AMERICAN THORACIC SOCIETY DOCUMENTS

Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines: Lymphangioleiomyomatosis Diagnosis and Management

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Background: Lymphangioleiomyomatosis (LAM) is a rare cystic lung disease that primarily affects women. The purpose of these guidelines is to provide recommendations for the diagnosis and treatment of LAM.

Methods: Systematic reviews were performed to summarize evidence pertinent to our questions. The evidence was summarized and discussed by a multidisciplinary panel. Evidence-based recommendations were then formulated, written, and graded using the Grading of Recommendations, Assessment, Development, and Evaluation approach.

Results: After considering the panel's confidence in the estimated effects, the balance of desirable (i.e., benefits) and undesirable (i.e., harms and burdens) consequences of treatment, patient values and preferences, cost, and feasibility, recommendations were formulated for or against specific interventions. These included recommendations for sirolimus treatment and vascular endothelial growth factor D testing and recommendations against doxycycline and hormonal therapy.

Conclusions: Evidence-based recommendations for the diagnosis and treatment of patients with LAM are provided. Frequent reassessment and updating will be needed.

Overview

This guideline synthesizes the evidence for emerging advancements in lymphangioleiomyomatosis (LAM) and then uses that evidence to formulate recommendations pertaining to the diagnosis and treatment of patients with LAM. The intent of the guideline is to empower clinicians to apply the recommendations in the context of the values and preferences of individual patients and to tailor their decisions to the clinical situation at hand. The guideline panel's recommendations (Table 1) are as follows:

- For patients with LAM with abnormal/declining lung function, we recommend treatment with sirolimus rather than observation (*strong recommendation based on moderate-quality evidence*).
- For selected patients with LAM with problematic chylous effusions, we suggest treatment with sirolimus before invasive management (*conditional recommendation based on very low-quality evidence*).
- We suggest NOT using doxycycline as treatment for LAM (*conditional recommendation based on low-quality evidence*).
- We suggest NOT using hormonal therapy as treatment for LAM (*conditional recommendation based on very low-quality evidence*). Hormonal therapies include progestins, gonadotrophin-releasing hormone agonists, selective estrogen receptor modulators like tamoxifen, and oophorectomy.

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- For patients whose computed tomography scan shows cystic abnormalities characteristic of LAM, but who have no other confirmatory clinical or extrapulmonary radiologic features of LAM, we recommend vascular endothelial growth factor D testing to establish the diagnosis of LAM before consideration of proceeding to diagnostic lung biopsy (*strong recommendation based on moderate-quality evidence*). The purpose of vascular endothelial growth factor D testing is noninvasive diagnostic confirmation of LAM. Other confirmatory features of LAM include tuberous sclerosis complex, angiomyolipomas, chylous pleural effusions or ascites, and cystic lymphangioleiomyomas.

Other questions pertaining to the management of LAM, such as issues regarding pregnancy, safety of air travel, pleural interventions, and use of bronchodilators, were deferred until the next version of the guideline.

Introduction

Lymphangioleiomyomatosis (LAM) is a rare, systemic neoplastic disease that is associated with cystic lung destruction, chylous fluid accumulations, and abdominal tumors, including angiomyolipomas and lymphangioleiomyomas (1, 2). LAM occurs

Table 1. Summary of the Recommendations Provided in This Guideline

Context	Recommendation	Strength of Recommendation	Confidence in Estimates of Effect
Treatment with mTOR inhibitors	For patients with LAM with abnormal/declining lung function, we recommend treatment with sirolimus rather than observation.	Strong	Moderate
	For selected patients with LAM with problematic chylous effusions, we suggest treatment with sirolimus before invasive management.	Conditional	Very low
Treatment with doxycycline	We suggest NOT using doxycycline as treatment for LAM.	Conditional	Low
Treatment with hormonal therapy	We suggest NOT using hormonal therapy as treatment for LAM. (“Hormonal therapy” includes the progestins, GnRH agonists, selective estrogen receptor modulators like tamoxifen, and oophorectomy.)	Conditional	Very low
VEGF-D as a diagnostic test	For patients whose CT scan shows cystic abnormalities characteristic of LAM but have no confirmatory clinical or extrapulmonary radiologic features of LAM, we recommend VEGF-D testing before consideration of proceeding to diagnostic lung biopsy. (“Confirmatory features of LAM” include tuberous sclerosis complex, angiomyolipomas, chylous pleural effusions or ascites, and cystic lymphangioleiomyomas.)	Strong	Moderate

Definition of abbreviations: CT = computed tomography; GnRH = gonadotrophin-releasing hormone; LAM = lymphangioleiomyomatosis; mTOR = mechanistic target of rapamycin; VEGF-D = vascular endothelial growth factor D.

almost exclusively in adult women, affecting approximately five per million (3), but has also been reported in adult men (4–7) and children (8). LAM occurs both sporadically and in patients with tuberous sclerosis complex (TSC), an inherited neoplastic syndrome associated with seizures, cognitive impairment, and tumor formation in multiple organs (9). Lung function declines at rates that can exceed typical age-related decline by two to four times or more (10–12). Dyspnea with daily activities, recurrent pneumothoraces, and hypoxia requiring supplemental oxygen develop in most patients within 10 years of symptom onset (13).

