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Review Article

Sarcoidosis associated pulmonary hypertension

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ABSTRACT

Sarcoidosis is a multisystem inflammatory disease of unknown etiology that can be manifested as non-caseating granulomas, predominantly in the lungs and intrathoracic lymph nodes. Pulmonary hypertension is known as one of the complications of sarcoidosis and is associated with increased mortality. The incidence of sarcoidosis associated pulmonary hypertension (SAPH) varies between 5 to 20% and the prevalence is unknown. SAPH is classified as group V because of its multifactorial mechanism, it can be caused by pulmonary arterial hypertension, sarcoid cardiomyopathy, hypoxia, chronic thromboembolic pulmonary hypertension disease, and other mechanism like thoracic lymphadenopathy and fibrosing mediastinal, and increasing pulmonary vasoreactivity. SAPH patients have worsening dyspnea or sometimes signs of right-sided heart failure. Patients with SAPH reduced in pulmonary function test (6-minute walk distance (6MWD), diffusing capacity for carbon monoxide (DLCO), another test can be done are chest X-ray, high-resolution chest computed tomography (CT) scan, echocardiography, and right heart catheterization (RHC) as gold standard. The optimal management strategy for pulmonary hypertension associated with sarcoidosis is still unknown. The treatment involved in use of supplemental oxygen, systemic anti-inflammatory medication, pulmonary vasodilators, prostacyclin, endothelin receptor antagonists, phosphodiesterase 5 inhibitors even lung transplantation. SAPH is associated with significant morbidity and mortality. Patients with SAPH have 7-fold increase in risk for all-cause mortality when compare to sarcoidosis patients without PH, even when adjusted for age and pulmonary function.

Keywords: Sarcoidosis, Pulmonary hypertension, Sarcoidosis associated pulmonary hypertension

INTRODUCTION

Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure ≥25 mm at rest or ≥30 mmHg during exercise, and often caused by increase in pulmonary vascular resistance that eventually may lead right ventricular failure.[1] Sarcoidosis is a multisystem inflammatory disease of unknown etiology that can be manifested as non-caseating granulomas, which predominantly in the lungs and intrathoracic lymph nodes.[1]

Pulmonary hypertension is known as one of complications of sarcoidosis and is associated with increased mortality. The epidemiology of sarcoidosis and PH demonstrates sarcoidosis associated pulmonary hypertension (SAPH) is prevalent, and independently associated with significantly increased in mortality and decreased functional capacity.[2]

The incidence of SAPH varies between 5 to 20% and the prevalence is unknown, but some studies showed that prevalence can be high around 75% depending on the population and method used to define pulmonary hypertension.[2] Patients with SAPH have 7-fold increase in risk for all-cause mortality when compare to sarcoidosis patients without PH, even when adjusted for age and pulmonary function.[3]

PATHOPHYSIOLOGY

PH is divided into 5 different group by the World Health Organization (WHO) (Table 1). The group are classified

by etiology, clinical presentation, pathological findings, hemodynamic characteristics and treatment strategy of PH. SAPH is classified as group V because of its multifactorial mechanism (Figure 1), and the most common cause of SAPH Is pulmonary fibrosis related destruction of the vascular bed.

Pulmonary arterial hypertension

PAH is known as PH patients with low mean pulmonary artery (PA) wedge pressure ≤15 mm Hg and high pulmonary vascular resistance (PVR) >3 Wood units. The pathologic features of PAH show an adventitial and medial thickening, smooth muscle hyperplasia, pathologic muscularization of non-muscularized arterioles, and intimal fibrosis and proliferation. In late-stage disease, disorganized whorls of endothelial cells called plexiform lesions develop.[4,5] Sarcoidosis patients are also characterized by an increase in inflammatory mediators, which are associated with increase in vasoactive substance such as endothelin-1. Growing evidence suggests that increase levels of various inflammatory and vasoactive substances in the active phase of the disease may affect the endothelial function and arterial wall properties.[6] On pathologic review, SAPH frequently demonstrates granulomas in the walls of the pulmonary vasculature, from elastic arteries to the collecting venules. Granulomatous inflammation has been described in all layers of the vasculature and can cause vessel fibrosis, leading to increased PVR.

