A cross sectional study of reversible airway obstruction in LAM: better evidence is needed for bronchodilator and inhaled steroid use.

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Supplementary methods.

Patient cohort and clinical assessment.

Women with LAM were recruited from the National Centre for LAM in Nottingham UK between 2011 and 2018. All subjects had definite or probable LAM defined by European Respiratory Society criteria[1]. The study was approved by the East Midlands Research Ethics Committee (13/EM/0264) and all participants gave written informed consent.

All measurements were taken as part of routine clinical care. At their first visit all subjects had a clinical assessment, including a detailed history, screening for tuberous sclerosis complex (TSC), full lung function and computerised tomography of the chest and abdomen to detect angiomyolipomas and lymphatic involvement. Routine bronchodilator testing was introduced during the recruitment of the cohort in 2015, from which time all subjects (95 of the cohort) also had bronchodilator reversibility testing. There was no difference between the mean baseline FEV_1 (unpaired 2-tailed t-test, p=0.72), DL_{CO} (p=0.83) or age (p=0.17) of the patients who had undergone bronchodilator reversibility testing and those who had not.

Age was that at baseline assessment, disease duration was defined as the time from first symptom that could be attributed to LAM to the baseline assessment. Clinical phenotype was defined as the presence or absence of a history of pneumothorax, angiomyolipoma, TSC or lymphatic manifestations at any point.

Drugs including all inhaled therapy and mTOR inhibitors were reported for the baseline visit only.

At each follow up visit, lung function was repeated. Follow up interval was determined by clinical need based upon disease trajectory and ranged from 3 to 12 months between visits. As treatment with mTOR inhibitors affects rate of loss of lung function we only used data on subjects prior to treatment with rapamycin for LAM and did not include FEV_1 values obtained once an mTOR inhibitor had been prescribed.

Not all subjects had data for bronchodilator reversibility testing or greater than one year of follow up spirometry

Lung function.

Lung function measurements were made to American Thoracic Society standards[2] in the same laboratory at each visit. Loss of lung function was measured prospectively from the first assessment to the last follow up at the time of writing. Rate of loss of lung function was calculated as the regression value for all FEV_1 measurements providing this period was greater than 1 year to reduce variation in this measurement as previously described[3,4]. Regression calculations were performed in Microsoft Excel.

Reversibility was tested in response to 2.5mg nebulized salbutamol, with a positive response defined as an increase in FEV_1 of at least 12% and 200ml[2]. In table 1, bronchodilator reversibility is presented as those fitting the above criteria for bronchodilator reversibility (defined as present or absent). In table 2 and elsewhere, bronchodilator reversibility is expressed as the mean percentage (+/- standard deviation) change in FEV_1 following administration of salbutamol.

Statistical analysis.

Differentiation between those with and without bronchodilator reversibility were performed by unpaired two tailed t-test for continuous parametric variables (age, disease duration, body mass index, and lung function) and chi square test for categorical variables (presenting symptom, phenotype and treatment).

Analysis of inhaler class and clinical and lung function variables was performed using two methods. Comparison of patients who used inhalers, versus those who did not, with disease duration, FEV_1 and DL_{CO}, was performed by uncorrected, unpaired two tailed t-test. Similarly, comparison of subjects not using inhalers versus those treated with four inhaler types and FEV_1 decline in those treated with ICS and bronchodilators compared with bronchodilators alone were performed by unpaired two tailed t-tests. Trends between increasing inhaler class use with bronchodilator response and rate of loss of FEV_1 were performed using linear regression.

A p value of 0.05 was accepted as significant and reported without corrections. Data were analysed using Microsoft Excel and Graphpad Prism.

Supplementary references.

1. Johnson SR, Cordier JF, Lazor R, et al. European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. *The European respiratory journal* 2010; **35**(1): 14-26.
2. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *European Respiratory Journal* 2005; **26**(5): 948-68.
3. Bee J, Fuller S, Miller S, Johnson SR. Lung function response and side effects to rapamycin for lymphangioleiomyomatosis: a prospective national cohort study. *Thorax* 2018; **73**(4): 369.
4. Johnson SR, Tattersfield AE. Decline in lung function in lymphangioleiomyomatosis: relation to menopause and progesterone treatment. *Am J Respir Crit Care Med* 1999; **160**.