LAM has been reported to recur in transplanted lungs, consistent with a metastatic mechanism for the disease (14, 15), but has not been reported to cause graft failure or to jeopardize eligibility for transplant. Genetic studies have revealed clonal origins for neoplastic cells harvested from pulmonary and extrapulmonary lesions of individual patients (16, 17). The neoplastic cells that infiltrate the lung in patients with LAM have smooth muscle characteristics and a benign histological appearance (18), arise from an unknown source, circulate in the blood and lymphatic fluids (19, 20), and harbor inactivating *TSC1* or *2* gene mutations (17). The resulting loss of TSC gene function constitutively activates the mechanistic target of rapamycin (mTOR) signaling pathway, which regulates multiple cellular functions, including growth, motility, and survival (21). LAM cells also express the lymphangiogenic growth factor, vascular endothelial growth factor D (VEGF-D), which likely facilitates access to lymphatic channels and metastatic spread (22, 23). Only a fraction of cells within the LAM lesion contain mutations in tuberous sclerosis genes, suggesting that robust recruitment of stromal cells plays an important role in disease pathogenesis (24).

The purpose of these guidelines is to provide recommendations for the diagnosis and treatment of LAM that reflect the progress that has been made during the 5 years since the European Respiratory Society LAM Guidelines were published (25). The guidelines are not intended to impose a standard of care. They provide the basis for rational decisions in the diagnosis and treatment of LAM. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view these recommendations as dictates. No guidelines or recommendations can take into account all the often compelling unique individual clinical circumstances that guide clinical decision making. Therefore, no one charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines by rote or in a blanket fashion. Statements about the underlying values and preferences, as well as qualifying remarks, accompanying each recommendation are integral parts and serve to facilitate more accurate interpretation; they should never be omitted when quoting or translating recommendations from these guidelines.

Methods

Committee Composition

These guidelines represent a collaborative effort between the American Thoracic Society (ATS) and the Japanese Respiratory Society (JRS). The guideline development panel was co-chaired by F.X.M. and J.M. and consisted of clinicians and researchers with recognized expertise in LAM, including 22 pulmonologists, two pathologists, one radiologist, one nephrologist, and one molecular biologist. The pulmonologist panel consisted of experts in LAM (n = 14), interstitial and rare lung disease specialists (n = 3), general pulmonologists (n = 1), transplant pulmonologists (n = 3), and pleural disease specialists (n = 1). Two methodologists (J.L.B. and K.C.W.) with expertise in the guideline development process and application of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (26) were also members. Patient perspectives on the questions to be addressed by the Committee were provided through questionnaires distributed to the LAM community by the LAM Foundation.

Conflict-of-Interest Management

Guideline panelists disclosed all potential conflicts of interest according to ATS policies. The ATS conflict-of-interest and documents departments reviewed the disclosures and categorized potential panelists as having no conflicts, manageable conflicts, or disqualifying conflicts. Panelists with no conflicts were allowed to participate in all aspects of guideline development. Panelists with manageable conflicts were allowed to discuss evidence but were recused from formulating, writing, and grading recommendations related to their conflicts. Panelists with disqualifying conflicts were not allowed to participate. At least one co-chair and more than half of the panelists had to be completely free from all conflicts. The methodologists did not participate in the formulation of recommendations.

Guideline Panel Meetings

Several face-to-face meetings were held between 2008 and 2015, coinciding with the ATS annual conference, the LAM Foundation conference, and the American College of Chest Physicians conference, during which the guideline development panel discussed the scope of the document, the questions to be addressed, and the evidence. Multiple conference calls were held and frequent email correspondence was used to discuss issues requiring the input from all panelists.

The cosponsoring societies (the ATS and JRS) provided financial support for the meetings and conference calls as well as travel expenses. Additional support for travel of panelists to meetings was provided by the not-for-profit LAM Foundation and LAM Treatment Alliance. The ATS, JRS, and foundations had no influence on question selection, evidence synthesis, or recommendations.

Formulating Questions and Outcomes

The guideline development panel was divided into six groups: (*1*) natural history, modifiers, and prognosis; (*2*) nomenclature and diagnosis; (*3*) lifestyle; (*4*) treatment; (*5*) management; and (*6*) future directions. Clinical questions were developed, circulated among the panelists, and rated according to clinical relevance, with the goal of addressing the top 10 to 20 questions. Patient-important outcomes were selected *a priori* for each question and categorized as critical, important, or not important (27).

Literature Search and Study Selection

In collaboration with an ATS methodologist (J.L.B.), a search strategy was designed using medical subject heading keywords and text words. The searches were limited to human studies and articles in English or in any language with English abstracts. A librarian from the National Institute of Health (K.S.) performed the initial literature search in 2009. Four databases were searched: MEDLINE, EMBASE, Web of Science, and Scopus.

European Respiratory Society guidelines on LAM (25) were published in 2010, so the decision was made to temporarily halt the project to allow the evidence base to evolve. The project eventually reconvened with a smaller writing group of eight panelists (F.X.M., G.R.F., L.R.Y., N.G., V.C., S.R.J., K.C.W., and J.M.), narrowing the scope to four questions and then updating the literature searches for those questions. The same principals regarding management and adjudication of conflicts that were described for the larger Committee were applied to the writing group. The writing group circulated all questions and recommendations to all Committee members and incorporated modifications and suggestions before initial submission and after the initial review was complete.

The literature searches were updated in July 2014 and July 2015, which included studies published before May 2015. Committee members were also queried for any additional studies not identified by the search. The search results were placed into a reference management software database (EndNote) and distributed to selected panelists.

Prespecified criteria were used to select relevant studies using a two-step process. The first step involved excluding or including studies on the basis of title and abstract alone. The second step involved excluding or including studies on the basis of a full text review. An independent reviewer verified all study selections; disagreements were resolved by discussion and consensus.

Evidence Synthesis

The body of evidence for each question was summarized in collaboration with one of the methodologists (K.C.W.). Extraction of crude data followed by pooling via metaanalysis to derive a single estimate of effect was planned; however, the studies identified were not amenable to pooling because outcomes were variably reported by different studies or, in some cases, incompletely reported. The strategy was then changed to a qualitative evidence synthesis rather than a quantitative evidence synthesis.