Sarcoid cardiomyopathy

Cardiac sarcoidosis (CS) is infiltrative cardiomyopathy that results from granulomatous inflammation affecting the heart. It is a poor prognosis and a rare condition. Less than 10% patients with sarcoidosis is reported as cardiac sarcoidosis and also reported up to 26% in patient with extracardiac sarcoidosis.[7] Cardiac sarcoidosis can involve pericardial, myocardial, endocardial tissue, and it most commonly involves the myocardium. Sarcoid granulomas can involve the left ventricle and extensive involvement of the myocardium usually results in restrictive cardiomyopathy leading to left ventricular dysfunction in up to 80% of cases. Still, clinical heart failure is seen in less than 30% of cases. And also, right ventricular involvement in sarcoidosis is usually a consequence of pulmonary fibrosis, pulmonary hypertension, or left ventricular dysfunction causing right heart failure but can also be from granulomatous infiltration of the right ventricle.[8]

But also, in retrospective study consisting of 130 sarcoids patient of all stages, with persistent dysnea, who went right heart catheterization after at least six months of immunosuppressive therapy, the prevalence of PH was 54 %. Interestingly, in 29 % an elevated PAWP >15 mmHg was measured, suggesting left ventricular disease as a cause of PH.[9]

Chronic lung disease or hypoxemia

Sarcoidosis patients may develop parenchymal lung disease and it is at greatest risk of developing PH, and indeed, the majority of patients with SAPH have evidence of pulmonary disease.[10] The primary mechanism for this is believed to be the destruction of vasculature from the lung disease, resulting in hypoxemia from ventilation/perfusion mismatch. Structure distortion of pulmonary vascular can also increase PVR.[11] Sarcoidosis patients are also reported have an increased rate of sleep disordered breathing. Obstructive sleep apnea is increased by the use of corticosteroid for treat the disease, and it causes nocturnal hypoxemia.[12] Vasoconstriction in response to low oxygen tension (hypoxia) in pulmonary arteries is an important physiological adaptation to reroute blood flow to areas of higher oxygenation for effective gaseous exchange. Hypoxic stress triggers cellular phenotypic alterations including increased proliferation and migration of vascular smooth muscle cells (VSMCs), as well as synthesis of extracellular matrix (ECM) proteins that remodel lung vasculature. Remodelling of vessels increases the risk of pulmonary hypertension (PH)—elevated pulmonary arterial pressure—and eventually right heart failure. Hypoxia-inducible factor-1α (HIF-1α) is a master regulator of transcription in hypoxic cells, up-regulating genes involved in energy metabolism, proliferation, and extracellular matrix reorganization. It is known that HIF-1α in smooth muscle contributes to pulmonary vascular remodelling and pulmonary hypertension in chronic hypoxia.[13,14]

Pulmonary hypertension because of chronic thromboembolic pulmonary hypertension disease (CTPHD)

Venous thromboembolism increase in patients with sarcoidosis, the association and the true incidence of sarcoidosis and venous thromboembolism is unknown. It is believed to be commensurate with active inflammation promoting a hypercoagulable state.[15] And it is also reported that patients with chronic sarcoidosis on steroid therapy that may resulting in immobilization because of pulmonary fibrosis, pulmonary hypertension, osteoporosis with fractures, obesity, and other, also at the highest risk of VTE.[16] The risk factor for the development of VTE in sarcoidosis might be related to clinical characteristics such as compression of pulmonary arteries by the enlarged mediastinal lymph nodes. Nevertheless, it is known that mediastinal lymphadenopathy more associated with thoracic vein thrombosis than pulmonary artery thrombosis.[17]

