Potentially ‘game-changing’ benefits for patients with rare diseases

Jo Pisani, a LifeArc Trustee, shared an impressive story of how drug repurposing has transformed the outlook for women with a rare progressive lung disease around the world.

34
The average age of onset of LAM in patients in the United Kingdom

Lymphangioleiomyomatosis (LAM) is a rare condition that affects almost exclusively women of childbearing age. While the condition mainly affects the lungs, it may also involve the kidneys and lymphatic system.

In people with LAM, abnormal smooth muscle cells (LAM cells) start to grow in certain organs or tissues, particularly in their lungs, lymph nodes and kidneys. Over time, the abnormal growth and movement of LAM cells can damage healthy lung tissue, causing holes or cysts, preventing oxygen from getting to the rest of the body.

Symptoms of LAM include breathlessness, tiredness, coughing and bleeding around the kidneys. If left untreated, the condition can cause serious and life-threatening complications.

LAM is a progressive disease, but how quickly it worsens varies from person to person. Before 2015, lung transplantation was the only approved treatment option for women with severe disease.

Repurposing rapamycin for LAM patients

Rapamycin (also known as sirolimus in the clinic) is a natural product first isolated from bacteria in a soil sample from the island of Rapa Nui.

Researchers subsequently discovered that rapamycin exhibits several properties, including immunosuppressive effects - which ultimately led to its approval as a treatment for kidney transplant patients.

Further laboratory research revealed that the drug inhibits cell growth by targeting the mTOR cellular pathway, which plays a key role in cell growth, survival and movement.

Scientists discovered that LAM is caused by faults in the *TSC1* and *TSC2* genes that encode proteins involved in the mTOR pathway. Laboratory studies showed that LAM cells have overactive mTOR signalling and rapamycin can slow down cell growth. These data indicated that rapamycin could be an effective way to slow down the progression of the disease in LAM patients.

Following the encouraging results of an early-phase clinical trial in the UK, an international, randomised, placebo-controlled trial (the MILES trial) was set up to find out if rapamycin could benefit patients with LAM. The impressive results showed that the drug was safe and effective for LAM patients - stabilising lung function and improving their quality of life.

Rapamycin is now the standard of care for women with LAM. In most cases, taking the drug has replaced the need for lung transplantation, transforming the lives of women living with the condition.

“Rapamycin is an example of successful repurposing – it’s almost a wonder drug for women with LAM.” said Jo.

Changing lives

Sarah Sharples (pictured above) is 40 years old and was diagnosed with LAM ten years ago. Before going on rapamycin, her lung function had been slowly declining and she was struggling to stay awake past 7pm. She thought she would have to reduce her hours at work and couldn’t carry out a lot of her usual activities. But her life has hugely improved since starting on rapamycin around five years ago.

"Combined with inhalers, taking rapamycin has ensured that I can take part in all the activities I enjoy. I’ve been able to keep working full time and, most importantly, I can keep up with my daughter!"

A brief history of Rapamycin

1972
Rapamycin was discovered from a soil sample from Rapa Nui. Subsequent laboratory studies revealed several properties, including immunosuppressive effects.

1990s-2000s
Basic research uncovers that rapamycin inhibits the mTOR signalling pathway. Faults in *TSC1* and *TSC2* genes, encoding proteins involved in the same pathway, are identified in LAM patients.

1999
Rapamycin receives marketing authorisation from the US Federal Drugs Administration (FDA) as an immunosuppressant for kidney transplant patients.

2001
Rapamycin receives marketing authorisation from the European Medicines Agency (EMA) as an immunosuppressant for kidney transplant patients.

2004-2006
Early-phase trial involving patients with LAM in the UK.

2006-2010
A randomised placebo-controlled clinical trial involving 89 patients with LAM in the USA, Canada and Japan (the MILES trial).

2011
Clinical trial results published, showing rapamycin is a safe and effective treatment for LAM patients.

2015
FDA licenses rapamycin for the treatment of LAM.

2018
EMA licenses rapamycin for the treatment of LAM.

> “Combined with inhalers, taking rapamycin has ensured that I can take part in all the activities I enjoy.
>
> **Sarah Sharples, LAM patient**