The quality of the body of evidence was rated using the GRADE approach (28). The quality of evidence indicates the panel's confidence in the estimated effects. It was based on systematic consideration of the following criteria: study design, risk of bias, precision, consistency, directness of the evidence, risk for publication bias, presence of dose–effect relationship, magnitude of effect, and assessment of the effect of plausible residual confounding or bias. On the basis of these criteria, the quality of evidence was categorized as high, moderate, low, or very low.

All panelists reviewed the evidence summary and the quality of evidence rating. Feedback was provided and revisions were made if deemed appropriate. Disagreements were resolved by discussion and consensus.

Development of Recommendations

The guideline development panel formulated recommendations on the basis of the evidence synthesis. Recommendations were based on the following: the balance of desirable consequences (i.e., benefits) and undesirable consequences (i.e., harms, burdens, and costs) compared with alternative management options, the quality of the evidence, patient values and preferences, and resource use. Recommendations were formulated by discussion and consensus; none of the recommendations required voting. The recommendations were worded using the GRADE approach. The final recommendations were drafted by the writing group and were reviewed and approved by the larger Committee.

The recommendations were rated as strong or conditional in accordance with the GRADE approach. The words "we recommend" indicate that the recommendation is strong, whereas the words "we suggest" indicate that the recommendation is conditional. Table 2 describes the interpretation of strong and conditional recommendations by patients, clinicians, and health care policy makers.

Manuscript Preparation

The working group (F.X.M., G.R.F., L.R.Y., N.G., V.C., S.R.J., K.C.W., and J.M.) drafted the final guideline document. The manuscript was then reviewed by the entire guideline development panel, and their feedback was incorporated into the final draft.

Updating

To remain useful, guidelines need to be updated regularly as new knowledge accumulates. These guidelines addressed a limited number of selected questions, which will require periodic additions and revisions. In addition, there exist numerous clinically important questions that were not addressed in these guidelines that should be addressed in future versions. The guideline development panel hopes to update these guidelines within the next 5 years.

Table 2. Interpretation of Strong and Conditional Recommendations for Stakeholders

Implications for	Strong Recommendation	Conditional Recommendation
Patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

Question 1: Should Patients with LAM Be Treated with Sirolimus?

Background

Sporadic and TSC-associated forms of LAM are both caused by inactivating mutations in one of the TSC genes. Defective TSC genes lead to loss of tuberin-hamartin protein complex function, resulting in constitutive activation of the mTOR pathway. Activated mTOR, in turn, causes perturbations in multiple cellular processes, including growth, motility, and survival (29). Sirolimus is an exquisitely targeted small molecule that forms a complex with FKBP12, which then binds to mTOR and blocks activation of downstream kinases, restoring homeostasis in cells with defective TSC function (21). Sirolimus shrinks tumors in TSC animal models (30, 31).

Summary of the Evidence

Our systematic review identified two uncontrolled trials (32, 33) and one randomized trial (34) that evaluated the effects of sirolimus on angiomyolipoma size, lung function, quality of life, functional performance, and/or adverse effects in patients with LAM.

The initial trial was an open-label, uncontrolled trial in which 25 patients with TSC or LAM were treated with escalating doses of sirolimus for 12 months, followed by an observation period of 1 year (33). The angiomyolipoma (AML) volume decreased from a least-square mean of 71.6 ml (95% confidence interval [CI], 24.9–118.2 ml) at baseline to 36.5 ml (95% CI, −10.2 to 83.2 ml) after 12 months of sirolimus therapy, a statistically significant volume reduction of 53.2% (95% CI, 46.3–60.2%). Eleven patients with LAM also had their pulmonary function assessed, which demonstrated improvement in the FVC (least-square mean increase of 390 ml; 95% CI, 180–600 ml) and a trend toward improvement in the FEV_1 (least-square mean increase of 120 ml; 95% CI, −10 to 240 ml). There was also a decrease in the residual volume (least-square mean decrease of 440 ml, 95% CI, −90 to −790 ml) but no changes in the total lung capacity, diffusion capacity, or 6-minute-walking distance. Ten serious adverse events occurred during the trial, six of which were considered probably or possibly related to the sirolimus (diarrhea, infections, stomatitis, and an AML hemorrhage). Preliminary results from a similar open-label, uncontrolled trial of six patients with LAM and seven patients with TSC who were being treated with sirolimus for 2 years were also published (32). An interim assessment after 1 year of therapy revealed that all of the patients had a reduction in the size of their AMLs (the mean reduction in the sum of the longest diameters was 26.1%). However, in the four patients with LAM with data available at 1 year, no change in lung function was reported. All of the patients had adverse events, including mouth ulcers, hyperlipidemia, and peripheral edema. The results of these trials, combined with the preclinical data and the need for assessment of the benefits and risks of sirolimus with potential confounders minimized, provided the rationale for conducting a randomized controlled trial for LAM.

The MILES (Multicenter International LAM Efficacy of Sirolimus) Trial was a double-blind, randomized, parallel group trial in which 89 patients with LAM and moderate lung impairment (defined as $FEV_1 < 70\%$ predicted) were randomly assigned to receive treatment with sirolimus or placebo for 12 months, followed by 12 months of observation (34). Sirolimus treatment resulted in stabilization of lung function decline compared with placebo (1 ± 2 vs. -12 ± 2 ml/mo, respectively; $P < 0.001$). Patients who received sirolimus had improvement in their FVC, whereas those who received placebo had ongoing worsening of their FVC (8 ± 3 vs. -11 ± 3 ml/mo, respectively; $P < 0.001$). Quality of life measured by the EuroQOL scale improved in the sirolimus group and declined in the placebo group (0.39 ± 0.19 vs. -0.21 ± 0.20 units/mo, respectively; $P = 0.03$), and a trend toward better daily functioning was observed using the Functional Performance Inventory (0.005 ± 0.004 vs. -0.009 ± 0.004 units/mo, respectively; $P = 0.03$). During the subsequent observation year in which sirolimus and placebo were withdrawn, the lung function decline resumed in the sirolimus group and paralleled that of the placebo group. Adverse effects due to sirolimus were common; however, serious adverse effects were similar in both groups. The most common adverse events were mucositis, diarrhea, nausea, hypercholesterolemia, acneiform rash, and swelling in the lower extremities.

