SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2011; 28; 139-145

Ambrisentan for sarcoidosis associated pulmonary hypertension

M.A. Judson[1], K.B. Highland[1], S. Kwon[1], J.F. Donohue[2], R. Aris[2], N. Craft[1], S. Burt[2], H.J. Ford[2]

[1] Division of Pulmonary and Critical Care Medicine, Medical University of South Carolina; [2] Division of Pulmonary and Critical Care Medicine, University of North Carolina at Chapel Hill

Abstract. *Background:* Sarcoidosis associated pulmonary hypertension (SAPH) is associated with significant morbidity and mortality. There is a paucity of information concerning therapy for this condition. *Methods:* We performed a prospective, open-label, proof of concept trial of ambrisentan for SAPH. 21 subjects with SAPH received 5 mg/day of ambrisentan for 4 weeks and then 10/mg day for 20 subsequent weeks. *Results*: No significant change was noted in the 6-minute walk distance over the course of the study (mean change between week 0 and 24: 9.8 ± 54.6 meters, p: NS). There were also no significant differences between weeks 0 and 24 in terms of dyspnea as measured by the modified Borg scale, serum brain naturetic peptide, diffusing capacity, and quality of life as measured by the Short Form-36. There was a high dropout rate: overall: 11/21, 52%; social reasons: 3/21, 14%; medical reasons: 8/21, 38% because of dyspnea: 6/21, 29% and/or edema :4/21, 19%. Of those who completed the 24 week study (10/21, 48%), there was an improvement in their WHO functional class and a marked improvement in their health related quality of life as measured by the St. George Respiratory questionnaire (-15.3 ± 25.0). However both these improvments did not reach statistical significance possibly because of the small sample size. *Conclusion*: Although ambrisentan was not well tolerated by many of these subjects with SAPH, in those who remained in this 24-week trial, improvements in WHO functional class and in health related quality of life suggested a possible benefit of this drug in selected patients. *(Sarcoidosis Vasc Diffuse Lung Dis 2011; 28: 139-145)*

Key words: sarcoidosis, pulmonary hypertension, therapy, ambrisentan

Introduction

Sarcoidosis is a multi-system granulomatous disease of unknown cause that may affect any organ in the body. The lung is the most common organ involved with sarcoidosis (1). Although sarcoidosis commonly affects the respiratory system through deposition of granulomas within the lung interstitium, alveoli, and airways, it may also affect the pulmonary vasculature causing pulmonary hypertension (2). Sarcoidosis associated pulmonary hypertension (SAPH) often responds poorly to anti-granulomatous therapy such as corticosteroids (3).

SAPH has been estimated to occur in approximately 5% of all sarcoidosis patients (4) and with a much higher frequency in severely ill sarcoidosis patients such as those awaiting lung transplantation (5, 6). SAPH also has a poor prognosis with a mortality of over 27 percent in those awaiting lung trans-

Received: 20 January 2011
Accepted after Revision: 23 March 2011
Correspondence: Marc A. Judson, M.D., Professor of Medicine, Division of Pulmonary and Critical Care Medicine, MC-91 Albany Medical College, 47 New Scotland Avenue Albany, New York 12208 USA
E-mail: judsonm@mail.amc.edu

This research was funded by Gilead Sciences, Inc.

plantation (5, 7, 8). SAPH may be problematic to diagnose. The diagnosis should be considered in sarcoidosis patients whose pulmonary dysfunction and pulmonary symptoms fail to respond to corticosteroid therapy, whose diffusing capacity is discordantly reduced in relation to spirometry, or who have signs or symptoms of pulmonary hypertension and/or right heart failure (2).

There are very few reports of pulmonary vasodilator therapy for SAPH. In the majority of these reports, multiple pulmonary vasodilators were used in different patients, making the assessment of specific therapy problematic. In particular, there are few reports describing the effect of endothelin antagonists for the treatment of SAPH. In this report, we describe the results of a prospective, open-label trial of oral ambrisentan for the treatment of SAPH at two major American medical centers.

Methods

This study was approved by the Institutional Review Boards of the Medical University of South Carolina and the University of North Carolina at Chapel Hill.

