TRIALS AND THE TYRANNY OF ARBITRARY CUT-OFFS IN IDIOPATHIC PULMONARY FIBROSIS

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This case highlights the challenges physicians face in treating patients in the early stages of interstitial lung disease (ILD), when treatment is likely to have the greatest impact. In this case, of a patient with a probable diagnosis of usual interstitial pneumonia (UIP) but who had well-preserved lung function with no evidence of any clear decline, the problems associated with treating these patients are clear. In particular, the case highlights some of the difficulties of applying clinical trial evidence to a real-world situation, especially within a restrictive regulatory environment.
MEDICAL HISTORY AND TESTS

Initial visit: January 2011

- Male, 75 years old
- Ex-smoker:
  - 16 pack-years
- Occupation:
  - Former car factory worker and plumber; possible asbestos exposure but not thought to be significant
- Pets:
  - Owned budgerigars (small, caged pet birds) for 6 years but did not clean out the cages
MEDICAL HISTORY AND TESTS

Initial visit: January 2011

• Lung fibrosis (evidence of fibrosis on chest x-ray)

• Comorbidities:
  − Actinic keratosis, chronic kidney disease, gastroesophageal reflux disease, homonymous hemianopia (following a cardiovascular accident), hypertension, pulmonary embolism, spina bifida and type 2 diabetes; permanent pacemaker fitted

• Current medications:
  − Amlodipine, ASA, candesartan, bendroflumethiazide, doxazosin, insulin, lansoprazole, metformin and simvastatin
MEDICAL HISTORY AND TESTS

Initial visit: January 2011

- Physical examination:
  - On examination the patient appeared well
  - The patient had a dry cough (with a small amount of sputum) and experienced breathlessness on walking approx. 200 m
  - There was no orthopnoea and the patient was able to manage a flight of stairs reasonably easily
  - Oxygen saturation was 96%
  - There was no clubbing
SOUNDS

Initial visit: January 2011
- Bibasal fine inspiratory crackles on lung auscultation
LUNG FUNCTION

Lung function measurements (January 2011)
• Results of initial tests were all within the normal parameters
LUNG FUNCTION

Lung function measurements (January 2011)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Absolute</th>
<th>% of predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>2.84</td>
<td>104% predicted</td>
</tr>
<tr>
<td>FVC</td>
<td>3.74</td>
<td>103% predicted</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td>0.76</td>
<td>92% predicted</td>
</tr>
<tr>
<td>TLC</td>
<td>5.43</td>
<td>80% predicted</td>
</tr>
<tr>
<td>DL&lt;sub&gt;co&lt;/sub&gt;</td>
<td>4.7</td>
<td>57% predicted</td>
</tr>
<tr>
<td>K&lt;sub&gt;co&lt;/sub&gt;</td>
<td>1.0</td>
<td>86% predicted</td>
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</table>
Antibodies (January 2011)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear antibody</td>
<td>Negative</td>
</tr>
<tr>
<td>Budgerigar precipitins</td>
<td>Negative</td>
</tr>
<tr>
<td>Pigeon precipitins</td>
<td>Negative</td>
</tr>
</tbody>
</table>

- There were no signs of infection or connective tissue disease
Laboratory results (January 2011)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematocrit</td>
<td>0.45</td>
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<tr>
<td>Haemoglobin</td>
<td>14.2 g/dl</td>
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<tr>
<td>White blood cell count</td>
<td>9 x 10^9 /l</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>6.0 x 10^9 /l</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1.5 x 10^9 /l</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.3 x 10^9 /l</td>
</tr>
</tbody>
</table>
IMAGING

Chest X-ray (February 2011)

- Classic appearance of interstitial shadowing with “haziness” around the heart

→ Pathology characteristic of ILD
IMAGING

HRCT scan (February 2011)
• Subpleural distribution of reticular shadows
• Basal predominance
• No pleural plaques, no evidence of ground glass opacities
• Minor honeycombing

Following review by the ILD multidisciplinary team, the patient was diagnosed with probable UIP*

