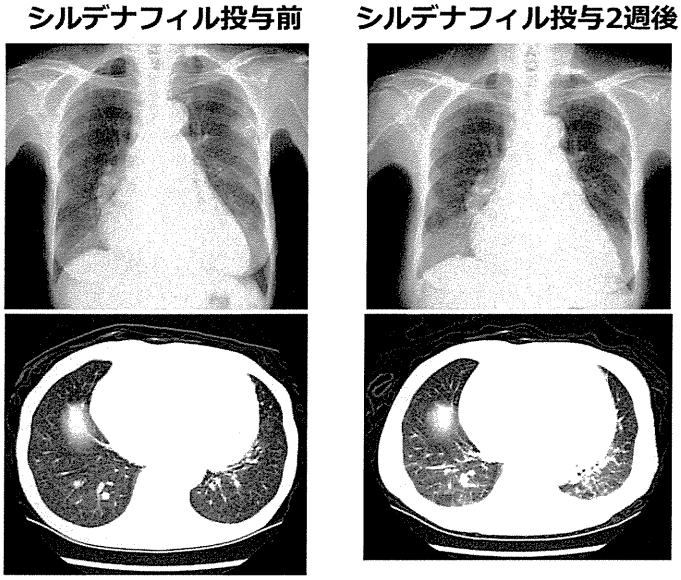
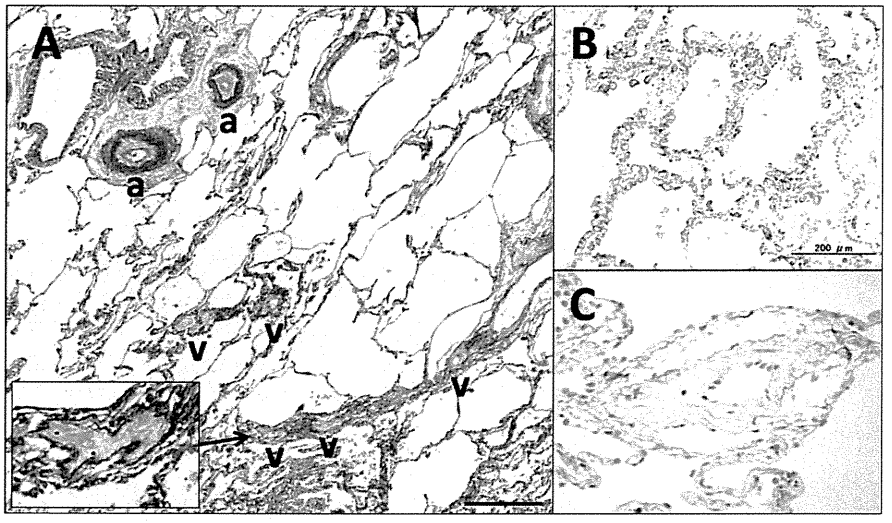
図３　シルデナフィル投与前後の経過



動脈血ガス分析(nasal 2L/min)		
PaO2 (torr)	88.4	58
PaCO2 (torr)	32.1	26.6
BNP (pg/L)	1771	2359
TRPG (mmHg)	80	119

胸部写真では心陰影の拡大と両下肺野のスリガラス状濃度上昇を認め、肺鬱血が示唆された。胸部CT でも両下葉のスリガラス状濃度上昇と小葉隔壁肥厚の顕在化を認めた。併せて低酸素血症の悪化と BNP 値、心エコーにての三尖弁逆流速度の上昇を認め、総合的に病態が悪化したと判断した。

図４　剖検所見



A. 小葉間隔壁内の静脈（vein）とより末梢の細静脈（venule）の線維性閉塞を両肺広汎に認めた。また肺動脈にも内膜・中膜の肥厚と内腔狭窄も同様に両肺に認めた。一部にヘモジデリン貪食マクロ―ファージの存在を認めた。縦隔リンパ節では

B.毛細血管腫様の変化（CD31 陽性の毛細血管組織の増生）

C.免疫組織学的にリモデリングを来した肺静脈/動脈に PDGFβの局在は示されなかった。

リンパ脈管筋腫症（LAM）診療の手引き 2015

林田美江[a]、安藤克利[b]、関谷充晃[b]、瀬山邦明[b]、井上義一[c]、巽浩一郎[d]

[a]信州大学医学部附属病院呼吸器・感染症・アレルギー内科
[b]順天堂大学大学院医学研究科呼吸器内科学
[c]国立病院機構近畿中央胸部疾患センター臨床研究センター
[d]千葉大学大学院医学研究院呼吸器内科学

CQ：LAM を有する成人女性において mTOR 阻害薬は第一選択となりますか？

A：LAM を有する成人女性において、呼吸機能低下の防止、QOL の向上を考慮した場合、mTOR 阻害薬を第一選択として提案する。

推奨の強さ：2（弱く推奨する）

エビデンスの強さ：B

呼吸機能の低下を抑制し、QOL も一部の評価で改善する。ただし、各種の有害事象がみられ、効果においては個人差がみられる。

解説

リンパ脈管筋腫症（lymphangioleiomyomatosis; LAM）は、主として妊娠可能な年齢の女性に発症し、肺の嚢胞性破壊と体軸リンパ管系の異常を特徴とする緩徐進行性の多臓器疾患である。気胸を反復することが多く、肺病変の進行により労作時息切れなどの症状や呼吸不全を呈する。腎血管筋脂肪腫、腹部リンパ脈管筋腫（lymphangioleiomyoma）、乳び漏（胸水、腹水）といった肺外病変を呈することがある。病理学的には、病変部において平滑筋細胞様の形態を示す LAM 細胞の増殖がみられる。

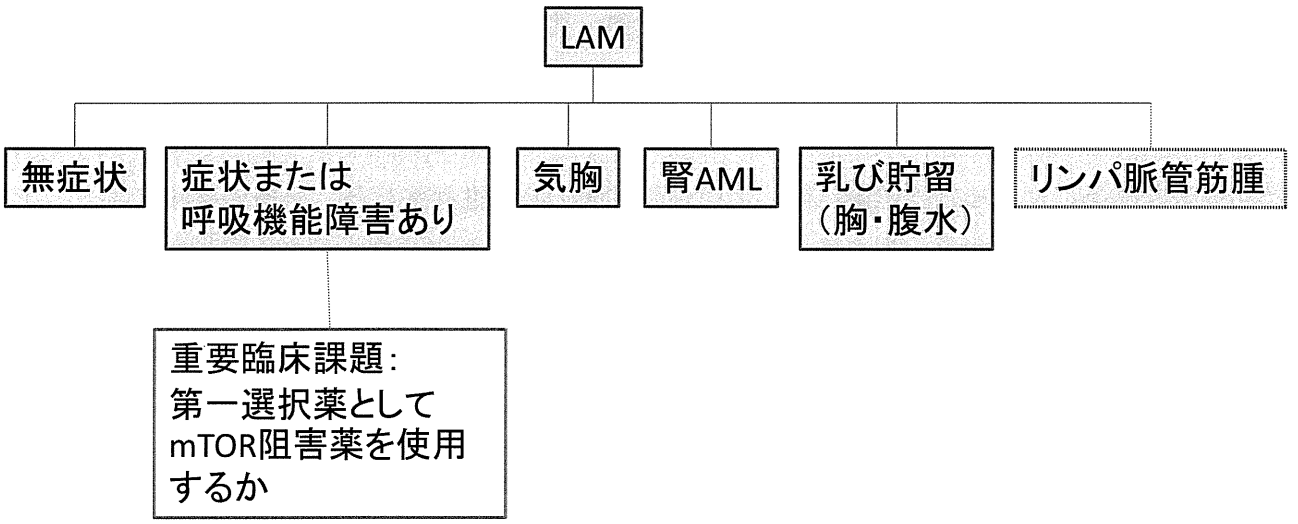
LAM には結節性硬化症（tuberous sclerosis complex; TSC）に合併して発症する TSC-LAM と TSC を伴わない孤発性 LAM（sporadic LAM）とがある。TSC はてんかん発作や多臓器の過誤腫性病変を特徴とする遺伝性疾患であり、原因遺伝子として腫瘍抑制遺伝子である *TSC1*（第 9 染色体）と *TSC2*