Entry criteria

Subjects were recruited for enrollment from outpatient clinics at the Medical University of South Carolina and the University of North Carolina at Chapel Hill if they meet all of the following inclusion criteria: a) had biopsy-confirmed sarcoidosis; b) had undergone right heart catheterization within the 18 months of study enrollment with the following findings: mean pulmonary artery pressure (MPAP) of greater than 25 mmHg at rest or 30 mmHg with exercise, pulmonary capillary wedge pressure of less than 15 mm Hg, pulmonary vascular resistance (PVR) of greater than 3 Woods units; c) forced vital capacity of greater than 40% of predicted [the predicted normals for Caucasian and African American were published by Hankinson and coworkers (9)]; d) WHO functional class 2 or 3; e) baseline 6 minute walk distance (6MWD) greater or equal to 150 meters and less than or equal to 450 meters; f) on stable anti-sarcoidosis therapy (e.g., corticosteroids) for at least 3 months prior to study entry. Subjects were excluded from participation if they had any of the following: a) use of any agent for treatment of pulmonary hypertension within one month of study entry; b) uncontrolled systemic hypertension; c) women who were pregnant; d) exercise limitation from a cause thought other than a cardiopulmonary cause (e.g., arthritis); e) pulmonary hypertension thought not to be related to sarcoidosis; f) WHO functional class IV; g) significant left ventricular dysfunction; h) hepatic dysfunction thought not to be related to sarcoidosis; i) the presence of a concomitant illness thought to potentially impact the primary or secondary outcome measures of the study.

Drug administration

Subjects were screened to evaluate their candidacy for participation within 30 days of enrollment. Enrolled subjects received 5 mg/day of ambrisentan orally starting at enrollment (week 0) for 4 weeks. All subjects were then up-titrated to 10 mg/day of ambrisentan which was continued to week 24 post-enrollment. The drug was given in an open-label fashion without a control group. Ambrisentan dose reductions were allowed in the study at the discretion of the investigators.

Study endpoints

The primary study endpoint was the change in the 6MWD between week 0 and week 24. Secondary endpoints included the change in the following parameters over the 24-week study period: a) WHO functional class; b) Modified Borg dyspnea scale (10) during the 6 minute walk test (6MWT); c) St. George Respiratory Questionnaire (SGRQ) score (11); d) diffusing capacity [the predicted normals were published by Crapo and Morris (12)] adjusted for hemoglobin concentration [using the criteria of Dinakara and coworkers (13)]; e) Short Form 36 (SF-36) scores including subscores; f) serum brain natriuretic peptide (BNP) level.

Data collection and safety monitoring

Subjects were questioned and examined at study visits every 4 weeks until study completion (week 24). Subject questioning included their level of dys-

pnea, the presence of peripheral edema, symptoms of cardiopulmonary disease, symptoms of liver disease, and the state of their sarcoidosis. At each visit, the subjects underwent: a physical examination including determination of their vital signs and oximetry and a formal examination for the degree of peripheral edema; serum liver function tests; 6MWT where 6MWD, heart rate, oximetry, and blood pressure were monitored; WHO functional class determination; Modified Borg scale; serum BNP; pregnancy test for all female subjects with child bearing potential. Spirometry, diffusing capacity, complete blood counts, SGRQ scores, and SF-36 scores were measured at weeks 0, 8, 16, and 24. An assessment of compliance with study drug and of possible study drug toxicity was made at the week 4 study visit and all subsequent visits. Subjects were allowed to receive diuretics to control peripheral edema as well as treatment of any other complications that occurred during this study.

Statistical analysis

This was an open label proof of concept study. Patient's demographics were analyzed using data from either the baseline or screening visit time point. Normal values for spirometry were calculated using the equations of Hankinson and colleagues (9).

SF-36 and SGRQ data were analyzed based on scoring algorithm provided by Hays (14) and SGRQ calculator (15) respectively.

For the chosen study outcome variables (6MWD, Borg score, DLCO, BNP, SF-36 global score, SGRQ total score), the score difference between baseline and 8, 16, and 24 weeks were calculated respectively. Student's t-tests were used to test the significance between baseline and week 24. For statistical analysis of the change in WHO functional class between week 0 and week 24, the McNemar's test for 2x2 contingency tables was performed using SAS v9.2.

