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

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Abstract.

Lymphangioleiomyomatosis can be associated with reversible airflow obstruction and although no guidelines around reversibility testing or inhaled therapy exist, many patients receive bronchodilators and inhaled corticosteroids. To better identify those who may benefit, we examined bronchodilator reversibility and inhaled therapy in a national cohort of 213 subjects. 20% of those tested had airway reversibility by standard criteria. 55% of patients used 13 different combinations of bronchodilators and inhaled corticosteroids. Increasing inhaler classes were associated with reversibility and more rapid FEV_1 decline. Reversibility testing should be performed in all patients and inhaled therapy should be formally studied.

Introduction.

Lymphangioleiomyomatosis (LAM) is a rare disease of women categorised by lung cysts, pneumothorax, lymphatic abnormalities and angiomyolipomas[1]. Loss of function of the tuberous sclerosis proteins, leads to activation of the mTOR-signalling node; resulting in a clone of 'LAM cells' that infiltrate the lungs and lymphatics causing tissue damage[2]. Treatment with mTOR inhibitors can slow disease progression[3,4]. LAM cell associated airway narrowing results in airway obstruction which can be partially reversible and may be associated with faster lung function decline[5,6]. Consequently, many women with LAM are treated with bronchodilators and also inhaled corticosteroids (ICS).

Reversibility testing and inhaled therapy are not covered by current guidelines and how different bronchodilator classes and ICS are used in women with LAM is unknown. This is of importance as bronchodilators may improve quality of life and beta adrenoceptor agonists have been suggested as potential adjuncts to mTOR inhibitors[7], whereas ICS have not been studied. To identify who may benefit from inhaled therapy and provide a baseline for interventional studies, we examined the prevalence and clinical associations of reversible airway obstruction and the use of inhaled therapy in a national cohort of women with LAM.

Methods.

Consecutive women with definite or probable LAM attending a national clinical centre were recruited between 2011-18[8]. At first visit, detailed clinical and drug history, lung function, computerised tomography of the chest and abdomen were obtained. From 2015 onward, reversibility was routinely tested in response to 2.5mg nebulized salbutamol. A positive response was defined as an increase in FEV_1 of at least 12% and 200ml. Prospective loss of FEV_1 was calculated from the slope of a regression line of sequential FEV_1 measurements[4]. The East Midlands Research Ethics Committee approved the study and all subjects gave written informed consent. Further details are given in the supplement.

Results.

213 subjects were recruited, the mean age at onset of symptoms was 37 (standard deviation (SD) 12.9) years and subjects were 50 (12.3) years at the time of the study. 95 subjects had had bronchodilator reversibility testing. Subjects tested for reversibility were of similar age and lung function to those who were not (see supplement). For those tested, the mean increase in FEV_1 after salbutamol was 9.5% (10) with 20% fitting pre-specified reversibility criteria.

In the 95 tested, reversibility was associated with airflow obstruction, younger age and lower gas transfer (figure and table 1). Unsurprisingly, those with reversibility were more likely to be treated with bronchodilators, but also ICS and rapamycin (table 1). 118 subjects (55%) were using at least one inhaled drug. Indications for inhaled therapy were LAM in 68%, LAM with co-existent asthma or COPD in 18% and a previous incorrect diagnosis of asthma or COPD in 13%.