（第 16 染色体）が同定されている。これに対して、孤発性 LAM は *TSC2* の体細胞変異により発症すると考えられている。 *TSC1* または *TSC2* の変異によって、細胞内シグナル伝達系においてラパマイシン標的蛋白質（mammalian target of rapamycin; mTOR）の恒常的な活性化が起こり、LAM の病態につながることが解明されてきた。

LAM の分子病態の解明が進むにつれ各種の治療ターゲットが注目されている。mTOR 阻害薬であるシロリムスにおいて LAM の呼吸機能の低下を防止する効果が報告され、本邦において 2014 年よりシロリムスは LAM の保険適用薬として承認された。mTOR 阻害薬を使用するうえで、免疫抑制作用を含めた各種の副作用を考慮する必要があり、また、どの程度呼吸機能の低下がみられた時点でシロリムスを開始すべきであるか、長期投与の効果と副作用、適正な投与量などについては課題が残されている。

呼吸不全に関する調査研究班による「リンパ脈管筋腫症（LAM）の治療と管理の手引き（2006 年）」は LAM に対して保険適用の医薬品がない時点において作成された。その後 mTOR 阻害薬に関する多くの報告がみられていることから、mTOR 阻害薬の治療薬としての位置づけにつきレビューを行った。

診療アルゴリズム



一つの RCT において、mTOR 阻害薬であるシロリムスは LAM による呼吸機能の低下を抑制し、QOL も一部の評価で改善することが報告された。他の複数の観察研究においても、シロリムスまたはシロリムスの誘導体であるエベロリムスの投与によって、呼吸機能の低下を抑制あるいは呼吸機能を改善した報告がなされている。しかし、mTOR 阻害薬投与に伴う各種の副作用が高い頻度で報告され、効果においては個人差も認められている。mTOR 阻害薬投与に際しては、口内炎や消化器症状をはじめ

とする頻度の高い副作用、各種感染症や薬剤性肺障害といった早期対応の必要性のある副作用に対して、常に対策を考慮し、かつ各個人における益と害のバランスを考慮しながら投与の継続を判断する必要がある。尚、LAM の肺病変に対する効果が報告されている mTOR 阻害薬は主にシロリムスであり、エベロリムスの効果を検討した報告は今回レビューを行ったうち一つの観察研究のみである。エベロリムスに関しては、今後の知見の集積をもって再検討される必要がある。

mTOR 阻害薬投与を開始すべき指標は明らかとなっていないが、上記の RCT においては気管支拡張薬吸入後の一秒量が予測値の 70%以下であることが参加基準となっており、この条件は有効性と安全性の示された一つの基準となり得る。ただし、LAM による呼吸機能低下の速度には個人差がみられる。さらに、国内においてシロリムスの安全性を検討した多施設共同医師主導治験（MLSTS 治験）では呼吸機能障害の程度を参加基準に含めておらず、12 ヶ月中間報告の評価対象者の 45%においてベースラインの一秒量が予測値の 70%以上であったが、このような群においても一秒量は 12 ヶ月間安定していたと考えられた。すなわち、一秒量が予測値の 70%を上回る場合でも、病態の進行が示唆される場合においては mTOR 阻害薬の投与を検討して良いと考えられ、逆に一秒量が予測値の 70%以下であっても比較的安定した経過が示唆される場合においては mTOR 阻害薬投与による益は少ない可能性がある。

なお、mTOR 阻害薬の長期間投与の有効性と安全性、生命予後の改善に関する知見は現時点において得られておらず、各患者においての総合的な評価と予測に立った判断が必要である。

mTOR 阻害薬投与に際しては、副作用への対策のほか、避妊が必要となる。また、創傷治癒を遅らせる可能性があることから外科処置に際しては休薬期間の必要性が生じる。肝炎ウイルスキャリアや結核等の既感染者に対しては、再活性化の可能性を考慮した対応が必要となる。これらへの理解と協力が得られることも投与への条件となる。

文献検索方法（エビデンスの検索）

Pubmed で“lymphangioleiomyomatosis” または “lymphangiomyomatosis” をキーワードとして検索し（#1）、次に“mTOR inhibitor”または“sirolimus”または“rapamycin”または“everolimus”をキーワードとして検索し（#2）、両方を満たす検索結果（#1 and #2）から publication type が症例報告であるものを除外した結果、150 文献が該当した。タイトル、アブストラクトから、臨床研究のデザインでないもの（Letter、系統的でない総説）、動物や培養細胞等を対象としたもの、対象（P）に LAM 症例を含まないもの、介入（I）が mTOR 阻害薬ではないもの、言語が英語でないもの、を除外し 11 報を抽出した。うち 2 報は 1 報のシステマティックレビュー（SR）文献に含まれるため除外

した。残る 9 報を 2 次スクリーニング用として文献を収集した。同様に The Cochrane Library, 医中誌 Web で検索し、新たに加えるべき文献はみられなかった。

2 次スクリーニングでは P（対象）・I（介入）・O（結果・効果）が一致し、かつ重要と思われる 4 報を選出し定性的 SR に用いた。

アウトカムが一致しない論文であっても 10 症例以上の成人 LAM 症例を含む他の 4 報に関して、有害事象の検索対象とした。また、国内においてシロリムスの安全性を検討した多施設共同医師主導治験（MLSTS 治験）の結果は論文として未発表であるため、ラパリムス®医薬品インタビューフォームより 12 ヶ月中間報告の結果を参照した。

