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Editorial

Lymphangioleiomyomatosis: New Therapeutic Approaches☆

Linfangioleiomiomatosis: novedades terapéuticas

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Lymphangioleiomyomatosis (LAM) is a rare disease that affects young women of child-bearing age. It is characterized by the presence of cystic changes in the pulmonary parenchyma, repeated pneumothorax, chylothorax and renal angiomyolipomas, and in the majority of cases it is accompanied by a progressive loss in lung function.[1]

In the last two decades, there has been an increase in the understanding of LAM, both in its clinical as well as physiopathological aspects and molecular biology. The first case of sporadic LAM was published in 1937,[2] but the first national registries were not initiated until the 1990s. In the year 2000, somatic mutations were reported in the genes of tuberous sclerosis (TSC2) in LAM patients.[3] Since then, LAM research has grown exponentially, and recently the results have been published from a multicenter, randomized, placebo-controlled clinical assay with sirolimus in this disease.[4]

The true incidence and prevalence of LAM are unknown. In the United States, The LAM Foundation has 1300 registered patients. In Spain, in recent years the LAM registry has been begun through the Integrated Research Project (*Proyecto de Investigación integrada* – PII) for Diffuse Interstitial Pulmonary Diseases (*Enfermedades Pulmonares Intersticiales Difusas* – EPID) of the Spanish Society of Pulmonology and Thoracic Surgery (*Sociedad Española de Neumología y Cirugía Torácica* – SEPAR). To date, 72 cases have been included, which have been contributed by 23 centers in 8 autonomous Spanish communities (provinces).[5]

Due to its low prevalence, LAM is a disease that is rather unknown, even in the medical setting. Many of the symptoms of the disease (dyspnea, cough) are similar to those of other lung diseases, such as asthma or chronic bronchitis, which results in its late diagnosis.

Lung transplantation is the best therapeutic option in the advanced phases of the disease.[6] LAM treatment has been based on the use of therapies with anti-estrogenic effect, such as oophorectomy, progesterone, tamoxifen and gonadotropin-releasing hormone analogue. There are no placebo-controlled clinical assays with these therapies in LAM, and its use is due to the beneficial effects observed in isolated cases or in small series of cases.[7] The guidelines of the European Respiratory Society on the diagnosis and treatment of LAM, published in the year 2010, does not recommend the standard use of progesterone. It may be used in patients who experience a rapidly progressing deterioration in lung function.[8] In recent years, there have been clinical trials with new drugs in the treatment of LAM, such as sirolimus (rapamycin), doxycycline and aromatase inhibitors (letrozole).

The "LAM cell", an immature smooth muscle cell that grows in an anomalous manner in the lungs of LAM patients, is the cornerstone of this disease.[9] LAM is associated with mutations in the genes of tuberous sclerosis (TSC1 and TSC2), which entails a deficiency in the hamartin proteins (TSC1) and tuberin (TSC2). These proteins regulate their signal by means of mTOR *(mammalian target of rapamycin)* and control cell size and growth.[10] Sirolimus, an mTOR inhibitor, could counteract the deficiency of these proteins and re-establish the cell cycle.

A study with sirolimus in phase II, uncontrolled with placebo, in 25 patients with LAM and renal angiomyolipomas (AML) demonstrated a significant reduction (53.2%±26.6%) (P<.001) in the AML volume 12 months after treatment when compared with the baseline volume. In addition, a mean increase was observed in FEV_1 118±130 ml and in FVC of 390±570 ml.[11]

These potential beneficial effects have contributed to the use of sirolimus as a compassionate-use drug in this disease. Our experience in 3 patients treated with sirolimus in recent years suggested that sirolimus could slow down the decline in the lung function in LAM.[12]

