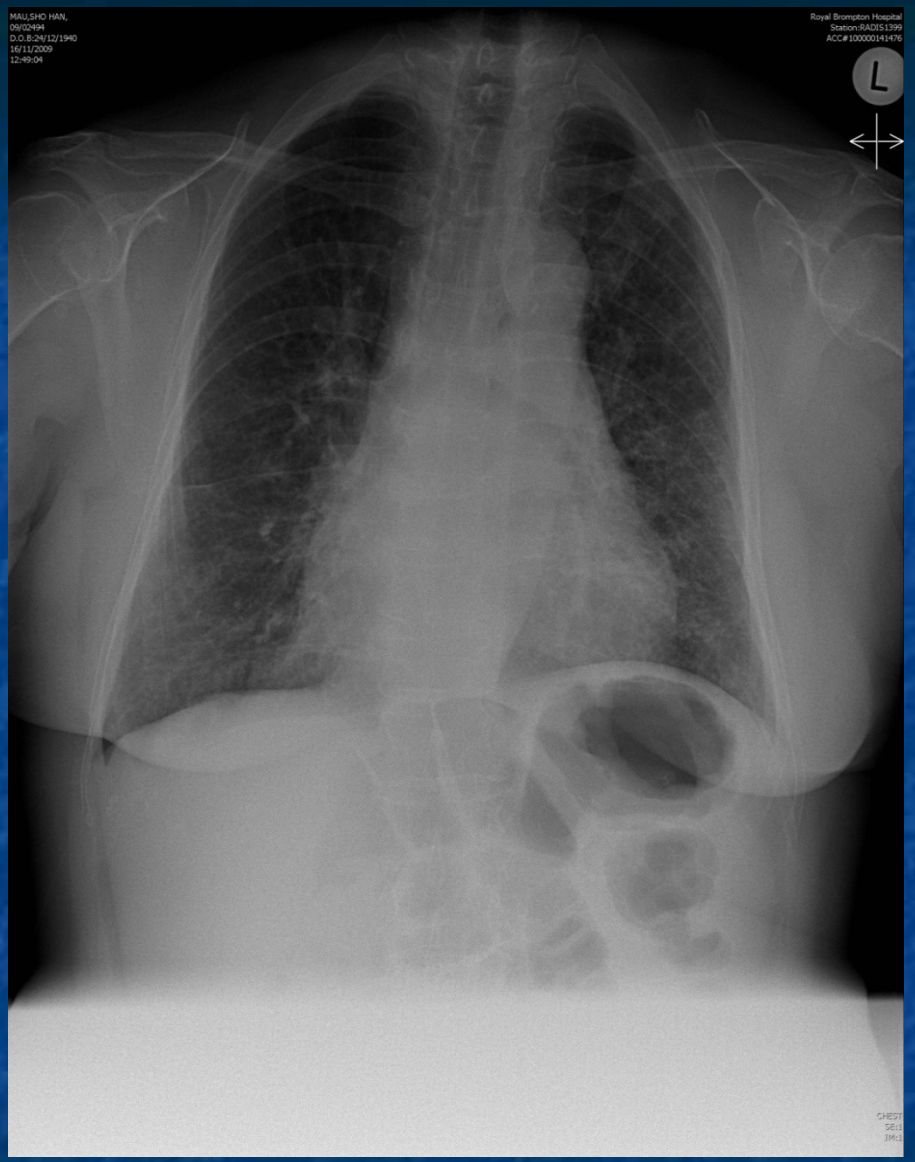
All showed improvements in
- lung function testing
- dyspnoea and exercise tolerance
- oxygen requirements

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

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Thank You