In addition to the progressive cystic destruction of lung parenchyma, patients with LAM can develop chylous complications secondary to infiltration of lymphatic channels, lymph nodes, or the thoracic duct by migrating LAM cells (35). The most common lymphatic manifestations of LAM include formation of lymphangioleiomyomas and collection of chylous fluid in the pleural and peritoneal cavities (35, 36).

Our systematic review identified one open-label, uncontrolled trial (37) and six case reports (38–43) that addressed the role of sirolimus in the management of chylous effusions. Patients with chylous pleural effusions and other lymphatic manifestations of LAM were enrolled in an open-label, uncontrolled trial (37). Twelve patients with chylous fluid accumulations (pleural effusions and/or chylous ascites) were treated with sirolimus. All of the patients had complete or near-complete resolution of their chylous fluid accumulations. Adverse effects related to sirolimus were common, but manageable, and did not lead to drug discontinuation (37). Several case series have also supported the effectiveness of sirolimus in the management of chylous effusions (38–43).

Benefits

Sirolimus treatment improved lung function (as measured by the FEV_1 and FVC), functional performance, and quality of life in patients with LAM. It also reduced the volume of angiomyolipomas, lymphangioleiomyomas, and chylous accumulations.

Harms

In general, sirolimus was well tolerated, and adverse effects were mild. The most common adverse events were mucositis, diarrhea, nausea, hypercholesterolemia, acneiform rash, and swelling in the lower extremities. Additional toxicities that are encountered with mTOR inhibitors include ovarian cyst formation, dysmenorrhea, proteinuria, elevated liver function tests, drug-induced pneumonitis, and the risk of infections due to immunosuppression.

Other Considerations

The guideline panel's judgments regarding the effects of sirolimus in patients with LAM who have impaired lung function were informed primarily by a single randomized trial (the MILES trial) with

imprecise estimated effects due to the small number of patients; this constitutes moderate-quality evidence. The guideline panel's judgments regarding the effects of sirolimus in patients with LAM who have chylous fluid accumulations were informed by one small, uncontrolled trial and multiple case reports, which constitute very low-quality evidence.

Recommendation 1a

For patients with LAM with abnormal/declining lung function, we recommend treatment with sirolimus rather than observation (*strong recommendation based on moderate-quality evidence*).

Remarks. Abnormal lung function is defined as an FEV_1 less than 70% predicted. The goals of sirolimus therapy are to stabilize lung function, improve functional performance, and improve overall quality of life.

Recommendation 1b

For patients with LAM with symptomatic chylous fluid accumulations, we suggest treatment with sirolimus before invasive management (*conditional recommendation based on very low-quality evidence*).

Remarks. Chylous fluid accumulations include chylous effusions and chylous ascites. Invasive management refers to interventions such as intermittent percutaneous drainage and insertion of indwelling drainage devices. Importantly, chylous fluid accumulations may require several months to respond to mTOR inhibitors and can recur after treatment cessation.

Values and Preferences

These recommendations place a high value on the potential benefits of therapy and lower value on the adverse effects and costs associated with sirolimus treatment.

Research Opportunities

There exist potential practice-changing research opportunities involving dosing, patient selection, agent selection, the timing of initiation of therapy, and duration of therapy. With respect to dosing, the sirolimus dose was adjusted during the MILES trial to maintain a serum trough between 5 and 15 ng/ml. More recent retrospective data suggest that treatment with low-dose sirolimus (serum trough level $<$ 5 ng/ml) may also be effective in stabilizing lung function (42). Reducing the dose has the potential to reduce adverse effects related to the drug and may enhance the safety of long-term treatment with sirolimus.

With respect to patient selection, reduced FEV_1 has been used to define abnormal lung function in trials, and the recommendations above have been formulated based on that parameter. However, some patients with LAM present with normal or near-normal pulmonary spirometry but an elevated residual volume ($>$120% predicted), reduced diffusing capacity ($<$80% predicted), exercise-induced desaturation ($<$90% predicted with walking), or resting hypoxemia ($Pa_{O_2} < 70$ mm Hg). In clinical practice, several of the guideline panelists have interpreted these changes to represent a significant disease burden due to LAM, especially in patients who are symptomatic, and have offered sirolimus treatment on a case-by-case basis, in situations where the benefits of therapy outweigh the risks. A prospective trial will be required to establish the safety and efficacy of this approach.

When selecting therapy in patients with normal lung function, many of the guideline panelists consider factors including rate of FEV_1 decline and the patients' menopausal status. In patients with LAM who have normal spirometry, several of the panelists have offered sirolimus therapy to those who have estimated annual loss of FEV_1 of 90 ml/yr or greater. Although there are no prospective data available to support this arbitrary benchmark, the rationale is that it represents a rate of decline that is at least threefold greater than the normal rate of FEV_1 loss (approximately 30 ml/yr). The same principles may be applied to the patient with TSC-LAM, because the rate of lung function decline is similar in both sporadic LAM and TSC-LAM when matched for baseline severity (44, 45) and to postmenopausal patients, a population in whom the rate of lung function decline is typically slower (37, 46, 47). Given the inherent variation in the measurement of FEV_1, the panelists emphasized that in practice it is important to base decisions on at least three measurements over at least 6 months and preferably on three or more measurements made over 12 to 18 months.