Recently, the results have been published from the first multicenter, randomized, placebo-controlled clinical assay about the effectiveness and the safety of sirolimus in LAM.[4] Included in the study were 89 patients with LAM with a mean FEV_1 of 48.54%±13.77%, with moderate-severe airflow obstruction. Forty-six patients received sirolimus and 43 patients placebo. The primary objective of the study was to compare the fall in FEV_1 in both groups during a period of 12 months. In the placebo group, the change in FEV_1 was −134±182 ml, and in the sirolimus group, 19±124 ml, with an absolute difference of 153 ml in favor of sirolimus. Another variable analyzed was FVC: we observed a mean change in FVC of −129±233 ml in the placebo group,

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compared with 97±260 ml in the sirolimus group, with a mean absolute difference of 226 ml in favor of sirolimus. No significant differences were observed in other lung function variables, such as carbon monoxide diffusing capacity or the distance walked in the 6-min walk test. After the interruption in the treatment and during an observation period of 12 months, a similar fall in lung function was observed in both groups, which indicates a beneficial effect on the lung function only during the treatment period. Among the most frequent adverse effects were mucositis, diarrhea, nausea, hypercholesterolemia and edema of the lower limbs.

These results indicate that sirolimus could be useful in treating LAM patients with moderate or severe lung function affectation. In order to know the actual effect of sirolimus in LAM, more studies including patients with mild and very severe lung affectation are needed.

Doxycycline is another therapy that is being researched in LAM. In vitro studies show an increase in matrix metalloproteinases (MMP), particularly MMP-2 and MMP-9, in LAM.[13] The high values of these proteolytic enzymes can contribute to the destruction of the lung parenchyma. In addition, MMP can be quantified in urine. Doxycycline, a commonly used antibiotic, inhibits the synthesis and the activation of these MMP, as well as the proliferation of different cell types (smooth muscle cells, cancer cells).[14] It is postulated that it could have a beneficial effect in the treatment of LAM. Moses et al.[15] observed an improvement in FEV_1 and oxygenation during exercise in a patient with LAM treated with 100 mg daily of doxycycline. In the annual LAM conference in Cincinnati (2006), the preliminary data from 10 LAM patients treated with doxycycline were presented, showing improvements in the 6-min walk test distance and in the Borg dyspnea scale.[16] In both studies, the initially high levels of MMP-2 and MMP-9 in urine were undetectable after doxycycline treatment. A clinical assay with doxycycline in LAM is currently underway in the United Kingdom.

More recently, aromatase inhibitors have been proposed as a new therapeutic alternative in LAM. For years, research in LAM has suggested a relationship between this disease and cancer. The World Health Organization (WHO) defines cancer as uncontrolled and diffuse cell growth, which can affect any part of the body. Cancer cells can invade the surrounding tissues and can metastasize distant organs. LAM meets some aspects of the previous definition. It has been demonstrated that LAM cells grow out of control, invading the lungs, lymph nodes and other organs such as the uterus. LAM is disseminated through the lymph nodes and can metastasize the lungs.[17]

Matrix metalloproteinase inhibitors are a group of drugs used in the treatment of breast cancer and ovarian cancer in post-menopausal women.[18] Some types of cancer require estrogen to develop. In pre-menopausal women, the majority of body estrogens are produced in the ovaries. In contrast, in post-menopausal women, the estrogens originate in the transformation of the androgens in the adrenal glands and fatty tissue. Aromatase is an enzyme that converts androgens into estrogens by means of a process called aromatization. The inhibition of the aromatase blocks the synthesis of estrogen. Given the hypothetical relationship between estrogen, cancer and LAM, a blockage of the residual estrogen activity in post-menopausal women with LAM could contribute to stopping the progression of the disease.

Letrozole is an aromatase inhibitor. The TRAIL trial (Trial of Aromatase Inhibition in Lymphangioleiomyomatosis) intends to randomize 60 LAM patients, 30 of which will receive letrozole 2.5 mg/day and 30 will receive placebo for a period of 12 months. The hypothesis of the study proposes that the blockage of the residual estrogen activity in post-menopausal women with LAM will lead to a reduction in the loss of lung function. The study, which will take place in the United States and will be coordinated by the LAM Clinical Research Network,[19] has generated new expectations for the treatment of this minority respiratory disease.

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