*As the patient had many co-morbidities, it was felt that surgical biopsy would be high risk and the decision was taken not to proceed with this.
1. HRCT (February 2011)

- Predominantly subpleural reticular changes with a basal predominance (arrow) and mild honeycombing

- No pleural plaques or ground glass opacities
2. HRCT (February 2011)
LUNG FUNCTION

Lung function measurements (February 2011)

• Well-preserved lung function with no clear evidence of decline

• However, following a decline in lung function over the following 8-month period (to October 2011), N-acetylcysteine (NAC) 600 mg three times daily was prescribed

• Initially, NAC appeared to be well tolerated, the patient’s cough improved and he said he felt better; in addition, the patient’s lung function had stabilised after 18 months
LUNG FUNCTION

Lung function measurements (October 2011–June 2014)

<table>
<thead>
<tr>
<th>Time from diagnosis (months)</th>
<th>FVC</th>
<th>FEV₁</th>
<th>TLC</th>
<th>DL&lt;sub&gt;co&lt;/sub&gt;</th>
<th>K&lt;sub&gt;co&lt;/sub&gt;</th>
</tr>
</thead>
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<tr>
<td>0</td>
<td>3.74</td>
<td>2.94</td>
<td>–</td>
<td>–</td>
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<tr>
<td>4</td>
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<td>5.2</td>
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</tr>
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<td>14</td>
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</tr>
<tr>
<td>20</td>
<td>3.18</td>
<td>2.49</td>
<td>4.19</td>
<td>3.9</td>
<td>1.07</td>
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<tr>
<td>24</td>
<td>3.08</td>
<td>2.36</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>28</td>
<td>3.11</td>
<td>2.3</td>
<td>4.6</td>
<td>3.8</td>
<td>1.07</td>
</tr>
<tr>
<td>31</td>
<td>3.07</td>
<td>2.39</td>
<td>4.3</td>
<td>3.6</td>
<td>1.03</td>
</tr>
</tbody>
</table>
LUNG FUNCTION

Additional information (June 2014)

- At follow-up, the patient’s lung function had significantly deteriorated over the subsequent years. In addition, the patient reported considerably worse cough
  - Marked decline in DLco
In Idiopathic pulmonary fibrosis which of the following is true?

- An FVC above 80% predicted precludes the diagnosis? **False**
- Gastro-oesophageal reflux disease is rarely present **False**
- Ground-glass opacities on HRCT are key to diagnosing usual interstitial pneumonia **False**
- The variability of testing of FVC is ~8% **True**
ANSWERS

Answer 1
Forced vital capacity is a valuable measure to quantify disease progression in IPF.\(^1\) However, due to the high-degree of variability in the test (~5-10%) there has been much discussion within the clinical community on how best to evaluate change.\(^2\)

DIAGNOSIS

1. Diagnostic tests revealed evidence of ILD
   → Following multidisciplinary evaluation, the patient was diagnosed with IPF

2. Patient experienced a gradual decline in lung function between 2011 and 2014

3. A repeat HRCT scan in December 2014 demonstrated progressive fibrosis and traction bronchiectasis

4. Further therapy options were limited since the patient was not eligible for IPF specific treatments (FVC values above the upper threshold as of 2014, in the country of reference)
QUESTION 2

In patients with idiopathic pulmonary fibrosis which of the following is true?

- Treatment with N-acetylcysteine has been proven to be efficacious False
- Treatment with prednisolone and azathioprine slows down progression of the disease False
- In the UK, treatment of patients with IPF specific medication is only reimbursed (as of 2014) in patients with an FVC between 50-80% predicted True
- Treatment with N-acetylcysteine alone slows down progression of disease False
Answer 2

According to the 2015 NICE guidance in the UK, IPF specific treatments are only available to those patients who have a forced vital capacity between 50% and 80% predicted.¹

LEARNINGS FROM THE CASE

1. Identify potential predisposing factors for ILD in order to aid early diagnosis
2. Encourage the involvement of the ILD multidisciplinary team to help facilitate an accurate diagnosis
3. Understand what treatment options are available (and current restrictions on their use) within each country of practice