A Lay Description of a Two Year Randomised Placebo Controlled Trial of Doxycycline for Lymphangioleiomyomatosis

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Doxycycline is an antibiotic commonly used for respiratory and other infections over short periods of time. One of the features of doxycycline is that it inhibits enzymes called metalloproteinases which are increased in the blood of patients with LAM and it has been suggested that metalloproteinases contribute to the lung cysts that damage the lungs of women with LAM. As Doxycycline is a safe and cheaply available drug some patients with LAM started taking doxycycline to try and prevent decline in lung function. We therefore performed a randomised placebo controlled trial to see if doxycycline could reduce the decline in lung function seen in women with LAM and indeed could be a potential treatment.

The study was funded by grants from the British Lung Foundation and LAM Action, the UK patients group. Patients with LAM and deteriorating lung function were recruited to take either doxycycline for two years or an identical matched placebo. In order to recruit as many patients as possible, other treatment was allowed other than rapamycin, providing treatment level stayed stable over the two year study. When patients were recruited to the study they had baseline measures of FEV1 (forced expiratory volume in one second), a measure of airflow and one of the key markers for monitoring change in LAM over time, but also measurements of gas transfer (DLCO), exercise performance (assessed by shuttle walk test) and quality of life measurements, assessed by questionnaires.

We also took blood and urine samples to measure the effect of doxycycline on MMPs and other biomarkers over the course of the two year study. Twenty-three patients were recruited and were randomised to take either doxycycline or placebo. For the first three months, patients took 100mg of doxycycline and, if tolerated, increased to 200mg for the remainder of the two years. Patients on placebo had their tablets increased at three months also. Every three months patients attended the study centre in Nottingham and had measurements of safety MMP levels and FEV1. At one year and two years patients had a full assessment, including full lung function shuttle walk test and quality of life assessment. In order to avoid patients taking placebo for two years if they had progressive disease, anyone who's FEV1 fell by 300ml or more was, on two occasions, withdrawn from the study. Patients were also withdrawn from the study if they had a pneumothorax or other severe adverse event.

Twenty three patients started the study and whilst not all completed the two years, over this time, the main study outcome, the change in FEV1, did not differ significantly between the two groups, meaning that doxycycline had failed to reduce the decline in lung function in patients who were taking it. Similarly, although doxycycline did reduce the levels of MMP-9 protein in patients who took the active drug, there was no effect on vital capacity, gas transfer, exercise performance or quality of life by doxycycline.

As we are unable to recruit quite as many patients as we originally intended to the study, the conclusions are somewhat guarded, but from the work we have done, there is no evidence to suggest that women with LAM should take doxycycline to try and stop the progression of the disease. Although the drug was quite well tolerated by most patients who took it, side effects including skin rashes, nausea and tinnitus, were more common in the patients who took doxycycline than placebo and overall we would not recommend people took this long term. Doxycycline remains a useful antibiotic for respiratory infections for women with LAM and other problems.

Although this is slightly disappointing news, we will continue to study mechanisms by which LAM damages the lung tissue and search for treatments to specifically target this. We are very grateful to the patients who participated in the clinical trials, those who fundraised for us and the lung function department at our hospital who worked very hard to make the study measurements. The paper is published in full in the European Respiratory Journal at:
http://erj.ersjournals.com/content/43/4/1114

The Doxycycline Team