レビューサマリー

国際多施設共同試験として行われた女性LAM患者を対象とするシロリムス投与のランダム化比較試験[1)]において、一秒量の傾きはプラセボ群-12 ± 2 ml/月, 実薬群 1 ± 2 ml/月、FVC の傾きはプラセボ群-11 ± 3 ml/月, 実薬群 8 ± 3 ml/月であり、いずれも混合効果モデルを用いて実薬群における有意な改善が示された。すなわち、シロリムス投与により呼吸機能低下を抑制する効果が示された。また、Euro QOL visual analogue scale for QOL および FPI トータルスコアの傾きにおいてもプラセボ群に比して投与群で有意な改善を認めた。この比較試験において、気管支拡張薬吸入後の一秒量が予測値の 70%以下であることが参加基準の一つとされ、多量の胸水貯留は除外基準とされた。シロリムスの初期投与量は 2 mg/day、目標トラフ濃度は 5-15ng/mL とされた。その他、3 つの観察研究[2-4)]においても、成人女性 LAM 患者に対するシロリムスまたはエベロリムス投与による呼吸機能低下速度の減少あるいは呼吸機能改善が示された。平均 5 年間の比較的長期に投与された症例に対する解析[3)]、国内におけるシロリムス少量投与（シロリムス血中トラフ濃度は 5ng/mL 未満）の報告[4)]が含まれる。また、国内においてシロリムスの安全性を検討した多施設共同医師主導治験（MLSTS 治験）の 12 か月中間報告[5)]では、評価対象者の 45%においてベースラインの一秒量が予測値の 70%を超え、このような群においても一秒量は 12 ヶ月間安定していたと考えられた。

上記の報告に加え、10 症例以上の成人 LAM 症例を含む mTOR 阻害薬投与に関するシステマティックレビュー報告[6)]および研究報告[7,8,9)]から有害事象の検索を行った。LAM 症例のみを対象とした RCT では、有害事象の頻度はプラセボ群に比して実薬群で高かったが、grade 3 以上の重篤有害事象の頻度は両群間に有意差を認めなかった[1)]。いずれかの報告において mTOR 阻害薬投与群の 3 割以上にみられた有害事象は、口内炎、下痢、嘔気、高コレステロール血症、ざ瘡様皮疹、上気道炎を含む感染症、四肢の浮腫、頭痛、高血圧、白血球減少等であった。口内炎の頻度は 4 報告[1-4)]において 58~75%

と高く、MLSTS 治験では 89%と特に高い頻度で認められた。有害事象の重症度はほとんどが Grade 1, 2 であった。重篤な有害事象として急性心膜炎および心房性不整脈、ニューモシスチス肺炎、急性ウイルス性心膜炎および心不全、肺の空洞様病変へのアスペルギルス感染、重症 sporadic LAM 症例の気道感染による死亡が各 1 例認められた。重篤有害事象としての間質性肺炎の報告はみられないが、一つの観察研究において HRCT で間質性陰影の出現が 4 例(17%)に認められ(いずれも服薬は継続)[2)]、MLSTS 治験において 2 例に肺障害を認め、うち 1 例は回復し服薬を再開、1 例は服薬が中止となった[5)]。

文献

1) Efficacy and safety of sirolimus in lymphangioleiomyomatosis. McCormack FX, Inoue Y, Moss J, et al. N Engl J Med 2011;364:1595-1606.

2) Everolimus for the treatment of lymphangioleiomyomatosis: a phase II study. Goldberg HJ, Harari S, Cottin V, et al. Eur Respir J 2015;46:783-94.

3) Sustained effects of sirolimus on lung function and cystic lung lesions in lymphangioleiomyomatosis. Yao J, Taveira-DaSilva AM, Jones AM, et al. Am J Respir Crit Care Med 2014;190:1273-82.

4) The efficacy and safety of low-dose sirolimus for treatment of lymphangioleiomyomatosis. Ando K, Kurihara M, Kataoka H, et al. Respir Investig 2013;51:175-83.

5) ラパリムス®医薬品インタビューフォーム
(http://rapalimus.jp/pdf/1218_rapalimus_if.pdf)

6) Efficacy and safety of sirolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis: a systematic review. Peng ZF, Yang L, Wang TT, et al. J Urol 2014;192:1424-30.

7) Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis: extension of a randomized controlled trial. Bissler JJ, Kingswood JC, Radzikowska E, et al. Nephrol Dial Transplant 2015 Jul 8. pii: gfv249. [Epub ahead of print]

8) Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Bissler JJ, Kingswood JC, Radzikowska E, et al. Lancet

2013;381:817-24.
9) Changes in lung function and chylous effusions in patients with lymphangioleiomyomatosis treated with sirolimus. Taveira-DaSilva AM, Hathaway O, Stylianou M, et al. Ann Intern Med 2011;154:797-805.

リンパ脈管筋腫症（LAM）診療の手引き　参考論文

The Reductions in Pulmonary Function Detected in Patients with Lymphangioleiomyomatosis: An Analysis of the Japanese National Database of Intractable Diseases

Mie Hayashida[1]; Masanori Yasuo[1]; Masayuki Hanaoka[1]; Kuniaki Seyama[2]; Yoshikazu Inoue[3]; Koichiro Tatsumi[4]; Michiaki Mishima[5]; and the Respiratory Failure Research Group of the Ministry of Health, Labour, and Welfare, Japan

[1] First Department of Internal Medicine, Shinshu University School of Medicine, Matsumoto;
[2] Division of Respiratory Medicine, Juntendo University Faculty of Medicine and Graduate School of Medicine, Tokyo;
[3] Clinical Research Center, National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka;
[4] Department of Respirology, Graduate School of Medicine, Chiba University, Chiba; and
[5]Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Abstract

Background: In lymphangioleiomyomatosis (LAM), predicting lung disease progression is essential for treatment planning, especially in patients treated with mammalian target of rapamycin (mTOR) inhibitors. However, no previous Japanese studies have predicted the reductions in pulmonary function seen in LAM.

Methods: The data for 89 LAM patients who had undergone ≥3 spirometry tests and whose data had been registered in the Japanese national database between October 2009 and March 2014 were analyzed after excluding patients who had undergone lung transplants; mTOR inhibitor treatment; or treatment for pneumothorax or pleural effusion during the study period. The rate of change (slope) in pulmonary function was calculated, and its associations with clinical background factors were investigated.

Results: Among the whole study population, the median (quartiles) slope of the forced expiratory volume in 1 second (FEV_1) was -46.7 (-95.2; -15.0) mL/year. The patients were divided into those who exhibited initial FEV_1 (% predicted) values of >70% (Group A) and ≤70% (Group B). The median FEV_1 slopes of Groups A and B were -37.1 (-88.5; 14.0) mL/year and -59.2 (-114.7; -27.4) mL/year, respectively; i.e., FEV_1 fell at a significantly faster rate in Group B than in Group A. In Group B, a weak positive correlation was detected between age and the FEV_1 slope.

Conclusions: Young LAM patients whose initial FEV_1 (% predicted) values are ≤70% tend to subsequently exhibit rapid reductions in their FEV_1 values, and hence, require treatment. However, the FEV_1 reduction rate varies markedly among individuals and should be monitored in all cases.