With respect to selecting an agent, everolimus has been reported to stabilize lung function in a small, open-label, uncontrolled trial (48). Additional studies are necessary to confirm and better delineate the risks and benefits of everolimus; however, several of the guideline panelists have offered everolimus as an alternative choice. Combination therapies with sirolimus or everolimus and other drugs targeting signaling pathways important in disease pathogenesis also need to be explored.

With respect to timing the initiation of therapy, the need for continuous treatment for sustained benefit and the understudied long-term safety profile of sirolimus in patients with LAM emphasize the importance of acquiring a better understanding of the differences in outcomes among patients in whom treatment is initiated early versus those who are carefully monitored initially and then treated later. Prospective trials are needed to help fill these knowledge gaps.

Finally, with respect to optimal duration of therapy, less than 5 years has passed since the MILES trial was published, and data on the risks and benefits of long-term sirolimus treatment in LAM remain incomplete. Because mTOR treatment in LAM is suppressive, durable benefit requires continuous treatment. However, the rate of lung function decline is known to slow after menopause, and in clinical practice many of the guideline panelists incorporate this knowledge into decision making regarding duration of therapy. The longest reported follow up of patients with LAM treated with sirolimus to date demonstrates durable safety and efficacy over 3.5 years (49). A study of the long-term safety and efficacy of sirolimus in this patient population is being addressed by establishment of a registry of patients with LAM who are on treatment or being considered for treatment with mTOR inhibitors (clinicaltrials.gov, NCT02432560).

Question 2: Should Patients with LAM Be Treated with Doxycycline?

Background

Degradation of the extracellular matrix by proteolytic enzymes such as matrix metalloproteinases (MMPs) likely contributes to cyst formation in patients with LAM (50). MMP-2 and MMP-9 are

overexpressed in the serum as well as lung tissue adjacent to cystic areas in patients with LAM (50–52). Doxycycline is a tetracycline antibiotic that inhibits the production and activity of several MMPs, including MMP-2 and MMP-9 (53).

Summary of the Evidence

Our systematic review identified a case report (54), two uncontrolled trials (55, 56), and one randomized trial (57) that evaluated the effects of doxycycline in patients with LAM. The case report was the first publication to suggest a potential benefit from doxycycline therapy (54). It described a patient with LAM who had severe pulmonary impairment; treatment with doxycycline was accompanied by an improvement in gas exchange, functional performance, and lung function (FEV_1 increased from 0.48 L [21% predicted] to 0.91 L [35% predicted], and baseline to peak exertion oxyhemoglobin desaturation decreased from approximately 14 to 4%). On the basis of these improvements, the patient was reportedly removed from the lung transplantation list. This publication led to an increase in off-label use of doxycycline in patients with LAM (58).

The scientific rationale and promising case report led to two open-label, uncontrolled trials of doxycycline in patients with LAM. In one trial, 41 patients with LAM were prescribed doxycycline in a dose-escalating manner for a total of 6 months, with serial measurements of serum and urine MMPs. Doxycycline treatment led to a reduction in serum and urinary MMPs and was well tolerated in most patients (55). Nausea, diarrhea, and epigastric pain were the most frequent side effects, but most were self-limited, and only one patient discontinued therapy due to the side effects. Clinical outcomes other than adverse effects were not measured. In the other trial, 31 patients were treated with 12 months of doxycycline (56). MMP levels were reduced by treatment in all patients, but the mean FEV_1 declined at a rate of 70 ml/yr. The patients appeared to fall into two groups, doxycycline responders (n = 13) and nonresponders (n = 18). The responders had a higher baseline FEV_1 (84% predicted) and a median FEV_1 increase of 70 ml over 1 year, and the nonresponders had a lower baseline FEV_1 (75% predicted) and a median FEV_1 decrease of 140 ml over the same period. The differential effects may have been due to greater doxycycline efficacy in patients with mild disease or, alternatively, due to responders and nonresponders having a differential rate of lung function decline due to variable baseline disease severities. A follow-up analysis supported the latter, demonstrating that most of the "doxycycline responders" continued to decline at a constant rate that was similar to the nonresponders (59).

A single-center, randomized, double-blind, placebo-controlled trial of doxycycline in 23 women with LAM and moderate lung function impairment (mean FEV_1, 58% predicted) followed the uncontrolled trials (57). Twelve patients were treated with doxycycline and 11 patients were treated with placebo for 24 months. The trial detected no differences between doxycycline and placebo groups in the rate of FEV_1 decline (−33.5 vs. −39.6 ml/yr, respectively; 95% CI, −67 to 79 ml/yr), shuttle walk distance (4 vs. −1 m, respectively; 95% CI, −207 to 197 m), diffusion capacity (0.04 vs. 0.08 mmol/kPa-min, respectively; 95% CI, −0.47 to 0.69 mmol/kPa-min, respectively), or quality of life. More adverse effects were reported by the doxycycline group, but only dyspepsia and photosensitivity were attributed to the drug.

Benefits

No beneficial effects due to doxycycline therapy were confirmed in patients with LAM who had respiratory impairment.

Harms

Potential adverse effects due to doxycycline include dyspepsia, photosensitivity, and possibly also nausea and diarrhea.

Other Considerations

The guideline panel's judgments regarding the effects of doxycycline in patients with LAM who have impaired lung function were informed primarily by a single randomized trial, whose estimated effects were imprecise due to the small number of patients and failure to meet enrollment targets required for adequate power. This constitutes low-quality evidence.

Recommendation 2

We suggest NOT using doxycycline as treatment for LAM (*conditional recommendation based on low-quality evidence*).

Values and Preferences

This recommendation places a high value on avoiding the risks and costs associated with a treatment that has not been proven to improve outcomes.