Other mechanisms of sarcoidosis

Sarcoidosis may present with thoracic lymphadenopathy and fibrosing mediastinital, and in this case, architectural distortion in the main lung tree circulation requires the effort of the pulmonary vessels to flow, causing pulmonary stenosis and segmental PH.[18] Other mechanisms that also

known is the increased pulmonary vasoreactivity in sarcoidosis, as founded by the favorable acute response to vasodilators, including nitric oxide (NO) and prostacyclin. The mechanism for this increased pulmonary vasoreactivity remains unclear, but may be explained by endothelial damage of the sarcoid granuloma. Endothelial dysfunction can lead to decreased synthesis and release of NO and prostaglandins, leading to an imbalance of endothelial-derived vasoactive mediators, followed by pulmonary vasoconstriction and remodeling.[19] Hepatic sarcoid infiltration and cirrhosis are complications of sarcoidosis, and as a result, port-pulmonary hypertension may develop. Although port-pulmonary hypertension is rare in sarcoidosis, hepatic ultrasonography is recommended in the investigation of SAPH.[20]

CLINICAL MANIFESTATION

The symptoms of sarcoidosis and pulmonary hypertension may be difficult to distinguish, but the doctor should suspect sarcoidosis to be SAPH if the patient has worsening dyspnea or signs of right-sided heart failure. Dyspnea on exertion is a common complaint in pulmonary sarcoidosis, cardiac sarcoidosis, and pulmonary hypertension, and it confounds the diagnosis of SAPH.[21] Shortness of breath symptoms or dyspnea often appear in patients without PH. Other considerations when the patient presents with unexplained dyspnea or exercise limitations can happen in patient with myopathy (skeletal or respiratory muscles), major airway obstruction, occult cardiac disease, depression, and anemia.[22] The most common symptom in patients with SAPH is progressive dyspnea on exertion. Other common complaints that may follow are cough, chest pain, palpitations and symptoms suggestive of right heart failure such as lower extremity edema and syncope. Only signs of right heart failure were an independent predictor of increased right-sided pressure, but their sensitivity was low.[10]

In physical examination, patients with pulmonary hypertension may be found a loud P2, S4, evidence of right sided volume overload such as elevated jugular venous pressure or peripheral edema, and a right ventricular heave, but these are often findings that are discovered late in the disease course.[23]

DIAGNOSIS

Clinical practice guideline for sarcoidosis recently published by the American Thoracic Society (ATS) recommend initial screening with echocardiography in patients who are suspected of PH. According to the recently published ATS clinical guideline for sarcoidosis, suspicion of PH is based on clinical manifestations including disproportional dyspnea (disproportional in relation to pulmonary function tests), exertional chest pain and/or syncope, prominent P2 or S4 during physical examination, reduced 6-minute walk distance (6MWD), desaturation with exercise, reduced diffusing capacity for carbon monoxide (DLCO), increased pulmonary artery diameter relative to ascending aorta diameter.[24]

Pulmonary function tests

Sarcoidosis patients often regularly undergo serial pulmonary function tests (PFT) during their management. A number of PFT variables including diffusing capacity for carbon monoxide (DLCO) and forced vital capacity (FVC) were also performed as potential predictors of SAPH. However, because of the multiple manifestations of pulmonary sarcoidosis (such as interstitial lung disease, bronchiectasis, significant emphysema, and airflow obstruction), this PFT examination alone may be difficult to differentiate pulmonary vascular disease from lung parenchymal disease.[10,25] The combination of PFT variables may be effective in predicting the risk of PH echocardiography in a cohort of sarcoidosis patients.[26] DLCO measures the forces at play in molecular movement with its concentration gradient from the alveolar surface through to the hemoglobin molecule and is the most sensitive parameter to detect a loss of functional alveolar surface area. A DLCO may be lowered in anemic patients because hemoglobin in the alveolar capillaries acts as a carbon monoxide sink. Hematologic abnormalities are quite common in sarcoidosis patients, with anemia brought on by non-caseating granulomas and the lack of iron stores in the bone marrow.[27,28] A lower DLCO in pulmonary arterial hypertension (PAH) may be the consequence of vascular remodelling and is connected to proportionate reductions in alveolar–capillary membrane diffusing capacity and total pulmonary capillary blood volume available for gas exchange.[29] In a study of 162 patients with sarcoidosis, Bourbonnais et al showed DLCO <60% predicted demonstrating an odds ratio of 7.3 of having PH.[25] Other test can be done for diagnosis of SAPH is 6-minute walk test (6 MWT), which noted to be decreased in SAPH. Bourbonnais et al demonstrated that oxygen desaturation below 90% on 6MWT correlated with an odds ratio of 12.1 (CI 3.7–19.7) of having SAPH.[25]