Keywords: database; disease progression; pulmonary function; lymphangioleiomyomatosis; rare lung disease

Short title: Reduction in Pulmonary Function in LAM

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a rare and slowly progressing lung disease that almost exclusively affects adult females. It is characterized by neoplastic LAM cell infiltration of the lungs and lymphatic system, and cystic destruction of the lungs[1,2]. Patients with advanced pulmonary dysfunction develop dyspnea on exertion and respiratory failure. In addition, a high incidence of recurrent pneumothorax is seen from the early stages of LAM, and extrapulmonary lesions, such as chylous effusions, lymphangioleiomyoma, and angiomyolipoma, are considered to be characteristic complications of the condition.

As the molecular pathology of LAM has been elucidated, various treatment targets have attracted attention[3-5]. Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, has been demonstrated to prevent reductions in pulmonary function in patients with LAM [6-8]. It was approved as a pharmaceutical drug in 2014 and has started to be used in clinical practice in Japan. However, no consensus has been reached regarding the grade of pulmonary hypofunction at which sirolimus treatment should be initiated. The risk/benefit ratio of sirolimus treatment including its effects and adverse reactions must be investigated, but the speed of the decline in pulmonary function seen in LAM varies among individuals[9,10]. It is difficult to accurately predict this interindividual variation, which in turn makes it more difficult to assess the benefits of particular agents.

In LAM, the LAM histological score (LHS) and the pathological grade of the associated pulmonary cystic lesions have been reported to be prognostic factors [11,12], and associations have been detected between abnormal pulmonary function, e.g., obstructive ventilatory impairment or a reduced pulmonary diffusion capacity, and the LHS or the grade of pulmonary cystic lesions according to high-resolution computed tomography (CT) [13-17]. At present, time-course monitoring of pulmonary function is the most useful method for assessing the severity and progression of lung disease in LAM[18].

It has been reported that a younger age and a lower initial pulmonary function are associated with a high mortality rate and a subsequent decline in pulmonary function in LAM[12,19,20]. In addition, we previously reported that LAM patients who initially present with dyspnea exhibit a lower survival rate than those who initially display pneumothorax[21]. However, pulmonary function has not been evaluated throughout the course of LAM in any previous Japanese study. In this study, using the Japanese national database of intractable diseases, we calculated the rate of change in pulmonary function and investigated its associations with various clinical background factors and initial pulmonary function test results in LAM.

In the Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus (MILES) trial[6], in which sirolimus was demonstrated to be effective against LAM, the subjects were patients who exhibited forced expiratory volume in 1 second (FEV_1) (% predicted) values of ≤70% after bronchodilator administration. Thus, an FEV_1 (% predicted) value of ≤70% could be a useful index for determining the optimal time to initiate treatment for LAM. In this study, we compared the pulmonary function parameters and the rate of change in these parameters between patients with FEV_1 (% predicted) values of >70% and ≤70%.

METHODS

Intractable diseases database

In Japan, LAM was included in the National Research Project on Intractable Diseases in October 2009, and as a result patients that were diagnosed with LAM were able to receive medical subsidies. To receive the subsidies, patients are required to submit an application form and a clinical research form (a questionnaire), the latter is completed by their physicians, every year. The questionnaire includes questions about the following items: age, gender, history of cigarette smoking, pregnancy/delivery, the presence/absence of the menopause, the presence/absence of tuberous sclerosis, symptoms, chest CT findings, abdominal imaging findings (ultrasonography, CT, or magnetic resonance imaging [MRI]), the pathological findings of lung or lymph node biopsies (including the results of immunostaining), the differentiation of LAM from other cystic lung diseases (chronic obstructive pulmonary disease, Langerhans cell histiocytosis, Birt-Hogg-Dubé syndrome, Sjögren's syndrome-associated pulmonary lesions, lymphocytic interstitial pneumonia, bullae/blebbing, amyloidosis, light-chain deposition disease, and cyst-forming metastatic lung tumors), pulmonary function test results (including the results of spirometry tests and data regarding the diffusing capacity of the lungs for carbon monoxide [DLco]), and the treatments administered. The results of tests other than chest CT are not essential, and findings are filled in when a test has been performed. For patients who have not been pathologically diagnosed with LAM, chest CT images are required, and the validity of the diagnosis is examined by specialists. The certified contents of the questionnaires are entered into the database by the administrative staff at each prefecture. The questionnaire data of 588 LAM patients (1,396 questionnaires) that were registered between October 2009 and March 2014 were analyzed.

This study was approved by the institutional review board of The University of Shinshu, which waived the requirement for patient informed consent because of the anonymous nature of the data (permission number: 3024).

Patient selection and data

The data of 269 LAM patients for whom questionnaire data were registered 3 or more times during the abovementioned registration period were extracted. The presence/absence of spirometry results and the dates of any spirometry tests were confirmed, and 133 LAM patients who had undergone 3 or more spirometry tests at intervals of 6 months or longer were selected. However, patients that had undergone 1) a lung transplant; 2) mTOR inhibitor treatment; or 3) thoracic drainage, pleurodesis, surgery, or thoracic duct ligation during the registration period were excluded. As a result, 89 LAM patients were included in the analysis.

We used the spirometric reference equations reported by the Japanese Respiratory Society in 2001[22] and Nishida's reference equations for pulmonary diffusing capacity intended for Japanese[23] to calculate the predicted pulmonary function values.

Statistical analysis

The rate of change in pulmonary function was calculated using linear regression in each case. The correlations between pairs of items were assessed using Kendall's rank correlation method. The Wilcoxon rank-sum test was used for comparisons between two groups. Multivariate analysis was performed by carrying out multiple regression analyses involving stratification factors. P-values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Patient characteristics

The number of LAM patients that have registered for medical subsidies has been reported by the Japanese Government every year since April 2010. In total, 1,886 LAM patients registered for such subsidies between April 2010 and March 2014 (the mean number of LAM patients registered annually was 472). The total number of LAM patients registered in the Japanese national database of intractable diseases during the abovementioned 4-year period was 1,252, and so the database registration rate was 66%.

The 89 LAM patients who met the inclusion, but not the exclusion, criteria accounted for 15% of the 588 LAM patients registered in the Japanese national database of intractable diseases. The clinical data extracted from the initial questionnaires of 567 patients (the whole group except the 21 patients that had undergone lung transplants) and the 89 analyzed patients (the analysis set) are shown in Table 1.

Of the 567 patients, 310 (55%) had been pathologically diagnosed with LAM. One hundred and forty-three patients (25%) were clinically diagnosed with the condition based on their chest CT findings; the exclusion of other cystic lung diseases; and at least one of the following clinical histories: tuberous sclerosis, abdominal lymphangioleiomyoma, angiomyolipoma, chylothorax, or chylous ascites. The remaining 114 patients (20%) were clinically diagnosed with LAM based on their chest CT findings and the exclusion of other cystic lung diseases. Of the 89 patients in the analysis set, 46 (52%) were pathologically diagnosed with LAM.

The patients in the analysis set had undergone a mean of 3.2 pulmonary function tests (range, 3-5 tests) over a mean period of 28 months (range, 13-48 months). The frequency of the menopause (including spontaneous and hormone therapy-induced menopauses) in the whole group was lower than the 95% confidence interval of the estimate for the analysis set (Table 1). Since patients that were treated for pneumothorax during the registration period were excluded from the analysis set, the frequency of patients with a history of pneumothorax was much lower in the analysis set than in the whole group. In the whole group, the median values of all of the pulmonary function parameters were within the 95% confidence intervals of the estimates obtained for the analysis set.