Patients who used inhalers had longer disease duration (mean difference 3 years, 95% confidence interval (C.I.) 0.5 to 5.6, p=0.019), lower FEV_1 (mean difference -19% predicted, 95% C.I. -25 to -12, p=0.0001) and DL_{CO} (mean difference -12% predicted, 95% C.I. -17 to -6, p=0.0001). Thirteen combinations of inhaler classes were used: these ranged from short acting beta agonists (SABA) alone in 20% of those treated; to SABA, long acting beta agonist (LABA), long acting anti-muscarinic (LAMA) and ICS in 23%. 55% were using a LAMA/LABA combination either alone or with other therapy (figure 1). We examined the relationship between inhaler use and rate of FEV_1 decline. As mTOR inhibitors affect FEV_1 decline these patients were excluded. 119 subjects had FEV_1 measurements greater than 12 months apart (mean of 5.5 (3.2) measurements over 47 (37) months). For all subjects, increasing inhaler class use was associated with bronchodilator reversibility (r^2 0.254, p<0.0001) and FEV_1 decline (r^2 0.052, p=0.012). Subjects not using inhalers had a mean loss of FEV_1 of 50 (110) ml/yr, whereas those treated with four inhaler classes lost 189 (480) ml/yr (mean difference 139 ml/yr, 95% C.I. -280 to -7, p=0.039). FEV_1 decline was not different in those treated with ICS and bronchodilators compared with bronchodilators alone (mean difference 15 ml/yr, 95% C.I. -146 to 116, p=0.81, table 2).

Discussion.

Twenty percent of women with LAM fitted standard criteria for bronchodilator reversibility. Patients with reversibility were younger, had lower DL_{CO} values, and more were likely to be treated with inhalers and rapamycin. Many had lower levels of reversibility that may also be clinically beneficial. Despite airflow obstruction and dyspnoea many patients were not tested for reversibility (table 1). Over half of all patients were prescribed inhalers, including ICS in almost one quarter. Inhaler use was associated with airflow obstruction and reversibility and both bronchodilator and ICS use were associated with higher rates of FEV_1 decline.

Our findings suggest that those with more advanced disease and rapid FEV_1 decline are preferentially treated with inhalers. Although the study was not designed to test efficacy, patients continued to take bronchodilators suggesting they may improve symptoms, however disease progression did not appear significantly improved by bronchodilators or ICS. Anecdotally, patients with airway obstruction and reversibility are likely to benefit from bronchodilators and recent evidence suggests beta agonists may affect disease activity in LAM[7]. However, which patient will benefit from which drug is unknown and currently, while many are not being evaluated or treated, others may be over-treated and no consensus on the optimal regimen exists. There have been no studies of ICS in LAM and their use may be based on an initial misdiagnosis of asthma. Although a number of women will have asthma and LAM, these individuals are likely to be identifiable from the history and investigations, whereas reversibility without other features of asthma is likely to be due to LAM alone. As ICS are associated with an increased risk of pneumonia, we suggest ICS be reserved for use in true co-existent asthma and clinical trials[9].

Collectively, these observations highlight the need for prospective studies to determine the effect of inhaled therapy on quality of life and disease progression in LAM. LAMA/LABA combinations are well tolerated, more effective than single agents in COPD[10], used frequently in LAM and seem appropriate candidates to evaluate prospectively for LAM.

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Author contributions. SJ devised the study, saw all patients, entered the study data, analysed the results and wrote the paper. JJ analysed the data and wrote the paper.

Competing interests. There are no competing interests for any author.

Table 1. Clinical associations with bronchodilator reversibility.

	Bronchodilator reversibility			**p**
	not tested	absent	present	(pres. v abs.)
n	118	70	25	
Age (years)*	50.7 (12.6)	50.7 (12.9)	44.9 (8.9)	0.04
Disease duration (years)*	9.2 (9.3)	9.0 (10.0)	7.2 (5.2)	0.41
Body mass index (m^2/kg)*	26.5 (6.4)	25.8 (6.1)	25.5 (5.2)	0.86
Presenting symptom†				
Dyspnoea	42 (50)	33 (23)	32 (8)	0.88
Pneumothorax	24 (28)	26 (18)	20 (5)	0.31
Other respiratory	11 (13)	11 (8)	16 (4)	0.42
Angiomyolipoma	14(17)	14 (10)	12 (3)	0.67
Other non-respiratory	3 (4)	3 (2)	4 (1)	0.70
Screened	1 (1)	6 (4)	4 (1)	0.51
None	5 (6)	9 (6)	4 (1)	0.10
Clinical phenotype†				
Ever had pneumothorax	20 (24)	36 (25)	28 (7)	0.23
Angiomyolipoma present	52 (61)	53 (37)	48 (12)	0.48
Lymphatic complications	11 (13)	16 (11)	8 (2)	0.08
TSC present	20 (24)	10 (7)	16 (4)	0.20
Lung function*				
FEV_1 (% predicted)	74.1 (26)	74.4 (25)	63.8 (19)	0.06
TL_{CO} (% predicted)	60.2 (19)	60.8 (16)	53.1 (13)	0.04
Treatment†				
SABA	40 (48)	34 (24)	72 (18)	0.00005
LABA	31 (37)	47 (33)	80 (20)	0.000001
LAMA	23 (27)	39 (27)	76 (19)	0.00004
ICS	22 (26)	20 (14)	44 (11)	0.0003
Rapamycin	14 (17)	34 (24)	72 (18)	0.0005