Imaging

Chest X-ray has been associated with SAPH, which presence of advanced lung disease. And some studies also have investigated the utility of CT scan for the detection of PH, with reported associations between PA diameter and the ratio of the main pulmonary artery to the ascending aorta (rPA). Ng et al showed that in using a mean pulmonary artery pressure greater than 20 mm Hg as indicative of PAH and a value of rPA >1, the sensitivity, specificity, and positive and negative predictive values for determining PAH were 70%, 92%, 96%, and 52%, respectively.[30] High-resolution computed tomography (HRCT) of the chest also may suggest as an additional examination. One study showed that 3 of 14 (21%) of a series of SAPH patients with pulmonary fibrosis also had extrinsic compression of large pulmonary artery. However, specific high-resolution chest CT findings are

not generally helpful for predicting the presence versus absence of SAPH.[31,32]

Echocardiography

Echocardiography is particularly useful in sarcoidosis because of the simultaneous need for assessment of cardiac sarcoidosis and as a screening for PH patients. The diagnosis of SAPH should be suspected when there are echocardiographic finding of right ventricular pressure overload, including right ventricular hypertrophy, systolic dysfunction, flattening of the interventricular septum or an abnormal ratio of the interventricular septum to posterior left ventricular wall thickness in the absence of tricuspid regurgitation. The absence of these findings, nevertheless, does not exclude the possibility of SAPH and therefore right heart catheterization (RHC) is currently still considered necessary for definitive diagnosis.[33]

Haemodynamic

The gold standard for the diagnosis of SAPH is direct measurement of pulmonary artery pressure with RHC. Pulmonary hypertension occurs when the mPAP exceeds 25 mm Hg at rest or 30 mm Hg during exercise. Measurement of the transpulmonary gradient [difference between mPAP and pulmonary capillary wedge pressure (PCWP)] is useful in excluding left ventricular disease associated with cardiac sarcoidosis or other causes. In most cases, the PCWP is also an estimate of left ventricular end-diastolic pressure (LVEDP). The normal pulmonary capillary wedge pressure is between 4 to 12 mmHg. Elevated levels of PCWP might indicate severe left ventricular failure or severe mitral stenosis. For patients with an elevated mPAP (>20 mm Hg), the results of the PAWP measurement will determine whether this is pre- or post-capillary PH (WHO group 2), PAWP >15 mm Hg confirms a post-capillary PH. If there is any uncertainty about the validity of the PAWP measurement, then direct measurement of the left ventricular end-diastolic pressure measurement should be considered. However, because LV end-diastolic volume can be compromised by septal flattening in severe pulmonary hypertension, PCWP measurements should be correlated with echocardiographic assessments of interventricular dependency.[34-36]

TREATMENT

The pathophysiology of SAPH holds relevance for treatment. The optimal management strategy for pulmonary hypertension associated with sarcoidosis is still unknown. The treatment (Table 2) involved in using of systemic anti-inflammatory medication, pulmonary vasodilators, endothelin receptor antagonists, supplemental oxygen, or even lung transplantation.

