

LAM ACTION



Report of the Annual LAM Action Meeting
12th June 2004
Nottingham City Hospital

WELCOME – Lucy Falconer

Lucy Falconer welcomed everyone to the 8th Annual Meeting in Nottingham.

ANNUAL GENERAL MEETING

The second Annual General Meeting of LAM Action was then held (LAM Action members see separate minutes).

LAM ACTION NEWS - Jan Johnson

The year in review

- This year's meeting had been sponsored jointly by Astra Pharmaceuticals, Allen & Hanburys and Experian, and a member of staff had kindly donated half the funds she had raised at a market stall.
- We have appointed a public relations consultant, Martin Powell Communications, until October to raise the profile of LAM and increase our fundraising potential. The importance of taking as much advantage of this before the contract ends was stressed.
- Jayne Torvill has agreed to be our patron and this is a great opportunity to raise the profile of LAM.
- LAM information stationery had been printed with a donation of £1,000 from the Yorkshire Building Society Trust. This included new fact sheets, bookmarks and small information cards.
- We have two new designs of Christmas cards for 2004 and T-shirts with our new logo are now on sale at £8.
- The London Marathon - over £7,000 had been raised this year thanks to our runners: Des Thomas, Andrew Moore, Andrew Gandon, Tim Malloch and Robin Page.
- Other ways in which everyone could help LAM Action include: making purchases through companies via our website (a percentage of the price being paid to LAM Action) and ensuring that Gift Aid declarations are completed to enable us to reclaim tax.

- We have 5 new patients this year making a total of 65 on the register. Membership of LAM Action has reached 54 but not all patients are members yet and we would like to increase this number.
- Two patients had had successful transplants this year

LAM – THE AMERICAN PERSPECTIVE – JOEL MOSS MD PHD (SUMMARY OF BOTH TALKS)

Introduction by Professor Anne Tattersfield

We were breaking new ground having a speaker from the United States – Joel Moss is Chief Pulmonologist at the National Heart & Lung Institute in Bethesda. He has a longstanding interest in basic laboratory research into LAM. He is carrying out a clinical programme over the last 10 years following over 300 patients – translational research - bringing the laboratory to the patients.

Dr Moss described how over 300 patients from around the United States and occasionally from further afield visit the NIH at 6-monthly or year intervals. He described how the patients underwent a range of investigations on each occasion, thus providing an invaluable data source of lung function, exercise tolerance, CT findings etc in a very large number of patients. He showed some pictures of the pathology in LAM, and noted that some patients with LAM had mainly lung nodules whilst others had more cysts. Combining these produces a LAM histology score, and this has been shown to correlate well with the lung function changes in LAM and the rate of progression with time. Patients are assessed by a combination of CT scan, histology score and breathing tests, including an exercise test. They have found some degree of osteoporosis in 70% of patients with LAM but this did not relate to progesterone treatment.

An unexpected finding from the NIH study was that a small number of women with LAM (4%) had a benign tumour of the covering of the brain called a meningioma. These tumours also occur in people without LAM and although they may grow, they usually do not cause symptoms. Three of 360 patients have required treatment. He explained that progesterone can increase the growth of meningiomas in the laboratory but from the figures he gave us the likelihood of getting a meningioma appeared to be similar in those who were and those who weren't taking progesterone (*ie*, 12 of 16 patients [75%] with a meningioma were taking progesterone but around 70% of all their patients are taking progesterone). (Whilst patients at the NIH have scans of the brain to see if they have a meningioma this is not a routine practice in the UK: if a meningioma does not cause symptoms treatment is not usually needed).

Dr Moss also talked about some new findings in which they have obtained abnormal LAM cells from the blood of patients with LAM and also in urine and in chyle – the fatty sputum that some patients cough up. They have also looked at the genes expressed in LAM nodules, and found that they are very similar (but not identical) to those seen in angiomyolipomas but differ from those in smooth muscle or melanoma cells. Finally they have looked to see whether they can identify other genes (modifier genes) that might speed up or delay the progression of LAM (*ie*, other than the genes for tuberin and hamartin). So far it looks as though a gene for surfactant B might be important and if this proves to be correct it might be possible to give surfactant to patients. It is hoped in the future to use information on modifier genes to predict who may have more rapidly progressive LAM to help decide when treatment should be started.

There was a lively question and answer session later in the day where these issues were discussed with members of the audience (see below).