Bronchodilator reversibility is defined by a >12% and >200ml increase in FEV_1 following nebulised salbutamol. *mean +/- standard deviation. †percentage of cohort (number of observations). SABA short acting beta agonist. LABA long acting beta agonist. LAMA long acting muscarinic antagonist. ICS inhaled corticosteroid. TSC tuberous sclerosis complex. p = comparison of present vs absent for bronchodilator reversibility (pres. v abs.) by uncorrected, unpaired 2-tail t-test (*) or chi-square test (†).

Table 2. Inhaler classes and lung function.

Inhaler classes used	**n**	**FEV_1** L (SD)	**FEV_1** % pred. (SD)	**n**	**reversibility** % (SD)	**n**	**ΔFEV_1** ml/yr (SD)
0	95	2.31 (0.68)	84 (22.6)	30	2.0 (5.6)	60	-50 (110)
1	23	2.32 (0.80)	85 (27.4)	9	10.8 (6.1)	14	-20 (100)
2	30	1.74 (0.64)	64 (21.5)	22	11.7 (11.7)	14	-84 (140)
3	37	1.72 (0.66)	66 (26.1)	21	13.3 (6.5)	20	-125 (177)
4	28	1.29 (0.62)	49 (17.9)	13	16.3 (13.1)	12	-189 (480)
BD no ICS	62	1.94 (0.71)	71 (24.6)	40	12.4 (9.4)	37	-96 (160)
BD plus ICS	45	1.56 (0.81)	58 (25.9)	25	13.8 (11.0)	23	-120 (351)

Inhaler class: number of separate classes of inhaled therapy used from SABA, LABA, LAMA, ICS. BD no ICS: any combination of SABA, LABA, LAMA. BD plus ICS: ICS and any combination of SABA, LABA, LAMA. % pred: percentage of predicted FEV_1 value. ΔFEV_1 ml/yr: regression slope of FEV_1 values in millilitres / year. L: litres. Reversibility: percentage change in FEV_1 following the administration of salbutamol. SD: standard deviation.

Figure legend

Figure 1. Reversibility and inhaler use in LAM. (a) Change in FEV_1 in women with LAM in response to salbutamol correlated with baseline FEV_1. N=95, Pearson's correlation r=-0.22 (95% confidence interval -0.406 to -0.023) p=0.049. **(b)** Percentage women with LAM fitting criteria for bronchodilator reversibility grouped according to baseline FEV_1. White figures in columns represent the number tested in each group. **(c)** Pie chart representing inhaler classes and combinations used to treat women with LAM. SABA short acting beta agonist, LABA long acting beta agonist, LAMA long acting muscarinic antagonist, ICS inhaled corticosteroid. Grey labels highlight bronchodilators only, white labels bronchodilators plus ICS.

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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.