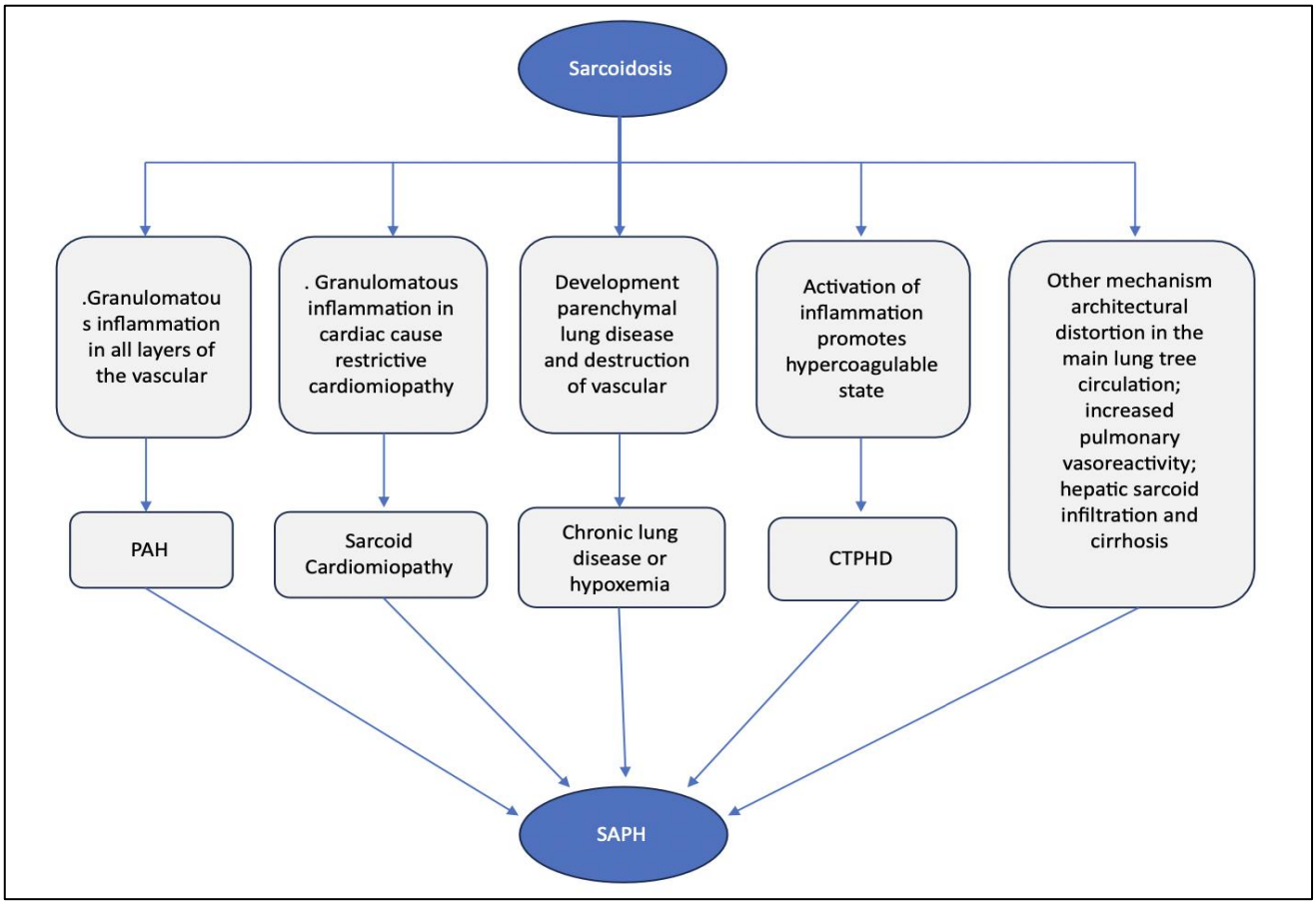

Figure 1: Pathophysiology of SAPH.

Table 1: WHO classification of pulmonary hypertension.