CT SCANS IN LAM – WHAT DO THEY SHOW? – KATE POINTON, CONSULTANT RADIOLOGIST

Anne introduced Dr Kate Pointon, Consultant Radiologist at the City Hospital, who has a long-standing interest in high resolution computer tomography (HRCT scans) and a more recent interest in LAM. Kate showed some chest X-rays and several CT scans of the lungs and kidneys – these pictures show thin slices across the lung. She pointed out that a chest X-ray can be normal in the early stages of LAM and the findings could be confused with emphysema or another rare disease (Langerhan's cell histiocytosis). A CT scan is particularly useful for making the initial diagnosis in LAM, and may be used for assessing progress, for assessing certain complications or for research purposes. In the lungs the CT scan shows the cysts very clearly, and it may show a pleural effusion (fluid around the lung), pneumothorax (collapsed lung) or enlarged lymph nodes or thoracic duct. In the abdomen the CT scan shows the renal angiomyolipomas (normal tissue in the wrong place) and sometimes fluid and lymph node masses. The cysts that are characteristic of LAM are usually spread throughout the lungs, and bigger cysts are not necessarily worse – the important question is how much normal lung there is between the cysts. Other imaging techniques, such as ultrasound and MRI, might occasionally have a place in the management of patients with LAM, but CT was the most useful because it measured the density of tissue and so was particularly useful for renal angiomyolipomas. Should we worry about radiation dose? Not too much. A chest X-ray is equivalent to a few days' background radiation, whereas a CT scan is equivalent to the background radiation experienced over several weeks to months (depending on how the study is done). CT scans should not be done unless indicated, but when indicated the risk was very acceptable.

LAM – HOW WILL A PUBLIC RELATIONS FIRM HELP LAM ACTION – MARTIN POWELL, PR CONSULTANT

Martin Powell Communications is a media relations agency with experience of healthcare and charity sectors. They provide an outside view of the organisation, an expert view on what will make a story, the ability to write press material, the ability and databases to contact media throughout the UK and they provide a single point of contact for the media. They have access to over 18,000 radio, television, newspapers, magazines and new media.

The primary aims are to raise awareness of LAM Action, to promote fundraising and gain credibility. Ideas include case studies, research into LAM at the University of Nottingham, stressing the rarity of LAM (how many patients are undiagnosed), fundraising events, ground breaking treatment such as lung transplants, and the international aspect.

Articles including a LAM patient's story and promoting fundraising events had been placed in the local press in the West Country; a press release about the annual meeting had been issued. National coverage would be achieved whenever relevant. Medical journals are not targeted as research papers are too specialist.

Interesting things happening to ordinary people, lay/human stories are the most effective, though care has to be taken as the press exaggerate facts and we need to be responsible.

The medical profession are the most difficult to reach as we are competing for attention with pharmaceutical companies but a slow drip of information works.

What is needed from you:

story ideas, co-operation in dealing with the media, case studies/real life events, fundraising initiatives that are fun, quirky or unusual tales and a geographical spread.

What it involves:

a short telephone conversation, a brief note or email, a possible media call or interview and a photograph.

LAM RESEARCH NEWS: Update from Nottingham – ANNE TATTERSFIELD AND SIMON JOHNSON

Anne Tattersfield and Simon Johnson gave a brief research update. With colleagues they had published a paper in Thorax entitled 'Lymphangiomyomatosis: a case control study of perinatal and early life events'. Many UK patients with LAM had taken part and early life events etc had been compared between patients and up to six controls (women of a similar age). The main finding was that there were no obvious features of family history or early life events that were associated with LAM. The three positive findings were:

- 1) patients with LAM were more often an only child
- 2) a small increase in fibroids in family members of patients with LAM
- 3) patients with LAM remembered having more medicines in childhood, but since no single type of medicine was involved this is probably recall bias – *ie*, patients with LAM are more likely to remember such matters.

A second paper, entitled 'Survival and disease progression in UK patients with lymphangiomyomatosis', will be published in Thorax later this year. This again involved many UK patients with LAM (72) and looked at how long on average patients took to reach various levels of disability and the need for oxygen. There was an average follow-up of 12.6 years and on average, it was about 9 years from the onset of symptoms to the time when patients noticed being breathless when walking on the level. The outlook appears to be better than has been stated in previous publications, in that 91% of patients were alive 10 years after the onset of symptoms, albeit in some instances with a transplanted lung. There was considerable variation however between patients.

