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Celecoxib in lymphangi leiomyomatosis: results of a phase I clinical trial

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COX2 inhibition is safe in LAM patients with mild disease. In the subset of patients with high VEGF-D (>800 pg per mL) COX2 inhibition appears to cause a decrease in VEGF-D levels and may provide clinical benefit. <http://bit.ly/395drXs>

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To the Editor:

Lymphangi leiomyomatosis (LAM) is a multisystem disease associated with progressive pulmonary disease that affects almost exclusively women. LAM is characterised pathologically by proliferation of abnormal smooth muscle-like cells carrying mutations in predominantly the tuberous sclerosis complex (TSC) gene *TSC2* and, rarely, in *TSC1* [1]. LAM can occur sporadically or in association with TSC. Mutations in the TSC genes lead to activation of the mammalian/mechanistic target of rapamycin complex 1 (mTORC1) [2]. In the landmark randomised controlled MILES (Multicenter International LAM Efficacy of Sirolimus) trial, the mTORC1 inhibitor rapamycin stabilised lung function and improved symptoms in LAM patients with moderate to severe changes in lung function (forced expiratory volume in 1 s (FEV₁) <70%) [3]. Recent *in vitro* and preclinical evidence showed that loss of *TSC2* resulted in upregulation of COX-2 and prostacyclin synthase (*PGTIS*) expression, independent of mTORC1. Treatment of *Tsc2*^{+/-} mice with celecoxib, a COX-2 specific inhibitor, resulted in a 50% decrease in renal cystadenomas volume, which occur spontaneously in this model [4]. In addition, LAM nodules were found to express higher levels of COX-2 in comparison with control lungs [4].