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Doxycycline in lymphangioleiomyomatosis: not all questions are answered

To the Editor:

We read with interest the article by CHANG *et al.* [1], which demonstrated doxycycline to have no effect on pulmonary function tests (PFTs) and is unlikely to have a potential benefit in lymphangioleiomyomatosis (LAM). An increase in metalloproteinases (MMPs) is considered one of the pathways involved in the pathogenesis of cystic lung destruction in LAM. As a result, doxycycline, a MMP inhibitor, may represent a potential therapeutic target [2–6].

One factor that could have determined a lack of effect on PFTs in the present study was that patients with LAM, treated with doxycycline, had moderate impairment in PFTs when compared with those receiving placebo, which had mild impairment. A recent nonrandomised study from our group has already suggested that patients who would most benefit with doxycycline are those with mild functional impairment [7]. Moreover, the small number of patients included may have limited the results in the present study.

From our previously published study [7], we re-evaluated the effect of the use of doxycycline (100 $mg \cdot day^{-1}$) in 24 patients for 3 years on PFTs. Baseline mean $\pm$ SD forced expiratory volume in 1 s (FEV_1) and diffusion capacity of the lungs for carbon monoxide (D_{LCO}) were 2.30 $\pm$ 0.67 L (81 $\pm$ 21% pred) and 18 $\pm$ 6.6 $mL \cdot min^{-1} \cdot mmHg^{-1}$ (69 $\pm$ 23% pred), respectively. After 3 years, there was a significant reduction in FEV_1 (2.09 $\pm$ 0.71 L; $p<0.001$) and in D_{LCO} (15.8 $\pm$ 6.2 $mL \cdot min^{-1} \cdot mmHg^{-1}$; $p=0.04$). Rate of decline in FEV_1 in 3 years was -73 $mL \cdot year^{-1}$. The majority of patients ($n=20$; 83%) showed a decrease in FEV_1. From the 13 patients that had a stabilisation of or an increase in FEV_1 after receiving doxycycline for 1 year, 11 patients continued follow-up and showed a reduction in FEV_1 after three years (group stabilisation/increase). From 18 patients that showed a reduction in FEV_1 in the first year, 13 continued follow-up and demonstrated the same tendency after 3 years (group decrease), figure 1.

The annual rate of decline in FEV_1 in the present study was slightly greater (-90 mL in the placebo group and -123 mL in the doxycycline group) compared with that observed in the re-evaluation performed by our group (-73 mL in patients that received doxycycline) and with that identified in the study of Taveira-DaSilva and colleagues (-75 mL) [1, 8]. Can we assign a greater decline in FEV_1 identified in the doxycycline group in the present study to a greater impairment in baseline pulmonary function? We believe that there is still no response to this question.

Although doxycycline reduces the levels of MMPs in patients with LAM, we also agree with the authors that based on these recent studies the potential mechanism of action of doxycycline in LAM may be independent of the blockade of MMPs [1, 2, 6, 7].

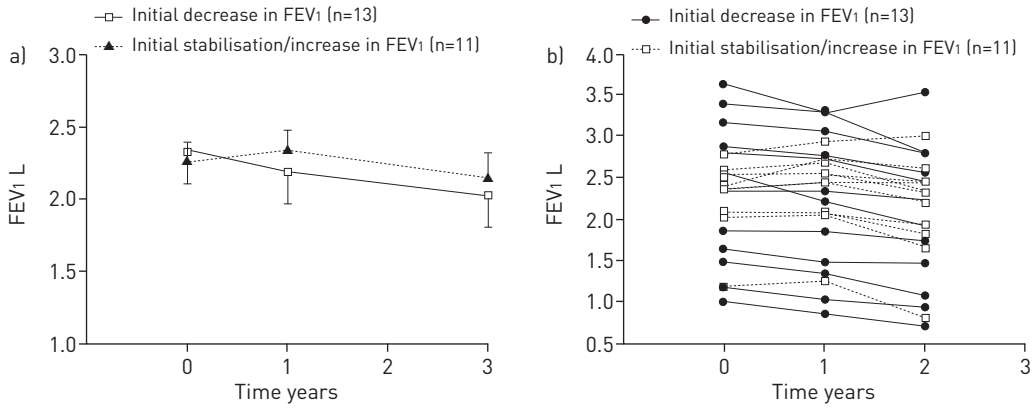

FIGURE 1 a) The mean forced expiratory volume in 1 s (FEV1) at baseline, 1 year and 3 years in the subgroup that initially had stabilisation/an increase in FEV1 and in the subgroup that initially had a decrease in FEV1. b) FEV1 at baseline, 1 year and 3 years in each patient of the subgroup that initially had stabilisation/an increase in FEV1 and in each patient of the subgroup that initially had decrease in FEV1.

Therefore, the present article [1] and our findings, after 3 years of treatment with doxycycline, suggest that the isolated use of this drug is not recommended for the long-term treatment in LAM. However, we believe that these results cannot exclude completely a potential benefit of this drug, mainly if it is used in combination with other medications, such as sirolimus [9] or even hormonal blockage [10], acting on different pathways involved in the pathogenesis of LAM, and in patients with mild functional impairment. In addition, although doxycycline is a safe drug, a limitation in evaluating the impact of this medication in LAM is that its optimal dosage has not yet been determined or in deed how long it should be taken for in order to achieve the proposed benefits.

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Isolated use of doxycycline is not currently recommended: there are doubts whether this drug has any role in LAM http://ow.ly/tJWfU

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