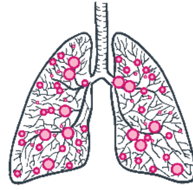

LAMPOSIUM IN YOUR LIVING ROOM

March 6, 2024 • 7:00 PM ET • 4:00 PT

Vera Krymskya, MBA,PhD & Rob Kotloff, MD

LAM Science Research Update + Rapamycin: From Fruit Flies to Easter Island, and MILES To Go

Please Note: Views in this presentation represent those of the speaker. Medical treatment decisions should be made in consultation with your medical team.

CHATBOX Q&A

What medications do you recommend to lower sugar and cholesterol?
There are a wide variety of medications to treat elevated blood sugars (diabetes) and the need for, and choice of, medications is best discussed with your primary care physician or diabetes doctor. With respect to elevated cholesterol, this is a common side effect of rapamycin but only needs to be treated if markedly elevated or if it is determined that you are at high risk for a serious cardiovascular complication (heart attack, stroke). There are a number of calculators available to determine risk. Most premenopausal women are at very low risk so that treatment of cholesterol is uncommonly required in this population but this can change after menopause. When treatment is necessary, the first line medications are the statins (eg, Lipitor, Crestor).

"You didn't mention high blood pressure being a side effect of Sirolimus.Have you found this?"
High blood pressure is a reported side effect of rapamycin but is most commonly seen in transplant recipients receiving multiple other drugs in combination with rapamycin. It is an uncommon side effect when used as a single agent for treatment of LAM, particularly with the low doses typically employed.

Should we be looking at DLCO effects in any of these studies?
This was examined in the MILES trial and there was no difference in DLco between treatment and placebo groups at one year. It is not yet clear whether rapamycin has a favorable effect in stabilizing DLco in the longer-term.

With regard to Paxlovid and Rapa, I'm post lung transplant and I'm on Tacrolimus and Sirolimus, would it be recommended to stop Rapa on Paxlovid in this case?
Paxlovid would not be recommended in your case as there is a strong interaction with both sirolimus and tacrolimus. Since these drugs cannot be held (as it would risk causing rejection of the lung), Paxlovid cannot be administered in this situation.

"Did the study on dosages show that a serum level of 2 is needed?
Did it find that lower serum levels were not effective?"
The one study I quoted suggested that rapamin trough levels of 2 or higher seem to be sufficient to stabilize lung function in most individuals. It did not examine lower levels. Since this is only one small study, it cannot necessarily be definitively concluded that levels of 2 are acceptable and some LAM doctors still aim for blood levels in the range of 4-6. Further studies are needed to see if very low levels are sufficient to control the disease.

Is the Rapamicyn reduce the cellular growth, are there specific cells?
I am not certain which cell types are most susceptible to the inhibitory effects of rapamycin. In LAM, rapa seems to inhibit growth of LAM smooth muscle cells. Rapa is also effective in inhibiting the growth of a variety of cancers. It also inhibits fibroblasts, the cells responsible for wound healing which is why the drug has to be stopped at the time of major surgery.

What are your thoughts regarding postmenopausal women continuing with rapamycin? I have not been on it since that time."
The MILES trial demonstrated beneficial effects in both premenopausal and postmenopausal women. In general, we do not stop rapamycin after menopause. If stopped for any reason, it would be appropriate not to resume it only if lung function remained stable off of rapa.

"We weren't sure of the answer to the question of if it is better to start rapa early?
Our daugher's lung function is normal, but she has started rapa."
We don't yet know if it is advisable to start rapamycin when lung function is normal or minimally impaired. The MILED trial, which has just finished enrolling patients, is examining this exact question but the result will not be known for a year or more. While the MILES trial only enrolled individuals with FEV1 < 70%, currently most physicians will start rapamycin with lesser degrees of lung impairment if there is evidence that lung function is declining significantly each year. We need to wait for the results of the MILED trial before starting the drug with normal lung function.

What is the outlook for when we have results of study of the bi-steric inhibitor rmc552? One year?
As far as I know, there are currently no clinical trials involving LAM patients. The initial trials are being conducted in patients with certain cancers.

