Review

Severe pulmonary hypertension as the initial manifestation of systemic lupus erythematosus: a case report and review of the literature

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Received on June 28, 2013; accepted in revised form on September 26, 2013.

Clin Exp Rheumatol 2014; 32: 267-274.

Key words: systemic lupus erythematosus, pulmonary hypertension, therapy, cyclosporine, mycophenolate mofetil

Funding: this work was supported by grant 2012 from the "SLE Italian Group".

Competing interests: none declared.

ABSTRACT

Severe pulmonary arterial hypertension (PAH) is rarely observed as the initial manifestation of systemic lupus erythematosus (SLE), and the diagnosis is often delayed. Here we present the case of a 32-year-old woman with severe PAH as the initial manifestation of SLE, who was successfully treated with mycophenolate mofetil and cyclosporine. This case offered the opportunity to critically review the epidemiology data, predictive markers, and pathogenic pathways of SLE-associated PAH (SLE-PAH) in relation to the currently available therapeutic options and to the main clinical trials of the last 10 years focused on the treatment of SLE-PAH. Mycophenolate mofetil and cyclosporine – currently used in the maintenance phase of the disease in certain clinical settings – should be considered, as an alternative to cyclophosphamide, in future clinical trials aimed at evaluating the most effective treatment of SLE-PAH at presentation.

Introduction

Pleuro-pulmonary manifestations of systemic lupus erythematosus (SLE)affect 4–5% of patients at presentation (1) and include – besides the more common pleural effusions and pulmonary infections – alveolar haemorrhage, shrinking lung syndrome, diffuse interstitial lung disease, pulmonary embolism, acute reversible hypoxemia and systolic pulmonary arterial hypertension (PAH) (1, 2). PAH is defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg by right heart catheterisation, and can be classified as "pre-capillary" or "post-capillary", depending on whether pulmonary artery wedge pressure is ≤15 mmHg or ≥15 mmHg, respectively (3). In this second case, PAH is usually due to left-heart diseases. Since pre-capillary PAH is the form strictly associated to SLE-histopathological changes affecting lung small vessels, we will refer hereafter to PAH to indicate exclusively pre-capillary PAH.

SLE-associated PAH (SLE-PAH) is a rare condition (4), being an uncommon cause of death after cardiovascular disease, infection, renal failure and non Hodgkin lymphoma in western countries (5). It usually occurs after 3.2 years (mean time) from the disease onset (6) and the diagnosis of this life-threatened complication is often delayed, due to its rarity and insidious onset (1). Indeed, more than 40% SLE-patients with early PAH are asymptomatic (7), while in the remaining patients the symptoms (dyspnea, fatigue, impaired exercise tolerance, chest pain, non productive cough, oedema) mimic other more frequent types of SLE lung involvement, such as pleural effusion, pericardial effusions or interstitial lung disease (1, 8).

Here we report the case of a young female who presented PAH as almost the only manifestation of SLE at presentation. She was successfully treated with mycophenolate mofetil and cyclosporine as first line therapy.

Clinical case

A 32-year-old woman of Moroccan origin was admitted to the Internal Medicine Department for a severe PAH of unknown origin. The patient had no history of cardio-vascular risk factors, evidence of portal hypertension or congenital heart disease. She had always enjoyed good health until 2 months before, when she started to experience generalised arthralgias, continuous-remittent fever and increasing weakness. After one month, she was admitted to a cardiology department due to the sud-

den onset of exertional dyspnea, chest pain and palpitations. A trans-thoracic echocardiogram revealed enlargement and overload of the right heart, dilatation of the inferior vena cava >22 mm, severe tricuspid regurgitation, an estimated pericardial effusion of 200–500 ml, an estimated systolic pulmonary arterial pressure (sPAP) of 90 mm Hg, a tricuspid annular plane systolic excursion of 22 mm and normal systolic function (EF 60%). Right heart cardiac catheterisation revealed a sPAP of 76 mm Hg and mPAP of 52 mmHg. Pulmonary embolism was excluded by computed tomography pulmonary angiogram; chest x-rays demonstrated cardiomegaly and signs of pulmonary congestion; chest high resolution computed tomography (HCT) revealed bilateral axillary lymphadenopathy (2 cm enlarged), interstitial lung involvement with ground-glass high-density areas, pulmonary congestion, enlargement of the mediastinum, bilateral pleural effusions and significant pericardial effusion (Fig. 1); a marked hypergammaglobulinaemia (IgG: 4700 mg/dl) was also recorded. A reduction of forced vital capacity (FVC) (83%), forced expiratory volume in one second (79%) and diffuse lung capacity for carbon monoxide (DLCO) (62%), measured by single-breath standard technique, was also observed.

