AUDIT, RESEARCH AND GUIDELINE UPDATE

A 4-year prospective evaluation of protocols to improve clinical outcomes for patients with lymphangioleiomyomatosis in a national clinical centre

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ABSTRACT

Lymphangioleiomyomatosis (LAM) is a rare multisystem disease. Progressive airflow limitation, pneumothorax and angiomyolipoma-related bleeding are major morbidities. As treatments are available for these complications, we prospectively audited loss of FEV_1 (ΔFEV_1), pneumothorax and angiomyolipoma bleeding against clinical standards over 4 years at the UK Clinical Centre. ΔFEV_1 for these patients is lower than previously reported and rates of pneumothorax and angiomyolipoma haemorrhage are low. This suggests that real-time analysis of clinical data with targeted interventions can reduce morbidity in LAM. These measures could be applied as quality standards to compare the emerging LAM clinical networks worldwide.

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a multisystem disease causing lung cysts, thoracic, abdominal and pelvic lymphatic abnormalities and in over half of patients, angiomyolipomas, a benign tumour generally occurring in the kidneys. LAM occurs sporadically in five to nine per million women but is common in adult women and some men with tuberous sclerosis complex (TSC). Lung cysts tend to increase in number causing pneumothorax, progressive airflow limitation and in some cases, respiratory failure. The clinical course is variable with average loss of FEV_1 between 75 and 140 mL/year;[1–3] although some progress more rapidly, others remain stable for many years. Angiomyolipomas can enlarge with those >4 cm prone to haemorrhage needing urgent treatment resulting in loss of renal function. Lymphatic masses can cause abdominal bloating, discomfort, chylous ascites and pleural effusions.[1] LAM lesions have dysregulation of the kinase mechanistic target of rapamycin (mTOR) and recently mTOR inhibitors have been shown to slow loss of lung function, reduce angiomyolipoma volume and lymphatic complications in patients with LAM.[2] Moreover, interventions for the main morbidities in LAM, namely pleural symphysis for pneumothorax and prophylactic embolisation or nephron sparing surgery for angiomyolipoma to prevent bleeding have been recommended in the European Respiratory Society (ERS) guidelines for LAM.[4] These interventions have not been formally evaluated and currently it is not clear how best to apply them for the benefit of individual patients.

Recently, specialist clinical networks have been established in several countries to improve care for women with LAM. In 2011, Highly Specialised Commissioning funded the UK LAM Centre, a comprehensive clinical service, to manage the national caseload of patients with LAM. At the outset, we hypothesised we could improve the outcome for patients by targeted use of mTOR inhibitors, surgery to prevent recurrent pneumothorax and tumour surveillance with embolisation or surgery for angiomyolipoma at risk of bleeding. We therefore established quality standards and recorded prospective data for the loss of FEV_1, incidence of pneumothorax and renal haemorrhage which are reported annually to Highly Specialised Commissioning. Here, we present evidence from a 4-year prospective audit that protocol-driven management of these major morbidities can improve outcomes for women with LAM.

METHODS

The diagnosis and management of patients are performed according to the ERS LAM guidelines.[4] All those with definite or probable LAM by ERS criteria attending the centre at least annually (termed the caseload) have serial lung function recorded with rate of decline in FEV_1 (ΔFEV_1) calculated prospectively as the regression line slope for FEV_1 values from first centre visit. Due to the variation in this measurement, data are only presented for observation periods of ≥12 months.[3] The use of mTOR inhibitors for individual patients with progressive lung disease or chylous complications is determined clinically based upon their level of dyspnoea, baseline FEV_1, DL_{CO}, ΔFEV_1, exertional hypoxaemia, lung cyst burden on CT, lymphatic disease, the presence of angiomyolipoma and TSC. In addition, prognostic factors including age, menopausal status and mode of presentation are considered. Patients are screened for angiomyolipoma by CT or MRI at first visit and tumour size is followed thereafter at least annually using ultrasound. In addition to their clinical assessment, those with ΔFEV_1 >−150 mL/year, pneumothorax or angiomyolipoma >4 cm in diameter are reviewed with a view to an appropriate intervention. All necessary investigations are performed on the consultation day to minimise travel.