Research Opportunities

The effects of doxycycline on clinical outcomes when used in combination with other treatment modalities like mTOR inhibitors (e.g., sirolimus) or hormonal therapy (e.g., progestins, gonadotrophin-releasing hormone [GnRH] agonists, selective estrogen receptor modulators (SERMs) like tamoxifen, and oophorectomy) have not been evaluated in patients with LAM.

Question 3: Should Patients with LAM Be Treated with Hormonal Therapy?

Background

Hormonal factors have long been believed to play a role in the pathogenesis of LAM. Evidence behind this notion arises from the following observations: symptomatic LAM occurs almost exclusively in women (29); there are reports of disease worsening in a cyclical pattern associated with the menstrual cycle (60), during pregnancy (61, 62), and after exposure to estrogen-containing drugs (63, 64); LAM cells are known to express both estrogen and progesterone receptors (65); and there is a relative stabilization of the disease course in postmenopausal women with LAM (11). On the basis of these observations, hormonal manipulation with various agents, especially progesterone, has been used for off-label treatment of patients with LAM for decades.

Summary of the Evidence

Our literature search identified a published systematic review (66) that included 30 case reports and case series related to the treatment of LAM with hormonal therapy. Once the studies included in the published systematic review were combined with those that we detected via our own systematic review, there were 37 relevant studies available to inform the guideline panel. These included eight case reports and case series that evaluated oophorectomy (67–74), four case reports and case series that evaluated anti-estrogen therapies (75–78), one case report that evaluated androgen

therapy (79), six case reports and case series that evaluated progesterone therapy (80–85), two controlled observational studies that evaluated progesterone therapy (11, 12), two case series that evaluated GnRH agonists (86, 87), and 14 case reports and case series that evaluated multiple therapies or various combinations of therapies (88–100).

Our synthesis of the evidence did not consider the case reports because of the high risk of publication bias (i.e., patients with successful outcomes are more likely to be submitted by clinicians as case reports). Instead, we used the controlled observational studies and case series to inform the guideline panel's judgments. Generally speaking, the reported effects of various hormonal therapies were inconsistent both within reports and across reports.

Oophorectomy. Oophorectomy was the subject of a small case series, consisting of three patients with LAM who had radiographic abnormalities, progressive dyspnea, and abnormal lung function (68). All three patients underwent oophorectomy. One patient improved dramatically after surgery (FVC improved from 58 to 88% predicted), another patient had modest improvement (FVC improved from 49 to 68% predicted), and the third patient stabilized (FVC remained at 79% predicted).

Serum estrogen response modulators. Tamoxifen was the subject of a small case series, consisting of three patients with LAM who had both pulmonary and abdominal manifestations (76). Two of the patients died from progressive pulmonary disease despite 4 months of tamoxifen therapy. The third patient stabilized before beginning tamoxifen and remained stable during the subsequent 5.5 years that she received tamoxifen. A randomized, controlled trial comparing an aromatase inhibitor, letrozole, with placebo in postmenopausal patients with LAM has been completed, but the results have not yet been published (NCT01353209).

Progesterone. In a retrospective cohort study of 275 patients with LAM, the rate of decline in the diffusion capacity was higher among those who received progesterone than among those who did not receive progesterone (2.8% predicted for intramuscular progesterone, 3.6% predicted for oral progesterone, and 1.6% predicted for no progesterone); however, there was no difference in the yearly rate of decline of FEV_1 (1.9% predicted for intramuscular progesterone, 2% predicted for oral progesterone, and 0.5% predicted for no progesterone [12]). These findings were contradicted by another retrospective cohort study of 43 English patients with LAM that similarly compared those who received progesterone with those who did not receive progesterone (11). Progesterone use in the British study was associated with a significantly decreased rate of FEV_1 decline among premenopausal patients (mean difference, 104 ml/yr; 95% CI, 7–201 ml/yr, respectively), a significantly decreased rate of diffusion capacity decline among premenopausal patients (mean difference, 1.96 ml/min/mm Hg/yr; 95% CI, 0.54–3.38 ml/min/mm Hg/yr, respectively), and a trend toward a lower rate of FEV_1 decline among all patients (mean difference, 123 ml/year; 95% CI, −23 to +269 ml/yr, respectively).

GnRH agonists. A case series of nine patients with LAM who were treated with the GnRH agonist goserelin revealed that treatment was associated with increases in the FEV_1 and FVC of 80 and 130 ml, respectively (87). In contrast, another case series evaluated the effects of the GnRH agonist triptorelin in 11 patients with LAM and found no evidence of benefit as spirometry, lung volumes, diffusion capacity, and exercise capacity all remained unchanged and oxygenation worsened over a 3-year period (86). Therapy was associated with loss of bone mineral density.

Combination therapy. Several case series evaluated more than one therapy and/or combination therapy (10, 88, 92). A case series described 16 patients with LAM who had undergone oophorectomy, 9 patients who had been treated with tamoxifen, and 19 patients who had been treated with progesterone (88). Among those who underwent oophorectomy, none improved, 4 (25%) remained stable, 11 (69%) worsened, and 1 was lost to follow up. Among those treated with tamoxifen, none improved, three (33%) remained stable, and six (67%) deteriorated. Finally, among those treated with medroxyprogesterone, 2 (11%) improved, 6 (32%) remained stable, and 11 (58%) deteriorated. Another case series evaluated 69 patients with LAM, among whom 57 (82.6%) had been treated with progesterone, tamoxifen, oophorectomy, or a GnRH agonist, alone or in combination. Only four patients (7%) had an improvement in their lung function while on hormonal therapy (10).

Benefits

No beneficial outcomes were consistently demonstrated in patients with LAM who received hormonal therapy.