Results

21 subjects were enrolled in this study. Table 1 displays the demographics and baseline characteristics of the cohort. The patients were predominantly African American women. Most had mild to mod-

Table 1. Demographics and Baseline Characteristics* (n=21, if it is not noted)

Age (years)	51.18 ± 10.71
Gender	
male	4 (18%)
female	17 (81%)
Race	
white	2 (10%)
black	19 (90%)
Sarcoidosis medication	
corticosteroid	19 (90%)
methotrexate	2 (10%)
hydroxychloroquine	2 (10%)
none	2 (10%)
Prednisone daily dose (mg.)	12.02 ± 8.79
CXR stage (n=20)	
0	2
1	0
2	8
3	2
4	8
Spirometry	
FVC (percent predicted§)	61.5 ± 16.5
FEV_1 (percent predicted§)	59.2 ± 20.8
DLCO† (percent predicted††)	33.0 ± 11.1
SF-36 global score (n=20)	33 ± 10.2
SGRQ total score (n=19)	58.4 ± 16.6
Cardiac catheterization data	
days prior to screening	128 ± 157
MPAP (mm Hg)	32.73 ± 7.28
CO, Fick (Liters/min)	4.45 ± 0.94
PVR (Woods units)	5.86 ± 2.28
Requiring supplemental O_2	17 (81%)
Supplemental O2 during 6MWT (n=20)	
None (room air)	4
2 liters/min via nasal canula	7
3 liters/min via nasal canula	1
4 liters/min via nasal canula	4
5 liters/min via nasal canula	1
6 liters/min via nasal canula	3
6 min walk distance (meters) (n=20)	303.8 ± 75.3
O2 desaturation during 6MWT	8.2 % ± 7.7
Modified Borg score (0-10) during 6MWT	5.21 ± 2.68
WHO functional class	
0	0
1	0
2	3 (14%)
3	18 (86%)
4	0
Serum brain naturetic peptide (pg/ml) (n=19)	160.20 ± 354.10

CXR: chest radiograph; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; DLCO: single breath diffusing capacity for carbon monoxide; SF-36: Short Form 36; SGRQ: Saint George Respiratory Questionnaire; MPAP: mean pulmonary artery pressure; CO: cardiac output; PVR: pulmonary vascular resistance; 6MWT: 6-minute walk test; WHO: World Health Organization; * all mean values include ± SD; § predicted values from reference 9; † adjusted for hemoglobin from reference 13; †† predicted values from reference 12

Table 2. Disposition of the study subjects

	N.	%
Completed the trial	10	48
Dropped out for medical reasons*	8	38
Dyspnea	6	29
Edema	4	19
Dropped out for social reasons	3	14

* Some subjects dropped out because of dyspnea and edema. Only one subject dropped out for a medical reason other than dyspnea or edema: hemoptysis from a mycetoma

erate pulmonary hypertension (mean MPAP = 32.7 ± 7.3 mmHg) which is consistent with previous reports of SAPH (16). Most (18/21, 86%) had WHO functional class 3 status at the time of enrollment.

Table 2 shows the disposition of the subjects. Only 48% (10/21) of subjects completed this 24-week trial. Of the 11 subjects who discontinued this study, 8/11 (73%) discontinued for medical reasons (edema or dyspnea except for one subject) while 3/11 (27%) discontinued for social reasons. In terms of timing of study discontinuation, 2/8 (25%) of those who discontinued for medical reasons did so within 8 weeks of enrollment and 6/8 (75%) discontinued after week 8. Subjects who discontinued ambrisentan because of medical reasons could not be predicted by development of edema, 6MWD, Borg scale, baseline supplemental oxygen requirement, WHO functional class, SF-36 score or SGRQ score (data not shown). No patient developed clinical or serologic evidence hepatic toxicity during this trial. Only one subject changed the dose of anti-sarcoidosis medications during the trial (reduction of prednisone from 15 mg/day to 7.5 mg/day, data not shown).

The study's primary endpoint, a significant change in 6MWD between week 0 and week 24, was not achieved by the study cohort (Table 3).

However, a change was seen in two of the secondary endpoints in those who completed this 24 week trial: improvement in WHO functional class and improved quality of life as measured by the SGRQ score (Table 3). The mean change in the SGRQ score (-15.3 ± 25.0) was far above the minimal important difference of the test in terms of improvement of quality of life (< - 4 points) (Table 3). However, this change did not reach statistical significance. The distribution of WHO functional class also improved, as at week 0, 86 percent (18/21) of the subjects were in WHO class 3 and the remainder (14%, 3/21) were in WHO class 2, whereas only at week 24 only 40 percent (6/10) were in WHO class 3 and the remainder were in class 2 (60%, 4/10). However, when only the patients who were followed for the 24 weeks were analyzed, the changes in WHO functional class failed to reach statistical significance.

