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LAM in the News
August 2013

TSC2/TSC1 Field:

Am J Respir Cell Mol Biol. 2013 Aug 15. [Epub ahead of print]

Statins in LAM: Some but not all?

Atochina-Vasserman EN, Goncharov DA, Volgina AV, Milavec M, James ML, Krymskaya VP.

Main points covered in the paper

The author's laboratory has previously reported that RhoA GTPase is activated in LAM-derived and human TSC2-null cells. Knowing that this particular protein requires modification with lipids that are synthesized from pathways that also control cholesterol synthesis, they have suggested that HMG-CoA reductase inhibitors (statins) can be used as potential co-therapies. Towards this goal, two different statins (simvastin and atorvastin) were studied in an in vitro cell model.

What is the relevance of the study?

Statins are widely used drugs in humans, therefore, demonstrating their use in LAM would be a breakthrough. Unfortunately, the study described in this article does not provide any support to the possibility that they can be used to treat LAM. The data should include at least an animal model to confirm the unexpected finding of statin selectivity. This selectivity is not found in humans treated for reduction of cholesterol.

Is there a public health implication of the research described in this paper?

None at this stage of the research.

LAM or TSC Disease Models:

Published online before print August 27, 2013, doi: 10.1073/pnas.1309110110
PNAS August 27, 2013

Integration of mTOR and estrogen–ERK2 signaling in lymphangioleiomyomatosis pathogenesis

Xiaoxiao Gu, Jane J. Yu, Didem Ilter, Nickolas Blenis, Elizabeth Petri Henske, and John Blenis

Main points covered in the paper

The results described in this study are a follow up to a previous study carried out in Dr. Henske's laboratory. Previously, it had been determined that the ERK-MAP kinase may play a role in LAM based upon the observation that estrogens promoted the MEK-dependent invasion of cells derived from Eker rat uterine leiomyoma (ELT3 cells) into the lungs of ovariectomized mice. In this report, TSC2-null LAM patient-derived angiomyolipoma (AML) cells were used as a platform to examine the cellular response to estrogen and to link the estrogen-MAPK pathway to the metastatic-like phenotype observed in LAM.

What is the relevance of the study?

The authors propose that two parallel pathways (Estrogen activated MAPK and mTORC1) are involved in modifying the metastatic potential of TSC2 null cells. The convergence is achieved at the Fra1–ZEB1/2 tran- scriptional network to promote migration and invasion of LAM cells. These findings should provide a working hypothesis to explore new therapeutically sound approaches and biomarkers of drug response.

Is there a public health implication of the research described in this paper?

These findings lend support to the development of combination therapies. Both antagonist of estrogen signaling (fulvestrant) and mTORC (rapamycin) are FDA approved and should facilitate the clinical testing of the above proposed hypothesis.

Clinical Trials/Clinical Studies:

Annals of the American Thoracic Society > *Volume 10, Issue 4*
http://www.atsjournals.org/doi/abs/10.1513/AnnalsATS.201212-125OC

Efficacy of Sirolimus Therapy for Chylous Effusions in Lymphangioleiomyomatosis

Pilar Barrera, Sami O. Simons, Bart Luijk, Marion J. C. Wessels, and Yvonne F. Heijdra

Main points covered in the paper

The report summarizes the clinical experience treating a patient with persistent chylous pleural effusion associated with lymphangioleiomyomatosis (LAM) that responded to Sirolimus, promptly relapsed after drug withdrawal, and completely resolved again when the drug was reintroduced.

What is the relevance of the study?

The results are in agreement with previous clinical experience (symptomatic relieve of chylothorax in LAM) that promptly relapsed after drug withdrawal, and completely

resolved again when the drug was reintroduced.

Is there a public health implication of the research described in this paper?

It is re-assuring to learn that an increasing number of LAM patients have been treated with Sirolimus and that this treatment is having a positive impact on patient quality of life.

Respir Investig. 2013 Sep;51(3):175-83. doi: 10.1016/j.resinv.2013.03.002. Epub 2013 May 30.

The efficacy and safety of low-dose sirolimus for treatment of lymphangioleiomyomatosis.

Ando K, Kurihara M, Kataoka H, Ueyama M, Togo S, Sato T, Doi T, Iwakami S, Takahashi K, Seyama K, Mikami M.

Main points covered in the paper

The clinical use of Sirolimus, an inhibitor of the mTOR pathway, has shown that it would lead to a decrease in the size of angiomyolipomas and stabilize pulmonary function in patients with LAM. However, the relationship between dose and response has not been established. In this report the authors performed an observational study of 15 patients with LAM who underwent Sirolimus therapy for more than 6 months at a lower dose of the drug.

What is the relevance of the study?

One of the main obstacles of Sirolimus therapy is its safety profile. Therefore, establishing a minimal effective dose is of primary importance.

In this study, the authors showed that at blood levels of Sirolimus below 5 ng/ml there was a similar response to treatment as it is observed when the levels are between 5-15 ng/ml.

Is there a public health implication of the research described in this paper?

An immediate impact since the study showed that lower dose of Sirolimus (trough level, 5ng/mL or less) performed as well as the higher doses used previously for improving pulmonary function and decreasing chylous effusion in patients with LAM. This should result in an improved tolerance of the patients for the drug.

Newsworthy:

An article published recently describes the experience of a LAM patient (Justine Laymond) that underwent double-lung transplant (http://www.eadt.co.uk/news/

essex_this_is_my_second_chance_at_life_and_i_won_t_waste_it_says_double_lung_transplant_woman_justine_laymond_1_2356945)

The following statement summarizes her feelings: "This is my second chance at life and I won't waste it".