Harms

Most studies did not report adverse effects, with the exception of one report of decreased bone density associated with therapy. However, the side effects of hormonal therapy are well known, and there is no reason to expect that they would occur less often in patients with LAM.

Other Considerations

The guideline panel's judgments regarding the effects of progesterone in patients with LAM were informed by two observational studies that provided inconsistent results. Its judgment regarding all other hormonal therapies was informed by small case series and case reports. This constitutes very low-quality evidence, which provides little confidence in the estimated effects of hormonal therapy.

Recommendation 3

We suggest NOT using hormonal therapy as treatment for LAM (*conditional recommendation based on very low-quality evidence*).

Remarks. Hormonal therapies include progestins, GnRH agonists, SERMs like tamoxifen, and oophorectomy. For patients who are already using hormonal therapy for nonpulmonary reasons, the guideline panel advocates discontinuing therapies with estrogen agonist properties, such as SERMs. We do not necessarily discourage the use of GnRh agonists or progestins in patients who are already on treatment with these agents for nonpulmonary indications or the use of low-dose, drug-eluting intravaginal or intrauterine devices (IUDs) that are believed to be safe for use in patients with other sex steroid–responsive tumors, such as breast or ovarian cancers.

Values and Preferences

This recommendation places a high value on the adverse effects and costs of treatment with hormonal therapy and a lower value on the sporadic benefits supported by very low-quality evidence.

Research Opportunities

Although the current evidence does not suggest a beneficial role of hormonal therapy in patients with LAM, there may be subgroups of patients with LAM who might benefit, such as premenopausal women with disease manifestations (such as dyspnea or pneumothorax) that vary with the menstrual cycle. In addition, progestins may be acceptable for use as contraceptives for patients with LAM. Randomized controlled trials of hormonal agents, either alone or in combination with mTOR inhibitors, are needed to better assess the impact of hormonal manipulation on the course of LAM.

Question 4: Should VEGF-D Be Used to Confirm the Diagnosis of LAM in Women with Compatible Cystic Change on Computed Tomography of the Chest?

Background

The diagnosis of LAM should be accomplished using the least invasive means possible. Although the accuracy of LAM diagnosis on the basis of high-resolution computed tomography (HRCT) of the chest is high for experts in LAM (101), basing the diagnosis on HRCT alone is inadvisable for many clinical decisions. A confident clinical diagnosis of LAM can be established when cystic change on HRCT is typical for LAM (e.g., diffuse, thin-walled, round) and accompanied by any of the following clinical features: TSC, renal angiomyolipoma, cystic lymphangioleiomyoma, or chylous pleural effusions in the chest and/or abdomen (25). In cases where none of these diagnostic criteria are met, or absolute certainty is required, a pathological diagnosis of LAM is most commonly obtained from biopsy of the lung by video-assisted thoracoscopy or by transbronchial biopsy (102, 103). Less commonly, tissue for histopathology can be obtained by thoracotomy, biopsy of abdominal or pelvic lesions, or cytological examination of aspirates from chylous fluids or lymph nodes (104). Serum VEGF-D has been proposed as a diagnostic biomarker that obviates the need for invasive procedures to establish the diagnosis of LAM in the subset ($\sim$70%) of patients with cystic lung disease who have elevated levels ($\geqslant$800 pg/ml).

Summary of the Evidence

Our systematic review identified seven studies that evaluated serum VEGF-D as a potential noninvasive diagnostic test for LAM (105–111). Serum VEGF-D levels were elevated in a majority of women with LAM but were normal in women with other cystic lung diseases, including pulmonary Langerhans cell histiocytosis, emphysema, follicular bronchiolitis, lymphoid interstitial pneumonia, and Birt-Hogg-Dubé syndrome. The optimal threshold for discriminating cystic lung disease due to LAM from cystic lung disease due to another cause varied across studies, ranging from 332 pg/ml (111) to 850 pg/ml (110), with most estimates falling between 600 and 800 pg/ml.

The guideline panel made an *a priori* decision to recommend serum VEGF-D as a diagnostic test if the evidence synthesis showed that it predicts LAM with a sensitivity greater than 70% and a specificity greater than 90%. The rationale was to minimize false-positive results (i.e., achieve high specificity), because an incorrect diagnosis of LAM will lead to missed opportunities to treat the correct disease, as well as the adverse effects and costs of inappropriate treatment of LAM. The guideline panel understood that minimizing false-positive results may come at the expense of more false-negative results (i.e., lower sensitivity), but this was deemed acceptable because the likely consequence of a false-negative result is that the patient will proceed to a lung biopsy, which would have been the usual next diagnostic test if the patient had not undergone VEGF-D testing.

Three diagnostic accuracy studies reported the test characteristics of serum VEGF-D (105, 106, 108). One study determined that, using a diagnostic threshold of 600 pg/ml, serum VEGF-D detected LAM with a sensitivity and specificity of 84 and 98%, respectively, in 48 patients with cystic lung disease of unknown etiology (106). The sensitivity and specificity changed to 73 and 100%, respectively, when the diagnostic threshold was increased to 800 pg/ml. A similar study enrolled 75 patients with cystic lung disease of unknown etiology and reported that serum VEGF-D identified LAM with a sensitivity and specificity of 87 and 90%, respectively, using 468 pg/ml as the diagnostic threshold (108). Finally, a study that included 38 patients with LAM, 29 healthy control subjects, and 27 patients with other cystic diseases demonstrated the serum VEGF-D identified LAM with a sensitivity and specificity of 86 and 91%, respectively, using 574 pg/ml as the diagnostic threshold, and with a sensitivity and specificity of 76 and 98%, respectively, using 750 pg/ml as the diagnostic threshold (105). Thus, all three studies found sensitivities and specificities that exceeded the guideline panel's *a priori* threshold for recommending testing.

