EDITORIAL

Patient Organizations and Research on Rare Diseases

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There are an estimated five women per million in the United States who suffer from lymphangioleiomyomatosis (LAM), a rare and devastating disease that almost exclusively strikes young women.[1-3] These patients have progressive loss of lung function, and many die from respiratory failure. Until recently, a diagnosis of LAM was a medical anomaly, and a woman who received this diagnosis had little cause for hope. The disease was likely to be managed symptomatically by physicians unfamiliar with the disease.

That all changed about 15 years ago, when LAM was diagnosed in a 22-year-old woman who had a bleak picture painted of her future. Her mother, who was not a medical professional, realized that very little was known about LAM, and that without an understanding of the pathobiology of the disease, effective treatments, or even cures, would never be forthcoming. With her tremendous drive and the networking power of the fledgling Internet, the LAM Foundation was born. The LAM Foundation succeeded in raising money and obtaining third-party funding for research into the biology of LAM.[4,5] As a result of the work funded by the foundation, we now know that LAM is characterized by the presence in the circulation of so-called LAM cells. These are specialized cells, with certain characteristics of smooth-muscle cells, that infiltrate organs, especially the lungs and to some extent the kidneys and other organs, via the lymphatics. The spread of these unusual cells leads some to categorize LAM as a low-grade neoplasm.

The increased understanding of the biology of LAM led next to treatment trials. These trials were feasible because patients with LAM were no longer impossibly hard to find. Rather, they had banded together not only to raise and secure research funding, but to place themselves at risk in clinical trials that were designed to study potential treatments for this rare condition. In this issue of the *Journal*, McCormack et al.[6] report the results of the Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus trial (MILES; ClinicalTrials.gov number, NCT00414648), which confirm observations from uncontrolled pilot studies[7,8] that had indicated that sirolimus, an inhibitor of mammalian target of rapamycin (mTOR), may ameliorate the course of this disease.

Sirolimus (also called rapamycin), which is used widely in the treatment of a variety of cancers and as an immunosuppressive agent in patients undergoing solid-organ transplantation, inhibits mTOR. Since research had shown that mTOR signaling is inappropriately activated in LAM, and mTOR regulates lymphangiogenesis and cell growth, it made sense to try sirolimus as a treatment for LAM.[9-12]

The MILES trial had two stages — a 12-month, randomized, double-blind trial that compared sirolimus with placebo, followed by a year of observation in which none of the patients were receiving the study treatment. The primary outcome, the difference between the treatment groups in the rate of change in the forced expiratory volume in 1 second (FEV_1), was positive, though not in every patient; in the group that received the active drug, pulmonary function was stabilized, whereas in the group that received the placebo, pulmonary function deteriorated. There were some reductions in symptoms and improvements in quality of life among patients in the sirolimus group, as compared with those in the placebo group. However, the differences between the groups reverted once the drug was stopped.

These data suggest that there is a need for continued sirolimus therapy, which requires consideration of its long-term toxic effects.

Even though these data offer women with LAM the prospect of only a long-term treatment rather than a cure, this is a big step forward. Twenty years ago, it would have been impossible to make this much progress in such a rare disease. This research study shows that when patients and researchers work together toward a common goal, advances can be made. The research community contributes ideas and investigative know-how, and patients who have the illness contribute their personal insights, biologic samples, and their time to prove principles. Most important, patients with such a rare disease are willing to put themselves at risk in order to find a treatment or a cure. This takes dedication and courage, and the women with LAM who participated in this work had both.

LAM is not the only medical condition in which patient groups have sponsored both clinical and basic research, have located patients to participate in trials, and have enlisted the help of expert clinicians and investigators. Other examples are cystic fibrosis, Huntington's disease, Waldenström's macroglobulinemia, oxalosis and primary hyperoxaluria, cystinosis, autosomal recessive polycystic kidney disease, and Duchenne's muscular dystrophy, to name just a few. In each case, patients have formed groups to drive research aimed at understanding and treating their particular illness. The key to success for such groups has been to support basic research that is held to the highest scientific standards. When appropriate, they can take the results of the basic work forward to test hypotheses in patients. Trials involving patients with the disease will help illuminate whether the investigators are headed in the right direction and will lead to more focused basic research and better ideas to test in patients. This is true "bench to bedside and back" research that fits the Pareto principle[13] of factor sparsity — in which the affected patients are the vital few and those caring for them work together with professional researchers to advance the field. It is a good model to emulate.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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