# The way forward in lymphangioleiomyomatosis: a trial for every patient, every patient in a trial

**O caminho à frente da linfangioleiomiomatose: um ensaio para cada paciente, cada paciente em um ensaio**

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Lymphangioleiomyomatosis (LAM) is a low-grade, metastatic neoplasm affecting women and is associated with cystic lung destruction and progressive respiratory insufficiency.[1] The pulmonary infiltration and remodeling that occurs in the LAM lung is driven by matrix-degrading enzymes that cleave collagen, elastin, and proteoglycans. Prominent among these are the metalloproteinases (MMPs), a large multi-gene family of zinc-dependent endopeptidases that are collectively capable of degrading all known matrix components.[2] It has been reported that, within LAM lesions, there is differential expression of certain MMPs and tissue inhibitors of MMPs (TIMPs), including MMP-1, MMP-2, MMP-9, TIMP-1 and TIMP-3.[3] Using immunological assays and zymography, Odajima et al. demonstrated that MMP-9 (but not MMP-2) is elevated in the serum of patients with LAM.[4]

Inhibition of MMPs is an attractive target for therapy in LAM. In theory, blocking proteolytic degradation of the lung matrix by infiltrating LAM cells could stabilize, if not improve, lung function. Doxycycline is a tetracycline antibiotic with zinc binding properties that might enable it to broadly inhibit the functional activity of matrix-degrading MMPs.[5] Various studies have suggested that doxycycline also affects the degradation or synthesis of MMPs, which could reduce serum MMP levels. Although doxycycline is the only MMP inhibitor that is clinically available, it is not currently approved for this use in any human disease, and clinical trials of potent MMP inhibitors in cancer and arthritis have been disappointing.[6] A sensational case report published in 2006 showed that doxycycline had a dramatic effect on oxygenation and exercise tolerance in a single patient with LAM, resulting in ill-advised, widespread off-label use of doxycycline within the LAM community.[7] Such studies and reports have heightened the urgency for properly conducted trials of MMP inhibitors in LAM.

Within this context, Pimenta et al. designed an open-label, single-arm, interventional, pilot trial of doxycycline in patients with LAM who presented to a single hospital in São Paulo, Brazil. The results are presented in the current issue of the Brazilian Journal of Pulmonology.[8] The levels of MMP-2 and MMP-9 were measured by ELISA in the serum and urine at baseline and at six months. The only other outcomes reported were safety endpoints based on symptoms; presumably, lung function and exercise tolerance data will follow. The authors found that MMP-9 was elevated at baseline in the serum and urine of patients with LAM and that doxycycline reduced those levels by 5% and 35%, respectively. However, MMP-2 was below the limit of detection at baseline, in both serum and urine, and was therefore uninformative. The adverse event profile of doxycycline in this trial was acceptable and included only one withdrawal for drug side effects. The limitations of the trial included the open-label design, a 17% loss rate, and the lack of assays of MMP function.

Pimenta et al.[8] demonstrated the feasibility of a single-site, interventional trial for a rare lung disease that affects only approximately five patients per million.[9] Although a remarkable body of knowledge about the molecular basis of the disease has accrued over the past ten years, there is no appropriate animal model to test experimental therapies for the lung disease in LAM, and trials in humans are critical to progress.[10] The trial by Pimenta et al.[8] and others pave the way for future definitive trials of the safety and efficacy, for the treatment of patients with LAM, of drugs that have already

been approved and are commercially available for other indications.

There is a particular need for the testing of combination therapies that could increase the durability of the responses, in terms of lung function and symptoms, obtained with sirolimus in the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) Trial.[11] The MILES study was a double-blind, randomized placebo-controlled trial of sirolimus in patients with LAM. The MILES data indicate that sirolimus stabilizes lung function, as well as improving functional performance and quality of life, for at least one year. However, lung function was found to resume its decline when the drug was discontinued. On the basis of these results and those of previous trials involving LAM patients,[12,13] we can conclude that sirolimus has more of a suppressive effect than a remission-inducing effect. Pilot studies recruiting candidates for future combination therapies that might complement or potentiate sirolimus effects are best conducted in areas of the world where large numbers of LAM patients have assembled in support groups, such as Brazil, the United States, Canada, Japan, Korea, China, Australia, Germany, France, Italy, Spain, and England. Patients with LAM have certainly done their part by organizing themselves in a manner that facilitates research and trial recruitment. More LAM investigators should follow the lead of Pimenta et al.[8] and conduct phase I/II trials of additional therapies for LAM.

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