She was given calcium antagonists (amlodipine 20 mg/die), angiotensin receptor blockers (losartan 100 mg/die), enoxaparin sodium (fractionated heparin 4.000 UI/die), an endothelin receptor inhibitor (bosentan 250 mg/die) and phosphodiesterase inhibitor (sildenafil 60 mg/die), and transferred to the Internal Medicine Department in view of the elevated anti-nuclear antibodies (ANA) titer and hence the suspicion of an autoimmune disease.

On admittance, clinical examination showed her to be 163 cm tall, weight 75 kg, with a body temperature of 38.5°C, blood pressure 145-90 mm Hg and irregular pulse, at 120 bpm. She presented a grade III systolic heart murmur and sour breath sound. There was painless hepatomegaly (2 cm below right costal margin) and splenomegaly (1 cm below the left one). Laboratory tests confirmed polyclonal hypergammaglobulinaemia (45.99% of 93 g/L of total protein). Albumin concentration was 26 g/L. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were 78 mm and 22.2 mg/L respectively. Haemoglobin was 105 g/L and platelet count was $136x10^9$/L. 24-hr urine collection showed proteinuria (2.2 g/ 24 hr); ANA, anti-dsDNA, anti-SSA, anti-Sm and anti-RNP were positive, whereas antiphospholipid antibodies (Abs), lupus anticoagulant and rheumatoid factor were negative. High levels of N-terminal pro-brain-natriuretic peptide (NT-proBNP) and D-dimers were detected. Liver and renal function were normal (Table I). Hepatitis virus tests were also negative. She was classified as NYHA functional class III, and a diagnosis of SLE was established with a total SLEDAI score of 21 (0-150) (fever, arthritis, pleuritis, pericarditis, haematuria, proteinuria, complement consumption, increased anti-dsDNA Abs) and a physician's global assessment score of 3.

To improve her cardio-pulmonary functions, in addition to sildenafil and bosentan, epoprostenol (iloprost 0.05 mg/kg for 5 days) was added, while corticosteroid cyclophosphamide-based immunosuppressive therapy was proposed. This regimen was refused by the young patient after she was informed about drug-related infertility. Therefore, besides corticosteroids (prednisolone; initial dose 1 mg/kg/die), therapy with cyclosporine (150 mg/die) and mycophenolate mofetil (1g/die) was started. After five days of treatment, her condition improved; she was reclassified as NYHA functional class II and discharged on the ninth day with a bi-monthly follow-up programme. After 14 days, estimated sPAP had decreased to 62 mm Hg, and FVC/DLCO increased to 94% of their predictive value. NT-ProBNP, ESR and CRP decreased to 1225 pg/ml, 59 mm and 14 mg/L respectively. Finally, her total SLEDAI score was 16 (pleuritis, pericarditis, haematuria, proteinuria, complement consumption, increased anti-dsDNA Abs) and a physician's global assessment score of 2.

After a 6- month therapy, her estimated sPAP was 69 mmHg and a chest HCT scan showed a reduction of the ground-glass high-density pattern and of pericardial effusion (Fig. 1B). Because of the persistence of a moderately high sPAP, mycophenolate mofetil was increased to 2 g/die. After 6 more months (one-year treatment), sPAP (by cardiac catheterisation) had further decreased to 48 mmHg (*vs*. 76 at diagnosis) with mPAP of 32 mmHg (*vs*. 52 at diagnosis). A disappearance of the ground-glass high-density pattern and pericardial effusion was also observed (Fig 1, C).

