Commentary

Sirolimus in lymphangioleiomyomatosis: A case in point for research in 'orphan' diseases

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Lymphangioleiomyomatosis (LAM) is a rare progressive lung disease that predominantly affects women of reproductive age.[1,2] It is characterized by nonneoplastic, peribronchial, perivascular, and perilymphatic proliferation of atypical smooth muscle, resulting in vascular and airway obstruction, cyst formation, and progressive decline in lung function. Associated features include systemic angiomyolipomas (AMLs) and lymphangioleiomyomas. LAM occurs either sporadically or in combination with tuberous sclerosis.[2,3] The invading cells arise from an unknown source and contain inactivating mutations in tuberous sclerosis proteins that result in mammalian target of rapamycin complex 1 (mTORC1) pathway-driven cellular proliferation, migration, and survival,[1] eventually contributing to the uncontrolled proliferation of LAM cells.[4] Further, elaboration of lymphangiogenic growth factors such as vascular endothelial growth factor-D (VEGF-D) by the mutant cells promotes access to lymphatic channels and lymphangitic spread and likely contributes to cystic destruction of the lung and development of chylous effusions and abdominal lymphangiomyomas.[5]

Sirolimus, a macrolide produced by *Streptomyces hygroscopicus* also known as rapamycin, binds to FK-binding protein-12 (FKBP-12) to form a complex (SRL/FKBP12) that binds to and inhibits the activation of mTORC1, leading to its antiproliferative action.[6] The drug has also been found to have immunosuppressive properties, but the mechanism of action of sirolimus in LAM is believed to be due to its antiproliferative effects.[7] Sirolimus has also been demonstrated to suppress the growth of spontaneously occurring renal tumors in various mice models such as $Tsc1^{+/-}$ and $Tsc2^{+/-}$ mice,[8] as well as in TSC2-deficient xenograft tumors in immune-deficient mice.[9]

Several clinical studies now support the efficacy of sirolimus in LAM. Bissler *et al*.[9] conducted the first trial, the Cincinnati Angiomyolipoma Sirolimus Trial, for the use of sirolimus in AML and demonstrated the significant effect of this drug in LAM, which was subsequently followed by many other studies supporting the effect of this drug in regression of this disease.

The landmark Multicenter International LAM Efficacy of Sirolimus (MILES) Trial demonstrated that the mTOR inhibitor sirolimus stabilized lung function, reduced serum VEGF-D, and improved functional performance and quality of life compared with placebo over 1 year, but the benefits waned when the drug was held in the 2nd year.[10] An observational study of 12 patients with lymphangioleiomyomas and chylous fluid collections demonstrated that sirolimus treatment resulted in complete resolution in most cases and provided evidence for durable efficacy and safety of sirolimus over an average of 2.6 years[11] Ando *et al*.,[12] in their observational study, further strengthened the observations of MILES Trial and in addition found that sirolimus was also effective in lower doses of 1 mg/day. Collectively, these and other data indicate that mTOR inhibition is an effective, exquisitely targeted suppressive therapy for LAM but that continuous and even lifelong therapy may be required for sustained benefit. In another phase 3 trial of patients with LAM, sirolimus improved lung function, quality of life, and functional performance.[13] Collectively, these studies led the US FDA to approve sirolimus for the drug treatment of LAM in 2015.

The current issue of *Lung India* carries a report by Ussavarungsi *et al*. of a patient with LAM having been treated with low-dose sirolimus[14] that resulted in the stabilization of the lung disease and effected a near-total regression of the abdominal lymphangioleiomyomas. The authors also present a comprehensive review of the use of sirolimus in abdominal lymphangioleiomyomas. In most of the studies, the blood trough level of sirolimus was maintained between 5 and 15 ng/mL, based on previous phase 1–2 trial. However, the optimal treatment dose was not given because a significant number of patients developed problematic side effects, such as stomatitis, and the potential risk of developing a malignant tumor increased with long-term use.[12]

Low-dose sirolimus treatment (trough level <5 ng/mL) has recently been shown by Ando *et al*. to improve lung function in 16 patients, nine without chylous effusion and seven with chylothorax with documented resolution of the effusion.[12] Several studies have demonstrated trends in improvement of FEV_1 and disease progression after low-lose sirolimus treatment.[15-17] However, Bee *et al*. in a prospective LAM national cohort, demonstrated that lower serum sirolimus level was associated with fewer adverse effects (AEs) but not necessarily with lower efficacy in FEV_1 decline.[15] Another mTOR inhibitor, everolimus, has recently been used for the treatment of LAM in open-label studies; this agent could also stabilize lung function and reduce angiomyolipomas and lymphangioleiomyomas with tolerable safety when administered in low doses.[16,17] The most common side effects seen with sirolimus therapy include hypercholesterolemia, dyspepsia, stomatitis, lower extremity edema, acne, and diarrhea.[10]

However, it is important to note that while lower dose is indeed cost-effective and capable of reducing AEs, it may be inferior in efficacy to the conventional dose.[18] This is particularly of pneumonias requiring hospitalization. This might result in lesser number of patients requiring discontinuation of therapy as a result of AEs. Although sirolimus did not increase the risk of infection compared with the placebo in phase 3 clinical trial involving patients with LAM,[13] considering the increased risk of infection with sirolimus treatment in transplant patients, these results were probably due to the effect of low-dose sirolimus. An important point of consideration is the high rate of renal complications in the TSC-LAM group of patients. Since sirolimus has the potential to exacerbate pre-existing or newly occurring renal lesions by causing massive proteinuria, glomerulonephritis, or thrombotic microangiopathy,[19,20] patients with TSC who already have impaired renal function might prefer low-dose sirolimus therapy.

Against this backdrop, low-dose sirolimus seems to be as efficacious as conventional dose sirolimus in patients with LAM, albeit at a risk of lower efficacy but with a lower frequency of AEs. Unfortunately, the design of adequately powered pivotal trials is challenging in rare diseases, for example, only few case reports exist in Indian literature regarding LAM,[21-23] and the largest Indian registry of interstitial lung disease, ILD India Registry, mentioned LAM in only 2 (0.2%) of 1047 cases.[24] Such data call for multicentric and multinational studies from densely populated countries such as India and China with a uniform protocol of diagnosis and treatment which might offer the opportunity to have adequate numbers for robust statistical conclusions on the management of such diseases. Professional international and international and national societies and non-governmental organizations need to chip in with support for such initiatives. This would ensure that the proper advancement of the science of such "orphan" diseases.

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