"Are you saying statin not needed because of high cholesterol?
How high before statin is needed?"
The decision to start a statin should be based on an assessment of the individual's risk of future cardiovascular events (stroke, heart attack). There are standard calculators that providers use to assess this risk. One such calculator is the American College of Cardiology ASCVD Risk Calculator. Using this calculator, a 40 year woman with a cholesterol of 250 and an LDL cholesterol of 150 (both values quite high) but otherwise

healthy would have a calculated risk of only 1% for a serious cardiovascular event over the next 10 years and would not need to start a statin. On the other hand, a 65 year old woman with a history of high blood pressure and the same cholesterol levels would have a risk of over 10% for future cardiovascular events and should be put on a statin.

"If rapamycin results in pneumonitis in an individual, can they go back on rapamycin after treatment with prednisone?"
That is controversial. If the episode of pneumonitis was mild and occurred in the setting of a relatively high rapamycin blood level, rapa could be cautiously reintroduced at a lower dose. In most cases, however, rechallenge is avoided. One option is to switch to everolimus which can often be accomplished without recurrence of pneumonitis (but can result in recurrent pneumonitis so close observation is mandatory when doing this).

"I used L-Lysine daily 2 months before beginning sirolimus & am still using both.
I have only had 2-3 mouth sores since using sirolimus. Have any of you informed LAMmies of this?"
I was unaware of this treatment. Thank you for bringing this to my attention.

Which is the correct percentage of Sirolimus in the blood for a TSC LAM with angiomyolipomas?
There is no standard blood level that is employed. Since there is usually no urgency in treating the AML (if there is urgency, an alternative approach such as embolization should be employed), a general approach is to initially aim for a level around 4-6 and obtain imaging (ultrasound, MRI) in 4-6 months to see if the AML is decreasing in size. If not, the dose of sirolimus can be increased. In the trial that was published in the New England Journal that studied rapamycin for AMLs, levels as high as 10-15 were used but we don't typically do that anymore because of an increased risk of side effects.

Any research for repairing damage to the lungs?
There are very preliminary studies that are investigating use of stem cells to repair other types of lung injury (not LAM) but nothing that is ready for clinical application in human lung disease.

If Sirolimus prevents the decrease of oxygen exchange rate?
I think you are referring to the diffusing capacity of the lung (DLco), a measurement on pulmonary function testing that assesses the ability of oxygen to move from the lungs to the bloodstream. This was examined in the MILES trial and there was no difference in DLco between treatment and placebo groups at one year. It is not yet clear whether rapamycin has a favorable effect in stabilizing DLco in the longer-term.

What about clinical trial of Loratadine with Rapa?
I am not aware of this trial.

Is it ok to drink grapefruit flavored waters?

I am not familiar with these products but would avoid them if they contain natural grapefruit juice.

What dosage is considered to be a high dose of Sirolimus? My doctor wants to start me out on 2mg.
The usual starting dose is 1-2 mg daily. Blood levels should then be checked a week or two later. Different physicians aim for different blood levels, depending in part on what the rapa is being used for. effusions. I can only speak for my own practice, which is to aim for a blood level of around 4-6 in most cases. Some clinicians aim even lower.

My question is if I have TSC and LAM with angiomyolipomas which should be the therapeutic range or the ideal percentage of Sirolimus recommended.
Similar to the question above, there is no standard blood level that is employed. Since there is usually no urgency in treating the AML (if there is urgency, an alternative approach such as embolization should be employed), a general approach is to initially aim for a level around 4-6 and obtain imaging (ultrasound, MRI) in 4-6 months to see if the AML is decreasing in size. If not, the dose of sirolimus can be increased. In the trial that was published in the New England Journal that studied rapamycin for AMLs, levels as high as 10-15 were used but we don't typically do that anymore because of an increased risk of side effects.

Are bio identical Testosterone pellets safe to use for someone that is menopause and has Lam? and if so, what about the possibility that testosterone can be converted to estradiol?
I would have to consult with my gynecology colleagues to answer this question.