Rate of change in pulmonary function

The rate of change (slope) in pulmonary function was determined by linear regression of the pulmonary function test values of the 89 patients in the analysis set. The median (quartiles) slope of forced vital capacity (FVC) was -20.0 (-79.3; 33.0) mL/year, and that of FEV_1 was -46.7 (-95.2; -15.0) mL/year. No correlation was detected between age or age at symptom onset and the slope of any pulmonary function parameter. A weak positive correlation was detected between the time since symptom onset and the DLco slope (measured value: r K=0.248, p=0.014; % predicted value: r K=0.246, p=0.015). Thus, DLco tended to fall more slowly in the patients who had been suffering with LAM for longer. Weak positive correlations were detected between the menopause and the slopes of FVC (measured value: r K=0.211, p=0.024; % predicted value: r K=0.218, p=0.019) and DLco (measured value: r K=0.315, p=0.007; % predicted value: r K=0.302, p=0.009). Thus, the postmenopausal patients exhibited slower reductions in FVC and DLco. When multiple regression analysis was performed using age as an additional explanatory variable, the menopause was associated

age-independently with the slopes of FVC (measured value: β=0.271, p=0.026; % predicted value: β=0.270, p=0.027) and DLco (measured value: β=0.366, p=0.013; % predicted value: β=0.349, p=0.019). However, when multiple regression analysis was performed using the time since symptom onset or the initial value of each pulmonary function parameter as an additional explanatory variable, the menopause was not associated with the DLco slope. A weak positive correlation was detected between renal angiomyolipoma and the slope of the FEV_1/FVC ratio (r K=0.235, p=0.018), but when multiple regression analysis was performed using tuberous sclerosis as an explanatory variable, no such correlation was observed.

The FEV_1 (% predicted value) recorded in the initial questionnaire was weakly positively correlated with the FEV1 slope (% predicted value) (r K=0.151, p=0.042). Furthermore, the initial DLco (% predicted value) was weakly positively correlated with the FEV_1 slope (% predicted value) (r K=0.219, p=0.009) and weakly inversely correlated with the DLco slope (% predicted value) (r K=-0.196, p=0.033). Thus, FEV1 tended to fall more slowly in the patients with higher FEV_1 and DLco, and DLco tended to fall more slowly in the patients with low DLco.

Comparison of pulmonary function test values and the rate of change between patients that exhibited initial FEV_1 (% predicted value) values of >70% (Group A) and ≤70% (Group B)

The results for Groups A and B are shown in Table 2. No significant difference in age or age at symptom onset was detected between the groups, but the time since symptom onset was significantly longer in Group B. All of the examined pulmonary function test parameters were significantly lower in Group B. Regarding the rate of change in pulmonary function, the slopes for FVC (measured and % predicted values) and FEV_1 (measured and % predicted values) were significantly lower in Group B; however, none of the other parameters differed significantly between the groups. Histograms of the distribution of the annual changes in FEV_1 (% predicted value) seen in the two groups are shown in Fig. 1.

Relationships between age or initial pulmonary function and the rate of change in pulmonary function in Groups A and B

No significant correlation was detected between age and the slope of any pulmonary function parameter in the analysis set, as described above, but a weak positive correlation was observed between age and the FEV1 slope in Group B (measured value: r K=0.306, p=0.009; % predicted value: r K=0.278, p=0.017) (Fig. 2a). No significant correlation was detected between onset age or the time since symptom onset and the FEV1 slope in Group A or B. In addition, no significant correlation was noted between the initial FEV1 and the FEV1 slope in Group A or B, but a weak positive correlation was detected between these parameters in the analysis set, as described above (Fig. 2b).

DISCUSSION

We analyzed the rate of change in pulmonary function seen in LAM patients using the Japanese national database of intractable diseases, which was started in October 2009. The mean reduction in FEV_1 in LAM patients has been reported to range from 60-118 mL/year[10,20,24,25]. In the MILES trial, which examined LAM patients that exhibited FEV_1 (% predicted value) values of ≤70% after bronchodilator administration, the mean reduction in FEV_1 seen over the course of the study in the placebo group was 134 mL/year6. In contrast, the mean reduction in FEV_1 was relatively small in our study; the mean reductions in FEV_1 in the analysis set and Group B were 58 mL/year and 95

mL/year, respectively. Since all patients that had been diagnosed with LAM were included in the National Research Project on Intractable Diseases regardless of the severity of their condition, our study might have included more data for patients with relatively mild LAM than previous studies. In addition, the low numbers of patients that were treated for pneumothorax during the observation period or suffered respiratory failure, in whom periodic pulmonary function tests are difficult, might also have affected our results.

One noteworthy finding of the present study was that Group B exhibited a significantly higher FEV1 reduction rate than Group A. In addition, a positive correlation was detected between age and the FEV_1 slope in Group B. Therefore, young LAM patients that exhibit FEV_1 (% predicted value) values of ≤70% are likely to display rapid reductions in FEV_1 in the future. In these patients, since the main effect of sirolimus on LAM is to prevent reductions in lung function[6,7], it is necessary to monitor disease progression at regular intervals and to consider the early stage treatment with a mTOR inhibitor. However, the FEV_1 reduction rate varies markedly among individuals. The actual onset time of LAM is often unclear, and the time taken to reach a specific (low) pulmonary function level varies among individuals. Therefore, in LAM it is necessary to regularly assess the degree of any changes in pulmonary function, even in elderly patients and those with relatively high FEV_1 values.

Regarding the weak positive age-independent correlations detected between the menopause and the slopes of FVC and DLco, the menopause was associated with the longer time since symptom onset (data not shown), which can lead to slower reduction in DLco, and when multiple regression analysis was performed using the time since symptom onset as an explanatory variable, no association between the menopause and the DLco slope was detected. Furthermore, the inclusion of patients who were receiving hormone therapy, which can lead to low initial pulmonary function values (data not shown) might have influenced our results, and when multiple regression analysis was performed using the initial pulmonary function as an explanatory variable, no association between the menopause and the DLco slope was detected. These relationships need to be examined in a study involving a greater number of subjects. Oprescu et al. reported that, in addition to age, angiomyolipoma was also an independent favorable prognostic factor in LAM[19]. In our analysis, renal angiomyolipoma, but not all forms of angiomyolipoma, displayed a weak positive correlation with the slope of the FEV1/FVC ratio; however, tuberous sclerosis might have acted as a confounding factor, and so the clinical significance of angiomyolipoma remains unclear.