S. no.	Classification
1	Pulmonary arterial hypertension (PAH)
1.1	Idiopathic PAH
1.2	Heritable PAH
1.2.1	BMPR2
1.2.2	ALK1, endoglin (with or without hereditary hemorrhagic telanglectasia)
1.3	Drug- and toxin-induced PAH
1.4	PAH associated with
1.4.1	Connective tissue disease
1.4.2	HIV infection
1.4.3	Portal hypertension
1.4.4	Congenital heart disease
1.4.5	Schistosomiasis
1.4.6	Chronic hemolytic anemia
1.5	Persistent PH of the newborn syndrome
1.6	Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
2	PH due to left heart disease
2.1	Systolic dysfunction
2.2	Diastolic dysfunction
2.3	Valvular heart disease
3	PH due to lung disease and/or hypoxia
3.1	Obstructive lung disease
3.2	Interstitinal lung disease
3.3	Other lung disease with mixed restrictive/obstructive pattern
3.4	Sleep-disordered breathing
3.5	Alveolar hypoventilation disorder
3.6	Chronic exposure to high altitude
3.7	Developmental lung disorders or abnormalities
4	Chronic thromboembolic pulmonary hypertension (CTEPH)
5	PH with unclear and/or multifactorial mechanism
5.1	Hematologic disorder: myeoloproliferative disorders, splenectomy
5.2	Systemic disoreder: sarcold, pulmonary Langerhans cell, histlocytosis; lymphangiolelomyomatosis, neurofibromatosis, vasculitis
5.3	Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorder
5.4	Others: tumor obstruction, fibrosing mediastinal, chronic renal failure on dialysis

Table 2: Drug therapy for SAPH.

Drug	Author	Result
Oxygen therapy	Galiè et al[37]	Reduce PVR in patients with PAHs, however, do not provide random data for the long-term oxygen therapy at SAPH
Anti-inflammatory	Savale et al[36]	May lead to reduction of the size of the nodes and relief of the compression that can causes SAPH
PH-specific therapy		
Calcium channel blockers (CCB)	Preston et al[38]	Decrease in PVR >20%
Prostacyclin	Bonhan et al[3]	Improvement in hemodynamics and clinical outcomes of patients with severe SAPH
Epoprostenol	Abston et al[39]	Improvement in hemodynamics and NYHA functional class
Iloprost	Baughman et al[40]	Improved pulmonary hemodynamics, quality of life (QoL), 6MWD
Endothelin receptor antagonist	Palmer et al[41]	Increase pulmonary vascular tone and the long-term effects of pulmonary vascular remodeling
Bosentan	Baughman et al[16]	Improved pulmonary hemodynamics and fall in PA mean pressure
Ambrisentan	Judson et al[42]	No improvement in QoL, and no change in 6MWD

Continued.

Drug	Author	Result
Macitentan	Mathijssen et al[43]	Four patients showed improvement of their functional class and three patients in exercise capacity after 12 months of therapy
Phosphodiesterase 5 inhibitor		
Sildenafil	Milman et al[44]	Improvements in hemodynamic parameters
Tadalafil	Ford et al[45]	No significant changes in 6MWD and QoL
Soluble guanylate cyclase stimulators	Baughman et al[46]	Improved 6MWD, and better in time to clinical worsening (TCW) compared with placebo

Oxygen therapy

Oxygen therapy is recommended in this subgroup of patients with hypoxaemia. Administration of oxygen can reduce PVR in patients with PAHs, however, do not provide random data for the long term oxygen therapy at SAPH. The ESC/ERS Guide to PH recommend the use of oxygen in patients with partial arterial blood oxygen pressure <8.0 kPa.[37]

Anti-inflammatory

SAPH may be caused by direct compression of the pulmonary artery by either mediastinal adenopathy or fibrosis. The using of anti-inflammatory therapy may lead to reduction of the size of the nodes and relief of the compression.[36]

PH-specific therapy

Because SAPH is often caused by fibrosis with end-stage "permanent" abnormalities of pulmonary microcirculation, it is also unclear whether these agents have a beneficial effect on pulmonary vascular resistance.

