



# Treatment of sarcoidosis-associated pulmonary hypertension: so close, and yet so far

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**More evidence that sarcoidosis patients with pulmonary hypertension respond to therapy** <http://ow.ly/H40c30fetN4>

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Patients with advanced sarcoidosis may develop pulmonary hypertension for a variety of reasons [1]. One of the earlier papers noting the incidence and severity of this problem came from the clinic run by Gianfranco Rizzato in Milan [2]. Despite the well documented association noted in that article, there were very few reports of sarcoidosis-associated pulmonary hypertension (S-APH) until 20 years later. Over the past 10 years, reports regarding S-APH have come from the USA [3–5], Europe [1, 6, 7] and Japan [8]. These studies found that S-APH was most frequently seen patients with fibrotic disease and was associated with increased mortality [9, 10].

The majority of the previously published studies were relatively small and usually reported data on patients followed at individual sites. In this issue of the *European Respiratory Journal*, BOUCLY *et al.* [11] report on the features and outcomes of S-APH in patients enrolled in the French Pulmonary Hypertension Registry. This paper provides data on a large group of patients followed over a 10-year period. The authors provide descriptive data on the initial presentation and outcomes of the 126 cases with moderate-to-severe S-APH after an average of 6 months of various treatments, including survival statistics as well as information about changes in haemodynamics and 6 min walking distance (6MWD). Therapy included both immunosuppressive medications for the underlying sarcoidosis as well as pulmonary hypertension directed treatment. Although not a randomised study, the large number of patients included in this report provides important insights into the role of treatment of S-APH.

11 patients were treated with anti-inflammatory therapy alone including three S-APH patients with radiographic stage 1 disease and evidence of extrinsic compression of the pulmonary arteries by imaging. All three had an improvement in their haemodynamics with treatment. These patients all had increased 2-fluoro-2-deoxy-D-glucose (FDG) uptake on positron emission tomography (PET) prior to therapy. Increased FDG uptake has been shown to be a marker for response to immunosuppressant therapy for sarcoidosis [12–14]. BOUCLY *et al.* [11] recommend performing PET scanning routinely to assess the role of immunosuppressive therapy for all S-APH patients. Given the cost and radiation risk of PET scanning, further studies need to be performed before this can become a standard of care. However, the cost of PET scanning is potentially outweighed by the benefit of identifying those patients in whom using immunosuppressive therapy alone is needed to treat their S-APH.

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In the French group, pulmonary hypertension directed therapy was administered to three quarters of the patients. While there was no specific protocol for therapy, the most commonly used agents were endothelial receptor antagonists or phosphodiesterase-5 inhibitors. After a median of 4 months of therapy, repeat haemodynamics and 6MWD were measured. There was a significant improvement in mean pulmonary artery pressure and pulmonary vascular resistance, similar to the data reported in prior studies [15–18]. Interestingly, there was no significant change in 6MWD. An improvement in haemodynamics with little change in 6MWD has been noted in two prospective clinical trials that evaluated S-APH patients after 4 months of therapy [15, 16]. Another study did report that some patients had improvement in their 6MWD after a median of 14 months treatment [17]. That study found that only those patients with none to moderate impairment in vital capacity had an improvement in their 6MWD. In the current French registry report, there was no change in 6MWD for any level of vital capacity impairment.

This finding highlights one of the problems with treatment of S-APH. What should a treating physician use to assess response to therapy? Similarly, should 6MWD be used as an end-point in future S-APH treatment trials? While there is increasing evidence that pulmonary hypertension directed therapy improves haemodynamics, the data on change in 6MWD is less clear. Baseline reduced 6MWD has been repeatedly reported in patients with S-APH [5, 19]. In the current French study, the 6MWD at presentation was independently associated with mortality. In sarcoidosis, changes in 6MWD may be influenced by multiple factors including parenchymal lung disease, cardiac disease, skeletal muscle involvement and sarcoidosis-associated fatigue [19], thus making it a suboptimal study end-point. Future studies of potential therapies for S-APH should be designed with this in mind. For proof of physiological plausibility of a drug as an effective treatment choice for S-APH, a shorter phase one or two clinical trial evaluating changes in haemodynamics after 3–4 months of treatment may be adequate. However, to determine the efficacy of a drug for changing the natural course of S-APH a larger trial would need to be performed. In group 1 pulmonary arterial hypertension, the time until clinical worsening has been shown to be improved by pulmonary hypertension directed therapy [20, 21], and a composite end-point that enables disease worsening to be captured through a number of objective measures may be a better choice for future long term clinical trials in S-APH.

The study by Boucly *et al.* [11] confirms data from prior studies about the reduced survival of sarcoidosis patients who develop pulmonary hypertension [22]. In this report, the 3- and 5-year survival rates were 74% and 55% respectively, similar to previously published papers [10, 18]. In a recent report, a Cox proportional hazards regression model found the presence of pulmonary hypertension to be an independent predictor of mortality from sarcoidosis [23]. However, it remains unclear whether or not S-APH is an adaptive phenomenon and a surrogate for other deleterious aspects of the disease. Although S-APH is clearly associated with worse outcomes, it still remains unproven that targeted treatment will result in improved outcomes. Therefore, the need to identify treatments for S-APH which not only improve haemodynamics but also delay progression of the disease is crucial. A current trial of riociguat to treat S-APH is an example of the types of trials needed in this area [24].

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