A meeting to try to set up Eurolam on a more formal basis is planned for Nottingham in September. We are contacting doctors in Europe who are likely to be interested, and so far 13 have said that they wish to be involved in Eurolam, although not all can come to the meeting. We are also asking the presidents of the LAM societies to the meeting, with perhaps one other patient from each country, and Frank McCormack from Cincinnati has been invited and plans to come. The main aim of the meeting is to discuss how Eurolam should be organised, whether we can get funding from Europe and to discuss collaboration in a new rapamycin study (see below).

Rapamycin study 1

The first study of rapamycin has started in the United States. The aim is to enrol 15 patients with LAM and 15 with tuberous sclerosis, all with kidney tumours (angiomyolipomas). The main aim is to see whether rapamycin reduces the size of the kidney tumour, but lung function is also being measured in patients with lung disease. A second purpose is to assess the safety of rapamycin in patients with LAM and TS, and so far this appears to be satisfactory. A few patients have developed an increase in cholesterol (a well-recognised complication of rapamycin) and have had to take a second treatment for that, and three have

developed mouth ulcers. The results of these studies are not known yet. The UK version of the same study has been delayed by new bureaucracy relating to ethics approval in the European Union but should be underway shortly.

Rapamycin study 2

Plans are also going ahead for a second rapamycin study specifically for patients with LAM to see definitively whether rapamycin alters the rate of change in lung function.

Rapamycin has been shown to slow the growth of the abnormal cells in LAM (LAM cells) in the laboratory and has also been effective in one animal model of tuberous sclerosis, a condition closely related to LAM. From the first study, it appears that rapamycin is relatively safe for patients with LAM. Despite these encouraging findings a trial is still necessary to show that the drug is effective in slowing or improving the rate of lung damage in LAM, and if positive to see how effective it is, and to test the safety of rapamycin in larger numbers of patients. We have been involved in meetings with investigators from the USA, Europe and Japan to plan such a trial.

This study plans to involve 200 patients with LAM from the USA, UK, Europe and Japan. Of these 200, 100 would receive rapamycin and 100 would receive an identical dummy drug (placebo) on a random basis. Neither the patient nor the investigators conducting the trial would know which group the patient was in until the end of the study. At the start of the study patients would have a medical examination, lung function (breathing tests), blood tests for lipid levels and a chest X-ray. These tests would be repeated every 3 months until the end of the trial at two years. At the end of the study the groups would be compared to see if patients taking rapamycin had a slower decrease in lung function than those taking placebo. A safety committee of independent researchers will study the outcome of treatment before the end of the study at 6 and 12 months to see if rapamycin is highly effective (or harmful). If the drug were proven beyond doubt to be effective or harmful before the 2-year period the study would be stopped.

We hope this type of trial will give us a definitive answer and, if the drug is highly effective, the amount of time that patients take placebo will be limited. Complications from rapamycin such as raised lipid levels would be detected at the regular visits and treated with standard treatments.

QUESTION AND ANSWER SESSION – THE ANSWERS CAME FROM JOEL MOSS, SIMON AND ANNE

Q: Surfactant – will it improve the quality of life?

A: It probably would. It helps premature babies with surfactant deficiency. Getting it to the right part of the lung is still a challenge.

Q: Are medium chain triglycerides (MCT) recommended for LAM patients?

A: Chyle is transported from the bowel to the blood stream via the lymphatic system, so cutting down on fat intake may be helpful for patients with a chylous effusion. We don't particularly recommend the MCT diet as it isn't very palatable, but it could be tried if problems continued despite a low fat diet.

