Mepolizumab in refractory eosinophilic asthma

In a recent Lung Alert reviewing our study of mepolizumab in severe eosinophilic asthma,1 Barratt states that the study population represented a minority of patients with asthma and that they had corticosteroid-resistant disease.2 These comments require clarification. While we accept that the population studied by us represents about 3% of the total asthma population, it was 30% of patients with refractory asthma, a population with the greatest unmet need for new treatment. In contrast, only 13% of this population meet criteria set out by the manufacturer for treatment with omalizumab, and only a minority of these meet NICE criteria for use of the agent.

Our patients were corticosteroid resistant in the sense that they continued to have morbidity despite high-dose inhaled corticosteroids and, in many cases, oral prednisolone. However, many responded well to higher-dose oral prednisone, and a post hoc analysis showed that those who did tended to do better with mepolizumab treatment (table 1). In contrast, there was a poorer response to mepolizumab in patients with marked bronchodilator reversibility. The clear implication is that mepolizumab works best in patients who have airflow limitation and symptoms as a result of corticosteroid-resistant airflow inflammation rather than airway smooth muscle contraction. Interestingly, the exact opposite relationship between acute bronchodilator response and clinical efficacy has recently been reported for treatment with anti-tumour necrosis factor alpha,3 a treatment which targets airway smooth muscle function but not eosinophilic airway inflammation.4 It therefore appears that the population that does well with these different anti-cytokine strategies can be recognised by identifying the mechanism of airflow limitation.

We believe that clinicians who see large numbers of patients with inflammatory airway diseases will readily recognise patients with prednisolone-responsive bronchodilator-resistant airflow limitation and/or symptoms in their asthma, cough and COPD clinics. The challenge is that many of these patients have disease that is difficult to classify using current physiology-based classification systems. The optimum development of mepolizumab and other promising agents does require new and better ways of assessing and classifying inflammatory airways disease.

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| Table 1 | Exacerbation numbers by tertile of response to prednisolone and salbutamol |
|-----------------|-----------------|-----------------|
| Measure | Mepolizumab | Placebo | p Value |
| Change in FEV1 after prednisolone (ml) | | | |
| < −50 | 2.4 | 2.0 | 0.63 |
| −50 to 220 | 2.1 | 5.0 | 0.02 |
| >220 | 0.8 | 2.9 | 0.02 |
| Change in FEV1 after salbutamol (ml) | | | |
| <50 | 1.3 | 3.8 | 0.02 |
| 50 to 150 | 1.7 | 3.6 | 0.11 |
| >150 | 2.6 | 2.4 | 0.85 |

Oxygen or ventilation during flight for patients with neuromuscular disease?

We read with great interest the paper by Mistry et al1 which analysed hypoxic challenge flight assessments in patients with restrictive disorders. In their study they dispute the current British Thoracic Society recommendations, demonstrating that, in this subgroup, all patients planning air travel should have a pre-flight evaluation because, even in patients with normal baseline oxygen saturation (SaO2), arterial oxygen tension (PaO2) can fall below 6.6 kPa during hypoxic challenge.

We wanted to establish whether patients with restrictive disorders (with no lung disease) should be ventilated rather than oxygenated when they are hypoxaemic during flights. In fact, as has been shown by Masa et al,2 only nasal ventilation and not oxygen can normalise baseline nocturnal alveolar hypoventilation in patients with chest wall diseases.

Our group has previously evaluated oxygenation during real flights in healthy subjects,3 demonstrating a mean (SD) oxygen desaturation of 12.8 (6.5)% in long-distance flights (≥2 h) and 4.2 (2.6)% in short-distance flights (<2 h).

We have recently studied two patients with neuromuscular disease during a flight from Porto to Barcelona (duration approximately 1 h 50 min). The first patient was an ambulatory 36-year-old woman with mitochondrial myopathy with a vital capacity (VC) of 400 ml (14%) and the ability to perform an air stacking to a maximal insufflation capacity (MIC) of 1110 ml (35%). Both patients were on continuous non-invasive ventilation (NIV) with a volume-cycled ventilator (mean tidal volume 1200 ml) through a 15 mm mouthpiece during the day and a nasal mask during sleep.

The average SaO2 for the first patient was 97.9%, time with SaO2 <90% was 1.8 min and the minimum SaO2 was 81% (figure I). For the second patient, the average SaO2 was 97%, time with SaO2 <90% was 1.6 min and the minimum SaO2 was 84% (ventilator disconnection during micturition). The first patient needed to use a manual resuscitator connected to her mouthpiece to maintain adequate ventilation while the battery of her ventilator battery was being changed. Neither patient experienced respiratory distress during the entire flight and both returned home uneventfully.

In conclusion, when patients with restrictive disorders are correctly ventilated (even with a manual resuscitator) they may fly safely, with oxygen saturation profiles identical to healthy subjects, and may not need supplemental oxygen.
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