The pulmonary function abnormalities that are most frequently associated with LAM are obstructive ventilatory impairment and a reduction in pulmonary diffusion capacity. In case series studies conducted in the 1990s, 35-51% of LAM patients exhibited obstructive ventilatory impairment, while the incidence of reduced pulmonary diffusion capacity was even higher (about 80%)26,27. In later studies, the incidences of these conditions were found to be 52-58 and 53-87%, respectively[24,25,28]. It is not appropriate to compare the above findings with those obtained in the present study because the analysis set included patients for whom no pulmonary diffusion capacity measurements were recorded, but the median (% predicted value) values obtained in the present study suggested that the reduction in DLco progressed more markedly than the reductions in FEV1 or the FEV1/FVC ratio. In reports by Taveira-DaSilva et al. and Lazor et al., the frequency of subsequent FEV1 reductions was higher among the patients with low initial pulmonary diffusion capacities[20,25], and a similar tendency was noted in our study. Further investigations are necessary to determine whether it is possible to

predict LAM progression at an early stage by measuring pulmonary diffusion capacity.

The main limitation of our study was the use of a database in which substantial amounts of relevant questionnaire data had not been registered or were missing. Thus, the rate of change in pulmonary function was predicted from data for a limited number of patients. Nevertheless, the questionnaires were input into the database by the staff in each prefecture, probably at random, and there was no marked difference in pulmonary function data between the whole group and the analysis set. Another limitation was the use of test data obtained at multiple institutions. Spirometry tests are usually performed in the absence of bronchodilators; thus, our study protocol differs from that employed during the MILES trial[6]. Concerning patient selection, the exclusion of patients with concomitant pleural effusion or pneumothorax was not complete, and the influence of bronchodilator treatment should also be considered. An analysis of the accumulated data that takes these factors into consideration is required in future.

Acknowledgements

This work was supported by grants to the Respiratory Failure Research Group from the Ministry of Health, Labour and Welfare, Japan.

REFERENCES

[1] Meraj R, Wikenheiser-Brokamp KA, Young LR, McCormack FX. Lymphangioleiomyomatosis: new concepts in pathogenesis, diagnosis, and treatment. Semin Respir Crit Care Med 2012;33:486-97.
[2] Harari S, Torre O, Moss J. Lymphangioleiomyomatosis: what do we know and what are we looking for? Eur Respir Rev 2011;20:34-44.
[3] Taveira-DaSilva AM, Moss J. Management of lymphangioleiomyomatosis. F1000Prime Rep 2014;6:116.
[4] Hammes SR, Krymskaya VP. Targeted approaches toward understanding and treating pulmonary lymphangioleiomyomatosis (LAM). Horm Cancer 2013;4:70-7.
[5] Henske EP, McCormack FX. Lymphangioleiomyomatosis - a wolf in sheep's clothing. J Clin Invest 2012;122:3807-16.
[6] McCormack FX, Inoue Y, Moss J, et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med 2011;364:1595-606.
[7] Taveira-DaSilva AM, Hathaway O, Stylianou M, Moss J. Changes in lung function and chylous effusions in patients with lymphangioleiomyomatosis treated with sirolimus. Ann Intern Med 2011;154:797-805.
[8] Bissler JJ, McCormack FX, Young LR, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med 2008;358:140-51.
[9] Seyama K, Kira S, Takahasyi H, et al. Longitudinal follow-up study of 11 patients with pulmonary lymphangioleiomyomatosis: Diverse clinical courses of LAM allow some patients to be treated without anti-hormone therapy. Respirology 2001;6:331-40.
[10] Johnson SR and Tattersfield AE. Decline in lung function in lymphangioleiomyomatosis: relation to menopause and progesterone treatment. Am J Respir Crit Care Med 1999;160:628-33.
[11] Matsui K, Beasley MB, Nelson WK, et al. Prognostic significance of pulmonary lymphangioleiomyomatosis histologic score. Am J Surg Pathol 2001;25:479-84.
[12] Kitaichi M, Nishimura K, Itoh H, Izumi T. Pulmonary lymphangioleiomyomatosis: a report of 46 patients including a clinicopathologic study of prognostic factors. Am J Respir Crit Care Med 1995;151:527-33.
[13] Taveira-DaSilva AM, Hedin C, Stylianou MP, et al. Reversible airflow obstruction, proliferation of abnormal smooth muscle cells, and impairment of gas exchange as predictors of outcome in lymphangioleiomyomatosis. Am J Respir Crit Care Med

2001;164:1072-6.
[14] Paciocco G, Uslenghi E, Bianchi A, et al. Diffuse cystic lung diseases: correlation between radiologic and functional status. Chest 2004;125:135-42.
[15] Avila NA, Kelly JA, Dwyer AJ, et al. Lymphangioleiomyomatosis: correlation of qualitative and quantitative thin-section CT with pulmonary function tests and assessment of dependence on pleurodesis. Radiology 2002;223:189-97.
[16] Crausman RS, Lynch DA, Mortenson RL, et al. Quantitative CT predicts the severity of physiologic dysfunction in patients with lymphangioleiomyomatosis. Chest 1996;109:131-7.
[17] Schmithorst VJ, Altes TA, Young LR, et al. Automated algorithm for quantifying the extent of cystic change on volumetric chest CT: initial results in Lymphangioleiomyomatosis. Am J Roentgenol 2009;192:1037-44.
[18] Taveira-DaSilva AM, Pacheco-Rodriguez G, Moss J. The natural history of lymphangioleiomyomatosis: markers of severity, rate of progression and prognosis. Lymphat Res Biol 2010;8:9-19.
[19] Oprescu N, McCormack FX, Byrnes S, Kinder BW. Clinical predictors of mortality and cause of death in lymphangioleiomyomatosis: a population-based registry. Lung 2013;191:35-42.
[20] Taveira-DaSilva AM, Stylianou MP, Hedin CJ, et al. Decline in lung function in patients with lymphangioleiomyomatosis treated with or without progesterone. Chest 2004;126:1867-74.
[21] Hayashida M, Seyama K, Inoue Y, et al. The epidemiology of lymphangioleiomyomatosis in Japan: A nationwide cross-sectional study of presenting features and prognostic factors. Respirology 2007;12:523-30.
[22] Sasaki E, NakamuraM, KidaK, et al. Reference values for spirogram and blood gas analysis in Japanese non-smoking healthy adults. J Jpn Respir Soc 2001;39:383-99 (Japanese).
[23] Nishida S, Kambe M, Sewake N, et al. Pulmonary function in healthy subjects and its prediction. 5. Pulmonary diffusing capacity in adults. Rinsho Byori 1976;24:941-7 (Japanese).
[24] Baldi BG, Freitas CS, Araujo MS, et al. Clinical course and characterisation of lymphangioleiomyomatosis in a Brazilian reference centre. Sarcoidosis Vasc Diffuse Lung Dis 2014;31:129-35.
[25] Lazor R, Valeyre D, Lacronique J, et al; Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires. Low initial KCO predicts rapid FEV1 decline in pulmonary lymphangioleiomyomatosis. Respir Med 2004;98:536-41.
[26] Chu SC, Horiba K, Usuki J, et al. Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. Chest 1999;115:1041-52.
[27] Urban T, Lazor R, Lacronique J, et al. Pulmonary lymphangioleiomyomatosis. A study of 69 patients. Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). Medicine 1999;78:321-37.
[28] Ryu JH, Moss J, Beck GJ, et al; NHLBI LAM Registry Group. The NHLBI lymphangioleiomyomatosis registry: characteristics of 230 patients at enrollment. Am J Respir Crit Care Med 2006;173:105-11.