- Q: The fluid mentioned in the abdomen – could this potentially cause problems in the digestive system – especially digesting fat?
A: This is not a recognised complication of LAM but it could in theory occur.
- Q: Will the use of LAM Histology Score (LHS) be introduced into the UK or is this just seen as relevant for research at this stage?
A: At the moment it's a research tool.
- Q: Could having had TB as a child have anything to do with having LAM at present (30-40 years later)?
A: Not that we know.
- Q: I have been diagnosed with mild/moderate LAM. My doctor thinks my breathlessness is caused by lack of exercise. Is she right or is it caused by LAM?
A: It's difficult to say without seeing your tests. Exercise within your capacity is good for you.
- Q: Many LAM patients experience significant fatigue as well as breathlessness. Is fatigue a symptom of LAM?
A: A questionnaire survey by Marsha Cohen in the States reported high levels of fatigue as opposed to breathlessness in LAM patients. Muscles work less efficiently when oxygen levels are low.
- Q: I have metal staples in both lungs after surgery. What is their life span?
A: They last long enough for the lung tissue to heal – don't worry.
- Q: After pleurodesis is it possible to get pneumothoraces between the lobes of the lung?
A: Yes, interstitial pneumothoraces are common.
- Q: What is tuberous sclerosis?
A: Tuberous sclerosis is a condition that can be inherited (unlike sporadic LAM) and which affects many organs, including the brain and skin. Many patients with TS also have angiomyolipomas in the kidneys and some have LAM. Unlike LAM it usually causes problems in childhood, including epilepsy and some kidney problems. The association between TS and LAM has helped to unravel the cause of LAM.
- Q: What is the difference between cysts and nodules in LAM?
A: A nodule is solid whereas a cyst has a hole in the middle, and hence can pop to cause a pneumothorax.
- Q: Is there any correlation between location or size of cysts and pneumothoraces?
A: Cysts are normally spread throughout the lungs, cysts near the edges of lungs (near the pleura) can leak, causing pneumothorax.
- Q: Is there anything patients who have had a transplant can do to prevent them from developing osteoporosis?
A: Bisphosphonates help. Bone is laid down based on lines of stress so weight bearing exercises help. A sensible diet and adequate calcium are also important. Walking is very good, as is skipping! One patients said she was allergic to Fosamax – this is very rare and patients who are should speak to their doctor who may be able to offer alternatives.

- Q: Does HRT contribute to the spread or development of LAM?
A: There is some indication in the literature which would support this and it is recommended that patients with LAM do not use HRT.
- Q: Will LAM progress even if HRT is stopped after the menopause?
A: It is unlikely to stop progressing completely but we hope that progression will slow down.
- Q: Post-menopausal patients seem to stabilise. Is this true?
A: Progression of LAM may be slower after the menopause.
- Q: Women who have had a hysterectomy sometimes use testosterone patches to increase libido. Is this safe for LAM patients who are treated with progesterone?
A: This has not been tested, but it is unlikely to make LAM worse.
- Q: What causes panic attacks and how can they best be dealt with?
A: Patients with all types of lung disease are prone to so-called 'panic attacks'. Everyone increases the amount they breathe when they are a bit anxious, but people with normal lungs don't notice it. It becomes obvious when you have limited lung reserves. Panic attacks are usually due more to your lungs than your 'nerves'.
- Q: Are LAM patients allowed to give blood?
A: We think so – unless you have had a blood transfusion.
- Q: What are the symptoms of a meningioma?
A: Headaches sometimes, but it depends where the meningioma is.
- Q: Does the incidence of meningioma increase with age within the general population?
A: Yes, but the number in patients with LAM is higher than in non-LAM people of a similar age.
- Q: Are there any plans to give rapamycin as an anti-rejection treatment for patients with LAM who have had a transplant?
A: This may depend on when we know whether rapamycin helps the lungs in LAM – probably some time next year.
- Q: Is there any correlation between progression of LAM or its complications (eg kidney tumours, lung collapse) and intake of progesterone?
A: No trials have compared progesterone and a placebo so we can't be sure. Retrospective analysis of the UK data suggested a trend to slower decline with progesterone, but taking all the evidence together we conclude that if progesterone does have any effect in LAM it's very small. It may help some patients. If it causes weight gain which will increase breathlessness any possible benefit is likely to be lost.
- Q: The map suggests that there may be clusters of LAM patients around Chester, Newcastle and London.
A: This could be due to particular medical expertise in these areas or patients being more likely to know each other so more likely to register with LAM Action. Clusters can occur with any disease due to chance, and looking at the numbers we suspect the clusters aren't significant.

Associations aren't always due to cause and effect. In the US patients with LAM are more likely to have had a college education; this is presumably because graduates have better access to the internet and find out about LAM for themselves.

Q: Is there a link between endometriosis and LAM?

A: Not that we are aware of.

Q: Can LAM cells travel into limbs?

A: We assume so but they don't cause limb problems.

Q: Is LAM a form of cancer?

A: It looks as though LAM cells can migrate from lymph nodes or the kidney to the lungs and in that respect they resemble cancer cells. They differ however in their appearance down a microscope and their growth is more controlled.

Q: 'Regenerative Medicine' – why not grow lungs and when!?

A: Perhaps in the future, but the lung is a complex organ. Stem cells migrate – they would need to find the right place!

FEEDBACK OF FUNDRAISING IDEAS

See list in the July issue of LAMPost

CLOSING REMARKS

Lucy Falconer thanked everyone for coming and all who had participated in the meeting, especially Jan Johnson for her excellent organisation of the meeting.