The following secondary endpoints also did not significantly change after 24 weeks of ambrisentan therapy: Modified Borg dyspnea scale during the 6MWT, diffusing capacity adjusted for hemoglobin concentration; SF-36 scores including subscores, and serum BNP level (Table 3).

Table 3. Study Outcomes*

Study week compared to week 0	8	16	24	p¶
Δ 6MWD (meters)	-24.7 ± 51.4 (16)	-3.4 ± 64.6 (9)	9.8 ± 54.6 (9)	0.35
Δ Modified Borg score during 6MWT	-0.5 ± 2.5 (15)	-1.3 ± 3.8 (8)	-1.6 ± 4.0 (8)	0.55
Δ O_2 desat during 6MWT (%)†	0.3 ± 6.9 (16)	2.3 ± 6.3 (9)	-0.8 ± 7.2 (8)	0.84
Δ DLCO (% predicted§)	-0.6 ± 7.0 (17)	-6.4 ± 16.2 (10)	1.2 ± 4.2 (10)	0.22
Δ BNP	-70.6 ± 279.4 (15)	7.25 ± 59.7 (8)	3.68 ± 37 (8)	0.05
Δ SF-36, global score	2.9 ± 10.2 (16)	6.7 ± 12.9 (9)	5.8 ± 6.1 (9)	0.63
Δ SGRQ, total score	-0.7 ± 16.5 (14)	-17.3 ± 24.2 (8)	-15.3 ± 25.0 (9)	0.12
WHO functional class				0.13
0	0	0	0	
1	0	0	0	
2	2	4	6	
3	15	6	4	
4	0	0	0	

change from week 0; * all mean values include ± SD, the numbers in parentheses are the n used for the calculations; ¶ p value calculated for change between week 24 and baseline; O_2 desat: oxygen desaturation; †: only 1 subject had a change in supplemental oxygen over the course of this study, and this patient dropped out before week 24; DLCO: single breath diffusing capacity for carbon monoxide, adjusted for hemoglobin; § predicted values from reference 12; SF-36: Short Form 36; SGRQ: Saint George Respiratory Questionnaire; WHO: World Health Organization

Discussion

Our open label prospective study of ambrisentan administered to 21 subjects with SAPH did not demonstrate a significant change in the study's primary endpoint, the 6MWD. In addition, there was an extremely high (52%) dropout rate mainly as a result of medical issues. Peripheral edema is a known common side effect of ambrisentan and this was observed in our patients. Dyspnea also developed in a significant number of subjects. It is unclear whether worsening dyspnea represented a worsening of the subjects' SAPH irrespective of ambrisentan therapy or was a complication of ambrisentan therapy. It is possible that subjects who developed dyspnea experienced pulmonary arterial dilatation from ambrisentan without concomitant dilatation of the pulmonary venous system, resulting in the development of pulmonary venous hypertension and resultant pulmonary edema. Involvement of the pulmonary venous system has been demonstrated pathologically to be prominent with SAPH (2) so that this mechanism is plausible. Since repeat hemodynamic measurements were not performed, this hypothesis remains conjectural. We could not demonstrate any particular sign, symptom, or physiologic parameter that could predict which subjects were destined to tolerate ambrisentan as opposed to drop out of this study.

Of the patients who did tolerate ambrisentan for the 24 week duration of this study, our data did show a trend toward improvements in secondary endpoints that may be clinically relevant. First, the WHO functional class improved when all the week 0 assessments were compared to those at week 24. However, this improvement failed to reach statistical significance when the small number of patients who were followed for the duration of the 24-week trial were analyzed. Furthermore, the mean change in health related quality of life over the 24 week study as measured by a decline in SGRQ score far exceeded the minimally important difference established for this quality of life measure. However, this change did not reach statistical significance, possibly because of the small number of measurements (N = 9). We believe that the results of these secondary endpoints are important because in those subjects who tolerated ambrisentan, clinicians assessed that subjects were functionally improved and subjects assessed that they had an improved quality of life in terms of their respiratory status.

In addition, this study was a pilot proof of concept trial. It was not powered in terms of the primary endpoint so that a negative result may be the result of an inadequate sample size. Although the drug was not tolerated by many subjects, it is encouraging that those who continued ambrisentan for the 24 weeks of this trial had an improved functional status as well as improved quality of life as measured by SGRQ.