Table 1: Clinical characteristics of 567 LAM patients (all LAM patients from the database except those that had undergone lung transplants) and the 89 LAM patients included in the analysis (analysis set) based on their initial questionnaires*

	Whole group (n=567)		Analysis set (n=89)	
Age (initial questionnaire), yr	40	(35; 47)	44	(37; 50)
Age at symptom onset, yr	36	(29; 41)	37	(30; 46)
Years since symptom onset	4	(1; 8)	5	(2; 9)
Clinical features, % (no.†)				
Tuberous sclerosis complex	19.8	(105/529)	14.6	(13/89)
Post-menopausal‡	33.5	(172/514)	44.6	(37/83)
	§			
Hormone therapy	19.8	(105/530)	23.3	(20/86)
History of pneumothorax**	53.1	(207/390)	41.3	(26/63)
Pleural effusion	12.0	(57/475)	10.5	(8/76)
Angiomyolipoma	44.0	(197/448)	37.0	(27/73)
Abdominal lymphangioleiomyoma	33.1	(144/435)	43.1	(31/72)
Continuous oxygen therapy	19.6	(111/567)	16.9	(15/89)
mTOR inhibitor treatment	3.5	(20/567)	0	(0/89)
Pulmonary function††				
FVC, L		(2.30; 3.17)	2.80	(2.32; 3.24)
FVC, % predicted value	2.74	(n=423)	95.0	(81.7; 107.8)
	92.9	(78.3; 104.4)		
		(n=423)		
FEV_1, L		(1.27; 2.35)	1.93	(1.48; 2.38)
FEV_1, % predicted value	1.88	(n=425)	75.9	(59.6; 95.8)
	74.2	(51.3; 93.0)		
		(n=425)		
Ratio of FEV_1 to FVC	71.0	(49.9; 81.4)	72.0	(56.6; 80.6)
		(n=421)		
DLco, ml/min/mmHg		(8.2; 14.9)	11.5	(8.5; 14.4)
DLco, % predicted value	11.3	(n=308)	50.8	(n=70)
	49.4	(36.3; 67.8)		(41.0; 68.7)
		(n=308)		(n=70)
DLco/VA, ml/min/mmHg/L		(2.2; 4.3)	3.3	(2.3; 4.2)
DLco/VA, % predicted value	3.3	(n=318)	59.9	(n=73)
	58.6	(38.6; 75.7)		(43.9; 74.7)
		(n=318)		(n=73)

*Data are presented as median (quartiles) values, unless noted otherwise. FVC: forced vital capacity, FEV_1: forced expiratory volume in 1 second, DLco: diffusing capacity for carbon monoxide, DLco/VA: ratio of DLco to alveolar volume

†Some patients were missing data for some items. The denominator indicates the number of patients for whom data were available.

‡Patients treated with hormone therapy were included.

§Outside of the 95% confidence interval of the estimated value for the analysis set.

**Since the presence/absence of a history of pneumothorax was only investigated in the patients making new applications, we did not have any information about this topic for patients whose initial questionnaire data were not registered. Therefore, the denominators for this parameter were lower than those for the other items.

††Pulmonary function data other than spirometry test results in the analysis set could not be collected from some patients, and the number of patients for whom data were available is shown in parentheses.

Table 2: Pulmonary function according to the initial questionnaire and the annual rate of change in pulmonary function in patients with FEV_1 (% predicted) values of >70% (Group A) and ≤70% (Group B)*

	Group A (n=52)		Group B (n=37)		P-value
Age (initial questionnaire), yr	43	(36.8; 49.3)	45	(38; 51)	0.494
Age at symptom onset, yr	38	(31.8; 46.5)	36	(29; 43.5)	0.220
Years since symptom onset	4	(1; 7)	7	(3; 13.5)	0.007
Initial pulmonary function					
FVC, L	3.08	(2.69; 3.38)	2.32	(2.07; 2.73)	<0.001
FVC, % predicted value	102.7	(90.3; 112.3)	82.4	(70.4; 94.9)	<0.001
FEV_1, L	2.31	(2.03; 2.62)	1.38	(0.97; 1.58)	<0.001
FEV_1, % predicted value	92.6	(81.3; 104.8)	57.3	(44.5; 62.3)	<0.001
Ratio of FEV_1 to FVC	78.1	(72.2; 81.7)	53.3	(44.1; 63.6)	<0.001
DLco, ml/min/mmHg†	12.9	(10.3; 15.4) (n=47)	9.4	(7.2; 11.6) (n=23)	0.003
DLco, % predicted value†	56.9	(46.5; 69.7) (n=47)	44.4	(32.7; 50.0) (n=23)	0.003
DLco/VA, ml/min/mmHg/L†	3.5	(2.8; 4.3) (n=47)	2.7	(1.9; 3.3) (n=26)	0.005
DLco/VA, % predicted value†	60.8	(49.2; 77.8) (n=47)	48.0	(33.7; 61.4) (n=26)	0.007
Rate of the annual change in pulmonary function					
FVC, ml	-7.4	(-51.2; 47.0)	-49	(-130.7; 16.2)	0.025
FVC, % predicted value	0.7	(-0.9; 2.3)	-0.9	(-4.4; 1.2)	0.013
FEV_1, ml	-37.1	(-88.5; 14.0)	-59.2	(-114.7; -27.4)	0.048
FEV_1, % predicted value	-0.4	(-2.5; 1.3)	-2.1	(-3.9; -0.6)	0.005
Ratio of FEV1 to FVC	-1.2	(-2.1; -0.1)	-1.4	(-3.9; -0.1)	0.279
DLco, ml/min/mmHg†	-0.3	(-0.8; 0.1) (n=39)	-0.3	(-0.6; 0.3) (n=19)	0.836
DLco, % predicted value†	-1.0	(-3.2; 0.6) (n=39)	-1.2	(-2.5; 1.3) (n=19)	0.888
DLco/VA, ml/min/mmHg/L†	-0.03	(-0.1; 0.07) (n=41)	-0.01	(-0.1; 0.06) (n=22)	0.762
DLco/VA, % predicted value†	-0.3	(-1.8; 1.8) (n=41)	0.01	(-2.0; 1.1) (n=22)	0.753

* Data are presented as median (quartiles) values. FVC: forced vital capacity, FEV_1: forced expiratory volume in 1 second, DLco: diffusing capacity for carbon monoxide, DLco/VA: ratio of DLco to alveolar volume

The annual rate of change in pulmonary function was determined by linear regression of the results of pulmonary function tests, which were performed a mean of 3.2 times (range, 3-5 times) in the 89 patients over a mean period of 28 months (range, 13-48 months). P-values were calculated using the Wilcoxon rank-sum test.

†Since patients whose pulmonary diffusion capacities were not measured were included in the analysis set, the number of patients for whom data were available is shown in parentheses.