RESULTS

From 2011 to 2015, 177 patients were evaluated (all but one were women), 29 had cystic lung

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diseases other than LAM, 23 with LAM elected to be managed locally. The remaining 125 women with definite or probable LAM, 19 of whom also have TSC, seen at least annually, comprise the caseload. Of the caseload, 89 have ΔFEV_1 values of >12 months of observation (mean 26 months). Overall ΔFEV_1 was −53 mL/year (SD 144, n=89) with individuals having different levels of baseline lung function impairment and disease trajectory (figure 1). Mean ΔFEV_1 for those not receiving an mTOR inhibitor was −70 mL/year (SD 157, n=66). Eleven had a ΔFEV_1 >−150 mL/year: in two, the loss of FEV_1 was attributed to recent thoracic surgery and was kept under review and nine were treated with an mTOR inhibitor. Indications for mTOR inhibitor treatment not based upon the ΔFEV_1 > −150 mL/year criterion were progressive lung disease based on other criteria as above (10), lymphatic complications (4) or TSC complications including angiomyolipoma (2). ΔFEV_1 for all mTOR inhibitor treated women was −7 mL/year (SD 82, n=23).

Over two thirds of patients had been treated for pneumothorax prior to evaluation at the centre. Over the 4 years of the study, the annual incidence of pneumothorax ranged from 3.7% to 6.4% (SD 0.87) of caseload. Nine individuals had 17 pneumothoraces, the majority of which were managed at the patient's local service. No pneumothorax occurred during treatment with rapamycin. Where possible, a definitive surgical procedure was advised or arranged by the centre. Of four patients treated medically, three had a recurrence requiring surgery. Five patients had one or more surgical interventions comprising pleural abrasion, pleurodesis, pleurectomy or combinations thereof. The remainder who had had surgery previously and developed small recurrences were treated conservatively.

Half of those with sporadic LAM (53) and all with TSC-LAM (19) had (or had, presurgery) an angiomyolipoma. Eleven patients with angiomyolipoma >4 cm or with angiomyolipoma symptoms detected at initial screening or follow-up surveillance were considered for intervention by the centre's specialist renal tumour service. Nine received an intervention: selective embolisation (7), nephron sparing surgery (1) or an mTOR inhibitor (1), one was treated conservatively and one declined intervention. There was one renal haemorrhage in 2011, one in 2012 but have been none since.

DISCUSSION

Around 200 women are known to have LAM in the UK. We have evaluated the majority of these and provide regular care for more than half despite the need to travel to the centre.