SAPH may develop as a result of numerous mechanisms. Firstly, sarcoidosis may be associated with pulmonary venous hypertension. This may be caused from cardiac sarcoidosis (17), but is usually unrelated to cardiac involvement (16) and may result from the development of ischemic heart disease from diabetes mellitus and/or hypertension that are often associated with chronic corticosteroid therapy. Secondly, SAPH may occur from parenchymal sarcoidosis causing hypoxic pulmonary vasoconstriction. Thirdly, direct involvement of the pulmonary vasculature with granulomatous inflammation may lead to SAPH (18, 19). Fourthly, SAPH may be caused from pulmonary fibrosis causing distortion of the pulmonary vasculature. This is probably the most common mechanism leading to the development of SAPH (3, 4). Lastly, SAPH may develop from extrinsic compression of the pulmonary vasculature from mediastinal adenopathy. This is probably a very rare mechanism by which SAPH develops (20).

Given the myriad of mechanisms that may cause SAPH, it is unlikely that one specific agent will be efficacious of all SAPH patients. Several drug trials for SAPH have been reported. All have involved a small number of patients ($N \leq 22$), most have not used one specific drug regimen (regimens included calcium channel blockers, epoprostenol, phosphodiesterase inhibitors, endothelin antagonists, inhaled iloprost), have been retrospective, and have not contained a control group (6, 21-24). In general, these trials have not shown major benefit of pulmonary vasodilator drugs. One exception was the trial by Barnett and colleagues (24) who demonstrated a relatively good survival of 22 SAPH patients treated with pulmonary anti-hypertensive therapy. However, different medications were used in different patients without guidance as to method of selection of individual drugs. In the largest previ-

ous report of a single agent used for the treatment of SAPH, Baughman and associates reported their open label prospective experience inhaled iloprost in 22 subjects (25). Fifteen of the 22 completed the 16-week trial and 8 of these 15 (53%) were determined to be "responders." In one study of 22 SAPH patients, corticosteroids were generally ineffective (3). This may be because pulmonary fibrosis causing vasculature distortion is the most common mechanism of development of SAPH (3, 4) rather than a mechanism that involves granulomatous inflammation.

Our study had several potential limitations. First, this was an open label trial without a control group. It is possible that the natural course of SAPH is such that ambrisentan did not significantly affect the outcome of our cohort. We believe that this is unlikely as SAPH patients rarely spontaneously experience a significant improvement in quality of life or who functional class. Second, ambrisentan did not demonstrate a significant physiologic benefit in the cohort, and therefore, the benefit of ambrisentan in quality of life in those that tolerated the drug for this 24-week study could be called into question. This may have been because our study endpoints related to exercise such as 6MWD are dependent upon multiple factors, many of which are not directly related to SAPH. In addition, an improvement in hemodynamics may not directly affect improvement in gas exchange measurements. Most importantly, this study was a proof of concept open label trial which was not adequately powered to detect obvious differences in these parameters. Third, the exact cause of the high rate of dropout of subjects from the study for medical reasons was not clearly identified. Thirty-eight percent of subjects dropped out for medical reasons because of increasing dyspnea and/or peripheral edema. The cause of dyspnea could not be determined. It is unclear if this was related to a drug effect or to the natural course of their disease. The peripheral edema in those who dropped out was not different from those who remained in the study. It would be ideal to identify cohorts of SAPH subjects destined to improve or worsen with ambrisentan therapy. However, we could not identify any parameters to distinguish such subgroups.

A different dosing schedule of ambrisentan may have improved our results. Ambrisentan is known to have a significant hemodynamic effect at 5 mg/day and even 2.5 mg/day (26). In addition, although diuretic therapy was permitted for peripheral edema in this cohort, this approach was not standardized in the study protocol. It is possible that rigorous use of appropriate diuretic therapy may have positively affected the outcome of this study.

In conclusion, this open label drug trial of ambrisentan for SAPH was not tolerated by a large percentage of the subjects. No objective significant physiologic parameter improved in the subjects who did tolerate the drug for the study duration. However, in those who tolerated the drug, physician assessment of function and patient reported outcome of respiratory-related quality of life improved, although these outcomes failed to reach statistical significance. It remains conjectural if any modification in the dosing schedule used in this trial or more aggressive treatment diuretic therapy would have affected the outcome of this study. In addition, no baseline symptom, historical information, or physiologic parameter predicted which subjects would tolerate ambrisentan for the treatment of SAPH. These are areas for potential future investigation.