Figure legends

Figure 1. Histograms of the distributions of the annual change in FEV_1 (% predicted value) in the patients with initial FEV_1 (% predicted value) values of >70% (Group A) and ≤70% (Group B)

The annual rate of change in FEV_1 (% predicted value) was significantly lower in Group B than in Group A. In the histograms, the patient frequency distribution showed a greater shift towards negative annual changes in FEV_1 (% predicted value) in Group B than in Group A.

Figure 1

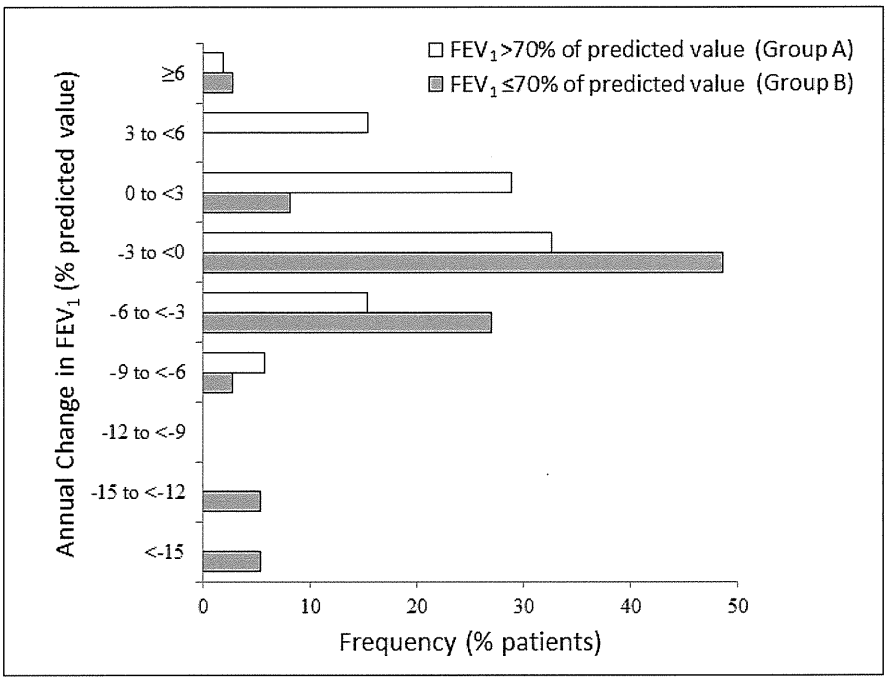
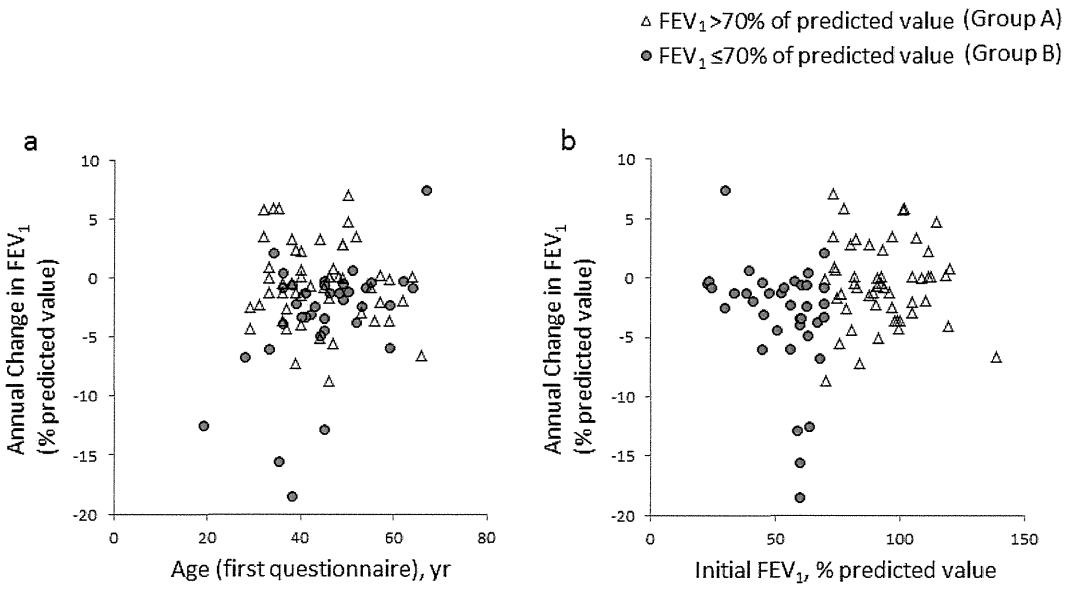


Figure 2. Relationships between age or the initial FEV_1 (% predicted value) and the annual rate of change in FEV_1 (% predicted value) in Groups A and B
(b) A weak positive correlation was detected between age and the FEV_1 slope in Group B (% predicted value: r K=0.278, p=0.017). (b) No significant correlation was observed between FEV_1 (%predicted value) and the rate of the subsequent change in FEV_1 in Group A or B, but a weak positive correlation was observed in the analysis set (r K=0.151, p=0.042).

Figure 2



α1-アンチトリプシン欠乏症 診療の手引き 2015

平井 豊博[1)]、瀬山 邦明[2)]、巽 浩一郎[3)]

1. 京都大学大学院医学研究科 呼吸器内科学
2. 順天堂大学大学院医学研究科 呼吸器内科学
3. 千葉大学大学院医学研究院 呼吸器内科学

はじめに

本手引きは、厚生労働科学研究費補助金（難治性疾患政策研究事業）「呼吸不全に関する調査研究」事業の一環として、本邦においてα1-アンチトリプシン欠乏症の診療に係る可能性のある呼吸器内科医を対象として作成した。そのため、内容の一部に専門性の高い医学用語が使われている。本症は専門性の高い診療が求められるので、本症を疑う患者（CQ5 参照）を診た医療従事者は専門施設での精査を奨めるべきである。

α1-アンチトリプシン欠乏症は、難病法（「難病の患者に対する医療等に関する法律」平成２６年法律第５０号）に基づいて平成 27 年７月１日施行された指定難病の一つ（疾病番号 231 番）である。従来は、「α1-アンチトリプシン欠損症」と呼称されたが、プロテアーゼ/アンチプロテアーゼバランス不均衡仮説から考慮すれば、肺の防御因子であるα1-アンチトリプシンの減少は COPD 発症素因になりうるため、「α1-アンチトリプシン欠乏症」と呼称することとなった。わが国では欧米よりもさらにきわめて希少な疾患であり、詳細な病態も不明な点が多いため、本手引きに記載している内容のほとんどは、欧米からの報告に基づいており、日本人の本症に関するエビデンスは乏しいのが実情である。わが国と海外諸国とでは、人種差のみならず、医療制度や社会的な環境なども異なっており、本症に関する日本人独自の内容を構築していくことは今後の課題である。

<総論>

CQ1：α1-アンチトリプシン（α1-AT）とは何ですか？

CQ2：α1-AT 欠乏症とはどのような病気ですか？

CQ3：なぜ肺気腫をきたすのですか？

CQ4：なぜ閉塞性換気障害をきたすのですか？

<診断>