mammalian target of rapamycin [mTOR]) has become the primary treatment of choice for LAM (5). However, pregnancy is contraindicated during treatment with rapamycin. Recent studies on the molecular pathology of LAM and mTOR pathway signaling have suggested the use of other drugs, such as statins (6), doxycycline (7), and biguanides (8), which are anti-diabetes mellitus drugs and might be promising candidates. Biguanides such as metformin function as activators of adenosine monophosphate-activated protein kinase, which in turn strongly suppresses mTOR (9). In fact, many recent reports have suggested that the use of an adenosine monophosphate-activated protein kinase activator alone or in combination with an mTOR inhibitor may be a promising choice for the treatment of various cancers. In addition, biguanides have been historically used for the treatment of infertility resulting from polycystic ovary syndrome. In patients with this condition, biguanides can be used safely without any concern of fetal teratogenicity. Considering the favorable properties of biguanides, exploration of their use as substitutes or additional drugs for the treatment of LAM may be warranted in the future. So far, no clinical trials of biguanides alone or in combination with other drugs for the treatment of LAM have been reported. One inexpensive study to perform might comprise the subanalysis of previous clinical trials of mTOR inhibitors. These studies would need to include subjects with LAM or renal angiomyolipoma who were also cotreated with biguanides for diabetes mellitus. Such an investigation would also shed new light on the treatment of LAM. ■

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Reply to Yanagisawa

From the Authors:

We thank Dr. Yanagisawa for his comments on the recently published American Thoracic Society/Japanese Respiratory Society (ATS/JRS) lymphangioleiomyomatosis (LAM) clinical practice guidelines (1). We agree that the approach to patients with LAM who are pregnant or contemplating pregnancy is a vexing problem in the field. Largely because of time constraints, the initial focus of ATS/JRS LAM Guideline Committee was narrowed to those LAM issues with evidence bases that had substantially expanded since publication of the European Respiratory Society LAM Guidelines (2). Because the group has not yet addressed the matter of pregnancy in patients with LAM, we do not feel it would be appropriate to express opinions or make recommendations on this topic without employing the same rigorous methodology used in parts 1 and 2 of the guidelines (1, 3). The panel hopes to examine this topic in the future, as well as others such as the use of bronchodilators and the safety of air travel. In the meantime, the study cited by Dr. Yanagisawa observed that although some women with LAM had uncomplicated pregnancies, both obstetric and maternal respiratory complications were very common during pregnancy. A retrospective comparison showed that women with LAM who had had children had poorer lung function than those who had not, although the two groups were unable to be rigorously matched for disease severity and other factors. It was also unclear in many of the subjects whether LAM was present during pregnancy or developed later (4). Sound advice regarding pregnancy in LAM will only become feasible when mechanisms to estimate risk in individual patients are developed.

We wholeheartedly support Dr. Yanagisawa's plea for the development of novel treatments for LAM, including for those who are pregnant or contemplating pregnancy. We agree that biguanides, either alone or in combination with sirolimus, warrant consideration as a possible therapeutic option for patients with LAM. Indeed, metformin has recently been studied in a randomized controlled trial in tuberous sclerosis complex-related angiomyolipomas, another entity categorized by mechanistic target

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of rapamycin hyperactivation, although the study results have not yet been reported (<http://www.isrctn.com/ISRCTN92545532>). Given the very favorable safety profile of metformin in pregnancy (5), if found to be effective, this biguanide might be a viable option for the treatment of pregnant patients with LAM. As mentioned by Dr. Yanagisawa, conducting subgroup analyses of previous mechanistic target of rapamycin inhibitor trials in LAM or retrospective case control analyses of patients with LAM already receiving biguanides are reasonable first steps toward the ultimate goal of performing pivotal trials. With respect to the other potential therapeutic options for LAM mentioned, the use of doxycycline in LAM has been the subject of a randomized, double-blind, placebo-controlled clinical trial (6). Although underpowered, this study failed to demonstrate clinical benefit from doxycycline, and routine use of doxycycline in LAM is not recommended (3). In a retrospective review of the NHLBI's intramural LAM cohort, the use of statins did not affect the rate of decline of FEV₁ and was associated with a faster rate of decline of diffusion capacity of carbon monoxide compared with age-matched control patients (7). A subsequent retrospective analysis of the same cohort demonstrated no increase in adverse effects when simvastatin was used in combination with sirolimus (8). A phase 1 clinical trial investigating the safety and efficacy of combined simvastatin and mechanistic target of rapamycin inhibitors in patients with LAM has recently completed enrollment (ClinicalTrials.gov identifier: NCT02061397), and the results should be available soon. However, the safety of statins during pregnancy remains questionable (9), and they may not be a viable option to treat pregnant patients with LAM. Numerous other agents have shown promise as therapeutic options for LAM in preclinical studies, and many are in early-stage clinical trials (10–13). We are hopeful that these studies will lead to an expanded repertoire of drugs for treatment of LAM in the near future. ■

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Rigor Is Needed When Making Comparative Analyses of Biologics in Severe Asthma

To the Editor:

We read with caution the study by Mukherjee and colleagues in which they reported observations from a 24-week single-blind study of 10 prednisone-dependent patients (1). The described study is nonrandomized and retrospectively compares intravenous reslizumab treatment with subcutaneous mepolizumab treatment in a subset of patients from the previously reported COSMOS (A Study to Determine Long-Term Safety of Mepolizumab in Asthmatic Subjects) study (2), described by the authors as phase 1. These elements of study design and population require further clarification because they have implications with regard to the robustness of the conclusions of the paper.

The patients included in the study by Mukherjee and colleagues were from one center of the multicenter, 52-week, open-label

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