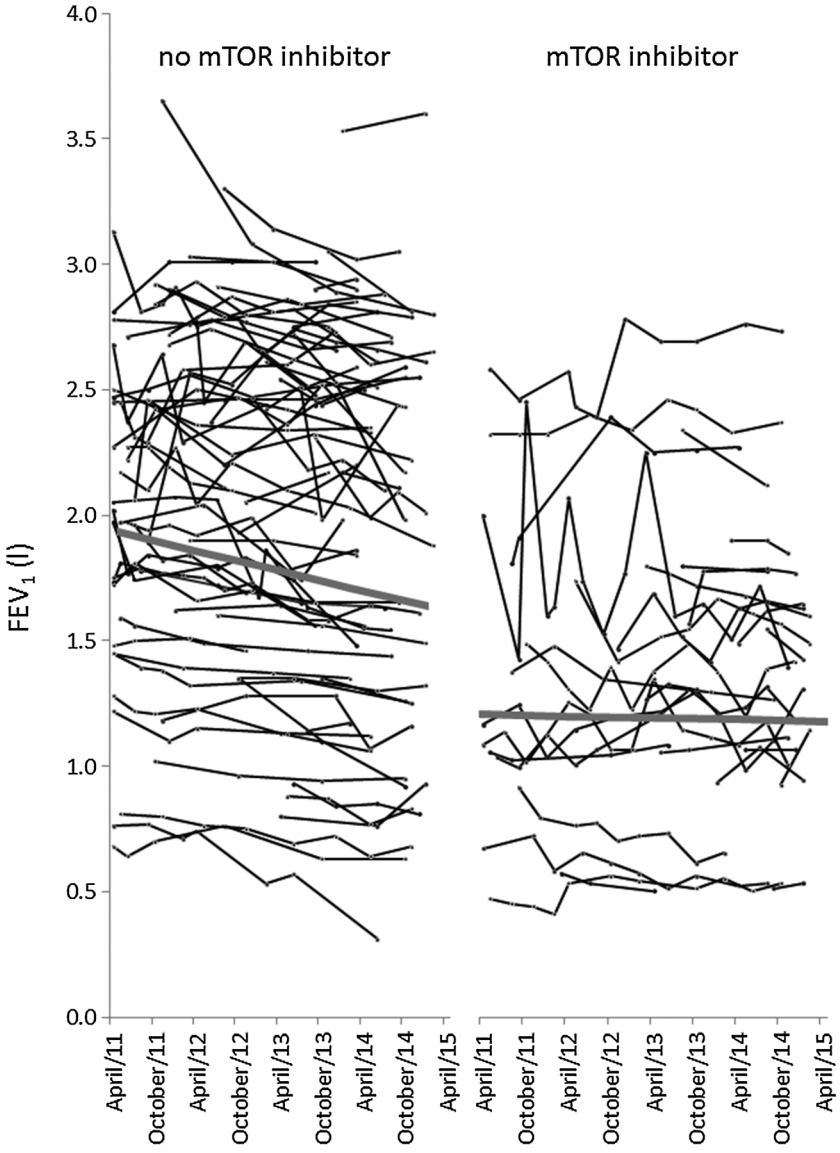

Figure 1 Prospective measurements of FEV_1 for individuals (represented as single lines) in the lymphangioleiomyomatosis centre caseload for those on no mechanistic target of rapamycin (mTOR) inhibitor treatment and those taking the mTOR inhibitor (all but one patient was taking rapamycin). Group mean decline is shown as a grey bar.

We have employed clinical guidelines to manage patients and have shown that using clinical data in real time is feasible and can direct care for LAM.

Our data suggest that ΔFEV_1 at −53 mL/year for all patients is lower than previous estimates which range from −75 mL/year for a large single centre registry to −120 mL/year in two comprehensive national cohorts and −134 mL/year for a clinical trial placebo group.[1 3] The approach taken here to treat those with progressive loss of lung function and lymphatic complications with mTOR inhibitors may be responsible for this. In line with recent clinical trials, treatment with mTOR inhibitors in our caseload was associated with a reduced loss of, or stable FEV_1.[2] However, it is also possible that other aspects of the service including aggressive treatment of respiratory infections and general supportive care may contribute to preservation of lung function. Differences in data collection and caseload may also affect these data: we have used prospective single centre measurements, rather than the retrospective multicentre measurements of most previous estimates. While a bias reducing the likelihood of patients with more advanced disease travelling to the centre is also possible, the spread of baseline lung function (figure 1) shows that those with more aggressive disease do make the effort to travel for their care. Despite, thorough clinical assessment, to evaluate patients for mTOR inhibitor treatment, the ΔFEV_1 threshold of >−150 mL/year triggered evaluation in 11 untreated patients and appears useful. The review threshold of −150 mL/year for ΔFEV_1 is high but was chosen due to the variability of FEV_1 over shorter time intervals.[3] More accurate methods of measuring disease activity and greater understanding of the role of mTOR inhibitors in early disease are being developed with the aim of intervening earlier to prevent disability.

Historical studies show that over their disease course, women with LAM average 3.5 pneumothoraces and five interventions leading to 1 month in hospital. Due to a recurrence rate of 66% for non-surgical interventions, ERS guidelines recommend surgery at first pneumothorax for LAM.[4] Although treatment of pneumothorax often occurs outside the centre and treatment prior to referral may have reduced recurrence rate in our cohort; it is possible that the adoption of these guidelines generally has reduced recurrent pneumothorax.

Although generally outside the remit of respiratory physicians, angiomyolipoma is present in half of those with sporadic LAM and almost all with TSC-LAM. Large tumours may be asymptomatic until presenting with torrential haemorrhage sometimes resulting in emergency nephrectomy.[5] The respiratory consultation may be the only opportunity to detect tumours that may otherwise enlarge undetected. Identification by CT or MRI is straightforward and can target patients at risk of haemorrhage. Using protocol-driven detection and monitoring, we have identified tumours in 50% of all patients with sporadic LAM of which over 20% were at risk of preventable haemorrhage. With this protocol we have experienced no tumour haemorrhage in our caseload in the previous 3 years.

Our findings suggest that a combination of comprehensive clinical assessment and protocols to tackle three major morbidities for women with LAM may improve outcomes. As specialist clinical networks for rare lung diseases are being established worldwide, we suggest that ΔFEV_1, pneumothorax and angiomyolipoma bleeding rates could be adopted as clinically important quality standards for LAM.

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Contributors SRJ conceived and designed the study, saw all patients, analysed the data, wrote the manuscript and is guarantor for the study. JB recorded the clinical data, helped analyse data and contributed to the final manuscript. RB and IM treated all angiomyolipoma referrals, contributed to data gathering and the final manuscript.

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