Acknowledgement

The authors wish to acknowledge Paul J. Nietart, PhD for his statistical assistance and Jihyun Ru for assistance with dta management.

References

1. Judson MA. Sarcoidosis: clinical presentation, diagnosis, and approach to treatment. Am J Med Sci 2008; 335: 26-33.
2. Diaz-Guzman E, Farver C, Parambil J, et al. Pulmonary hypertension caused by sarcoidosis. Clin Chest Med 2008; 29: 549-63.
3. Nunes H, Humbert M, Capron F, et al. Pulmonary hypertension associated with sarcoidosis: mechanisms, haemodynamics and prognosis. Thorax 2006; 61: 68-74.
4. Handa T, Nagai S, Miki S, et al. Incidence of pulmonary hypertension and its clinical relevance in patients with sarcoidosis. Chest 2006; 129: 1246-52.
5. Shorr AF, Helman DL, Davies DB, et al. Pulmonary hypertension in advanced sarcoidosis: epidemiology and clinical characteristics. Eur Respir J 2005; 25: 783-8.
6. Milman N, Burton CM, Iversen M, et al. Pulmonary hypertension in end-stage pulmonary sarcoidosis: therapeutic effect of sildenafil? J Heart Lung Transplant 2008; 27: 329-34.
7. Arcasoy SM, Christie JD, Pochettino A, et al. Characteristics and outcomes of patients with sarcoidosis listed for lung transplantation. Chest 2001; 120: 873-80.
8. Shorr AF, Davies DB, Nathan SD. Predicting mortality in patients with sarcoidosis awaiting lung transplantation. Chest 2003; 124: 922-8.
9. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999; 159: 179-87.

10. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982; 14: 377-81.
11. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med 1991; 85 (Suppl B): 25-31; discussion 33-27.
12. Crapo RO, Morris AH. Standardized single breath normal values for carbon monoxide diffusing capacity. Am Rev Respir Dis 1981; 123: 185-9.
13. Dinakara P, Blumenthal WS, Johnston RF, et al. The effect of anemia on pulmonary diffusing capacity with derivation of a correction equation. Am Rev Respir Dis 1970; 102: 965-9.
14. Hays RD, ed. Rand-36 Health Status Inventory. San Antonio: Pyschological Corporation, 1998.
15. Jones PW. St. George Respiratory Questionnaire Manual. St. George's, Univerity of London, London, England, 2008.
16. Baughman RP, Engel PJ, Taylor L, et al. Survival in sarcoidosis associated pulmonary hypertension: the importance of hemodynamic evaluation. Chest; 138: 1078-85.
17. Kim JS, Judson MA, Donnino R, et al. Cardiac sarcoidosis. Am Heart J 2009; 157: 9-21.
18. Rosen Y, Moon S, Huang CT, et al. Granulomatous pulmonary angiitis in sarcoidosis. Arch Pathol Lab Med 1977; 101: 170-4.
19. Takemura T, Matsui Y, Oritsu M, et al. Pulmonary vascular involvement in sarcoidosis: granulomatous angiitis and microangiopathy in transbronchial lung biopsies. Virchows Arch A Pathol Anat Histopathol 1991; 418: 361-8.
20. Westcott JL, DeGraff AC, Jr. Sarcoidosis, hilar adenopathy, and pulmonary artery narrowing. Radiology 1973; 108: 585-6.
21. Preston IR, Klinger JR, Landzberg MJ, et al. Vasoresponsiveness of sarcoidosis-associated pulmonary hypertension. Chest 2001; 120: 866-72.
22. Baughman RP, Engel PJ, Meyer CA, et al. Pulmonary hypertension in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2006; 23: 108-16.
23. Fisher KA, Serlin DM, Wilson KC, et al. Sarcoidosis-associated pulmonary hypertension: outcome with long-term epoprostenol treatment. Chest 2006; 130: 1481-8.
24. Barnett CF, Bonura EJ, Nathan SD, et al. Treatment of sarcoidosis-associated pulmonary hypertension. A two-center experience. Chest 2009; 135: 1455-61.
25. Baughman RP, Judson MA, Lower EE, et al. Inhaled iloprost for sarcoidosis associated pulmonary hypertension. Sarcoidosis Vasc Diffuse Lung Dis 2009; 26: 110-20.
26. Galie N, Badesch D, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol 2005; 46: 529-35.