Calcium channel blocker

Calcium channel blockers (CCB) have been tried in a small series of SAPH patients, who showed positive vasoreactivity in right heart catheterization. Preston et al study showed that during acute vasodilator testing, a decrease in PVR >20% was observed in two of five patients that were treated by calcium-channel blockers, but the two patients treated with calcium-channel blockers did poorly, dying with progressive right-heart failure and post-transplant respiratory failure, respectively.[38]

Prostacyclin

Intravenous epoprostenol use has been reported in SAPH. The studies showed improvement in hemodynamics and NYHA functional class.[39] Bonhan et al study showed that many patients with severe SAPH showed significant hemodynamic and clinical improvement on long-term IV or subcutaneous PG therapy and had survival outcomes similar to patients with moderate SAPH on oral vasodilator therapy.[3] Baughman et al suggested that inhaled iloprost improved pulmonary hemodynamics, quality of life (QoL), 6MWD.[40]

Endothelin receptor antagonist

Bosentan, ambrisentan, and macitentan are endothelin receptor antagonists that inhibit endothelin activity in the smooth muscle of the pulmonary vessels. Endothelin is a potent endogenous vasoactive molecule that is implicated in the pathophysiology of PAH through its ability to increase pulmonary vascular tone and the long-term effects of pulmonary vascular remodeling.[41] Baughman et al showed that the use of bosentan 23 patients with SAPH significantly improved pulmonary hemodynamics and fall in PA mean pressure.[16] But in Judson et al study showed that the use of amrisentan showed no improvement in QoL, and no change in 6MWD.[42] Mathijssen et al study showed the use of macitentan in six cases (three men) with a median age of 64 years (range 52-74 years), one patient experienced side effects and aborted therapy after five days of treatment and died 16 months later. Three patients were hospitalised during treatment for congestive heart failure. Four patients showed improvement of their functional class and three patients in exercise capacity after 12 months of therapy.[43]

Phosphodiesterase 5 inhibitor

Phosphodiesterase-5 (PDE-5) inhibitors inhibit the degradation of intracellular cyclic guanosine monophosphate in vascular smooth muscle, which leads to smooth muscle relaxation. Sildenafil and tadalafil belong to this class and both have been studied in small series in SAPH. The using of sildenafil treatment was associated with significant improvements in hemodynamic parameters.[44] But in the using of tadalafil treatment, there is no significant changes in 6MWD and QoL.[45]

Soluble guanylate cyclase stimulators

Baughman et al study showed that the using of riociguat in SAPH patient significantly improved 6MWD, and better in time to clinical worsening (TCW) compared with placebo.[46]

Lung transplantation

Without limitations brought on by severe extra-pulmonary sarcoidosis or comorbidities, lung transplantation is a possible therapeutic option for radiologic stage IV sarcoidosis and severe pulmonary arterial hypertension (PAH). Poor response to approved PAH treatments is seen in PAH with severe lung disease and an FVC (forced vital

capacity) of less than 50%, these patients should be referred for lung transplantation.[47]

PROGNOSIS

SAPH is associated with significant morbidity and mortality. It is associated with increased supplemental oxygen requirement and reduced exercise capacity and has high social impact for the individual patient with a decrease in quality of life.[48] Tiosano et al study showed that both sarcoidosis and pulmonary hypertension were found to be significantly associated with an increased risk of all-cause mortality (HR 1.82 and HR 2.31, respectively).[49] Patients with SAPH have 7 fold increase in risk for all-cause mortality when compare to sarcoidosis patients without PH, even when adjusted for age and pulmonary function.[3]

CONCLUSION

Pulmonary hypertension is known as one of the complications of sarcoidosis and is associated with increased mortality. The incidence of SAPH varies between 5 to 20% and the prevalence is unknown, but some studies showed that prevalence can be high around 75% depending on the population and method use to define pulmonary hypertension. SAPH is classified as group V because of its multifactorial mechanism. The gold standard for the diagnosis of SAPH is direct measurement of pulmonary artery pressure with RHC. The optimal management strategy for pulmonary hypertension associated with sarcoidosis is still unknown. The treatment involved in use of supplemental oxygen, systemic anti-inflammatory medication, pulmonary vasodilators, prostacyclin, endothelin receptor antagonists, phosphodiesterase 5 inhibitors even lung transplantation. SAPH is associated with significant morbidity and mortality.

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