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Title: Prolonged sirolimus therapy in advanced pulmonary lymphangiomyomatosis; a multicenter French experience

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Body: Introduction: Lymphangiomyomatosis (LAM) and tuberous sclerosis (TS) are orphan diseases associated with TSC1/2 gene mutation and dysregulated mTOR/Akt signaling. Usefulness of the mTOR inhibitor sirolimus (SIR) in slowing the decline of lung function in LAM has been shown. Aims and Objectives: Evaluate efficacy and safety of prolonged treatment with Sir in LAM patients. Methods: An observational retrospective study of 14 patients with LAM and declining lung function treated with Sir and follow-up over 18 months of SIR. Results: All patients included in the study were female with sporadic LAM (n=9) or TSC-LAM (n=5). Six patients had chylous effusion and 3 had pulmonary hypertension. The median dosage of SIR was 2.5 mg/d and the blood T0 was 5.5 mg/mL (1.8-10). Clinical and functional improvement from baseline was observed in all after 6 months of SIR therapy. At M18 and M24, the functional benefit remained for all except one, 5 of the 6 patients with chylous effusion experienced complete resolution of this condition and pulmonary hemodynamic normalized in two. Progression of the disease after routine discontinuation of SIR after 2 years in 3 patients encouraged rechallenge with SIR, with again restoration of disease control. Tolerance of SIR was good in 12 patients, and therapy was stopped for moderate adverse events in 2 cases but restarted at lower dosage in one without complication. Conclusion: This study demonstrates that mTOR inhibition with SIR is useful in advanced LAM. Decline in lung function was observed after discontinuation of SIR with benefit of subsequent rechallenge in uncontrolled disease. Therapeutic scheme of SIR over time in LAM should be defined.