We recommend that the higher VEGF-D threshold of 800 pg/ml be used (106). Assuming that 30% of patients who present with cystic lung disease of unknown etiology have LAM, and that the sensitivity and specificity of serum VEGF-D testing are 73 and 99% (a blended average of the two VEGF-D studies above that had higher thresholds), respectively, then for every 1,000 patients who undergo serum VEGF-D testing, 219 patients with LAM will be spared an invasive lung biopsy for diagnostic confirmation (true-positive results), 81 patients with LAM will proceed to lung biopsy for diagnostic confirmation (false-negative results), and 10 patients will be incorrectly diagnosed as having LAM (false-positive results). The true false-positive rate may be less than this, because the only study that established the 800 pg/ml diagnostic threshold reported 100% specificity at that level and used sample processing methods currently in use in the College of American Pathologists/Clinical Laboratory Improvement Amendments laboratory (106).

Serum VEGF-D levels appear to vary according to the disease manifestations. As examples, one study reported higher levels among patients with LAM with lymphatic involvement than in those without lymphatic involvement (107), whereas another study in patients with tuberous sclerosis complex reported that a serum VEGF-D level of 800 pg/ml effectively discriminated between patients with and without cystic changes on CT scan of the chest (105, 106).

Serum VEGF-D has also been evaluated as a potential prognostic and predictive biomarker. In the MILES trial, median serum VEGF-D concentrations were similar at baseline in the sirolimus and placebo groups but over the treatment year declined in the sirolimus group while

remaining stable in the placebo group. Moreover, a higher baseline VEGF-D level was associated with both better lung function response in the sirolimus group and more rapid lung function decline in the placebo group. Each one-unit increase in baseline log (VEGF-D) was associated with a between-group difference in baseline-to–12-month FEV_1 change of 134 ml ($P = 0.0007$) (112). In another study, a serum VEGF-D greater than 800 pg/ml was associated with a faster rate of decline of FEV_1 (120 ml/yr) compared to patients with a serum VEGF-D less than 800 pg/ml (50 ml/yr) (113).

Benefits

Serum VEGF-D testing had a low false-positive rate and a high false-negative rate, indicating that a positive result can be used to confirm LAM but a negative result should not be used to exclude LAM. In addition, serum VEGF-D testing frequently eliminated the need for an invasive lung biopsy in patients who presented with cystic lung disease that lacked confirmatory features of LAM.

Harms

Although uncommon, false-positive results may lead to missed opportunities to treat the correct disease as well as the adverse effects and costs of inappropriate treatment of LAM.

Other Considerations

Diagnostic accuracy studies provide high confidence in the estimated test characteristics if they enroll consecutive patients with legitimate diagnostic uncertainty and compare the results to a well-established reference standard. In this case, several studies estimated the test characteristics using populations that included patients with known LAM (i.e., there was not diagnostic uncertainty). This has the potential to bias the test characteristic and, therefore, decreases the confidence in the estimates.

Recommendation 4

For patients whose CT scan shows cystic abnormalities characteristic of LAM, but who have no confirmatory clinical or extrapulmonary radiologic features of LAM, we recommend VEGF-D testing to establish the diagnosis of LAM before consideration of proceeding to diagnostic lung biopsy (*strong recommendation based on moderate-quality evidence*).

Remarks. The purpose of VEGF-D testing is noninvasive diagnostic confirmation of LAM. In cases where the HRCT is compatible with LAM, but the clinical context is inconclusive and VEGF-D is unavailable or uninformative, biopsy is appropriate. "Confirmatory features of LAM" include tuberous sclerosis complex, angiomyolipomas, chylous pleural effusions or ascites, and cystic lymphangioleiomyomas.

Values and Preferences

This recommendation places a high value on the risk reduction and cost savings of noninvasive diagnostic approaches in LAM and a lower value on the logistical considerations of obtaining a specialized test that is available in only a limited number of commercial laboratories.

Research Opportunities

The role of serum VEGF-D as a prognostic biomarker needs further validation. If confirmed in future studies, serum VEGF-D may become a useful adjunct for making treatment decisions, particularly in patients with limited data about the rate of progression of LAM from prior pulmonary function tests or those who cannot perform pulmonary function tests, such as cognitively impaired patients with TSC.

Conclusions

Significant advances have been made in the clinical management of LAM in the past decade. A useful diagnostic biomarker that can obviate the need for biopsy in some patients has become available, and an effective therapy was developed, both of which received strong recommendations for their use. The guideline development panel also recommended against therapy with doxycycline and antihormonal agents due to a lack of clear evidence of a consistent benefit. Clinicians faced with making management recommendation for patients with LAM must individualize their treatment plans, however, because the evidence base generally provided low confidence in the estimated effects of many interventions.

Future Directions

Additional studies are required to determine the long-term safety and efficacy of treatment with mTOR inhibitors in LAM and to evaluate the risks and benefits of early, low-dose prophylactic therapy in patients with normal lung function. The use of serum VEGF-D as a prognostic and predictive biomarker appears to be promising, and studies to determine if early changes in VEGF-D might serve as a surrogate for improvement in lung function over time are warranted. New remission-inducing agents capable of killing LAM cells are needed, either alone or in combination with mTOR inhibitors. Although the use of hormonal therapies was not recommended, the evidence for the influence of hormonal fluxes on LAM progression is compelling. It is possible that future trials will demonstrate a benefit of other hormonal therapeutic approaches in patients with LAM. Development of additional biomarkers will reduce the need for surgical biopsy, assist patients and clinicians with treatment decisions, accelerate the conduct of trials, and facilitate the personalization of therapies. ■

This clinical practice guideline was prepared by an *ad hoc* guideline development committee of the Clinical Practice Committee.

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