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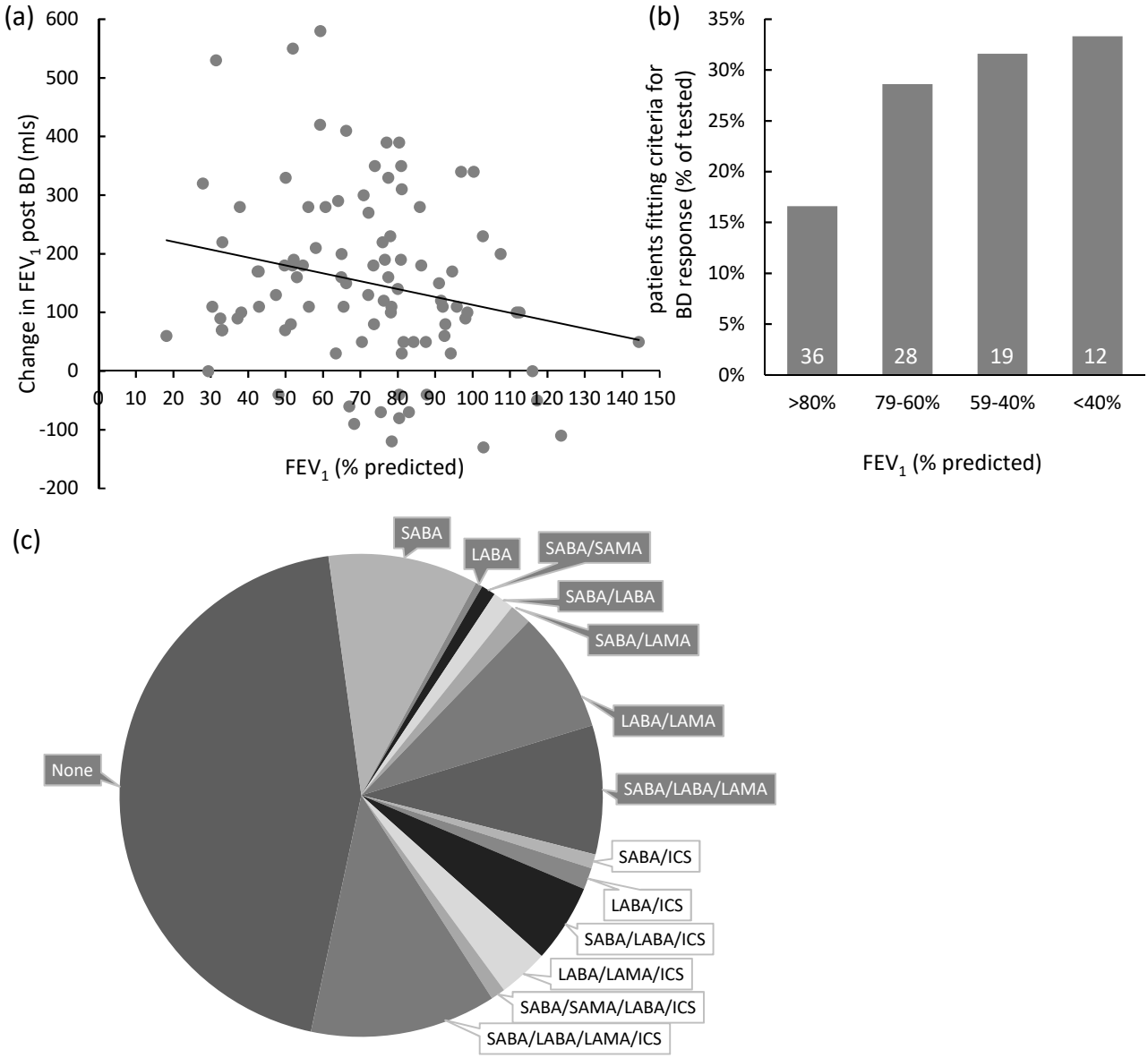
(a)
Change in FEV1 post BD (mls)
FEV1 (% predicted)
(b)
patients fitting criteria for BD response (% of tested)
36
28
19
12
>80%
79-60%
59-40%
<40%
FEV1 (% predicted)
(c)
SABA
LABA
SABA/SAMA
SABA/LABA
SABA/LAMA
LABA/LAMA
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None