Discussion

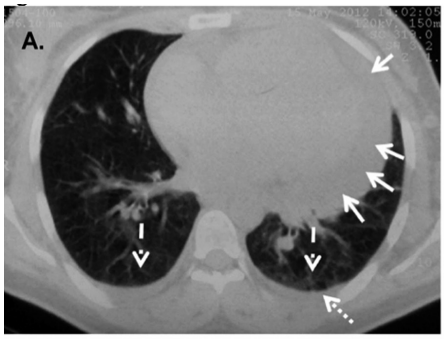
This case is noteworthy from both the clinical and therapeutic standpoints, in that severe pulmonary hypertension with minimal SLE disease was present at onset, while a prompt improvement of the PAH was observed following first line cyclosporine/ mycophenolate mofetil-based therapy.

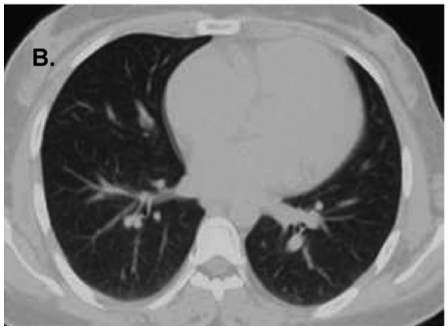
After suffering a two-month period of flu-like symptoms (arthralgias, vague muscle weakness) the patient was diagnosed with PAH, established according to the world-wide accepted criteria for PAH (3). Indeed, her mPAP, measured by right heart catheterisation, was markedly higher (52 mmHg) than the 25 mmHg established for a diagnosis of PAH (3) and 30 mmHg for a diagnosis of SLE-PAH (9).

The diagnosis of SLE was then made according to the American College of Rheumatology criteria (1997) on the basis of arthritis, the presence of high titers of ANA, anti-dsDNA, a non-nephrotic proteinuria (>0.5 g/24hr and <3.5 g/24hr) and pleural/pericardial effusions.

PAH: epidemiological and clinical considerations

According to the WHO classification, SLE-PAH can be included in group I PAH, namely connective tissue disease (CTD)-associated PAH (CTD-PAH) (3). In Western countries, the prevalence of CTD-PAH is comparable to that of idiopathic PAH (50.7 *vs*. 46.2, respectively) (10). The most frequent CTD associated with PAH are mixed connective tissue disease (MCTD) and systemic sclerosis (SSc), with a prevalence ranging between 5–14% (11) and 2.6–12.3% (12, 13) respectively.





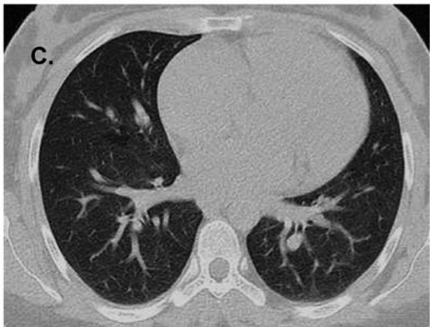


Fig. 1. A) Chest HCT scan showing the persistence of abundant pericardial effusions (continuous arrow) and a residual layer of pleural effusions (dotted arrows). Note the interstitial lung involvement shown by ground-glass high-density areas (slashed-dotted arrows). Chest HCT after 6 (**B**) and 12 (**C**) months treatment showed a progressive resolution of the "ground-glass high-density area" and of pleural and pericardial effusions.

More rarely, PAH occurs in primary Sjögren's syndrome (14), rheumatoid arthritis (15), anti-phospholipid syndrome (16), polymyositis/dermatomyositis (17) and SLE (9, 18).

Based on data obtained with cardiac catheterisation, the gold standard for the diagnosis of PAH, the SLE-PAH prevalence has been estimated to range between 0.005 to 14% (9, 18, 19). This wide range of reported percentages may be due to different cut-offs (mmHg) adopted for the diagnosis in the different studies – *i.e.* 25 mmHg (10, 20, 21) *vs.* 30 mmHg (8, 22) – and/or different patients ethnicity (8, 20, 22, 23). Indeed, the reported SLE-PAH prevalence in Western countries, Korea and China was 0.005 (4), 5 (22), and 23.3% (8), respectively, with a higher overall PAH prevalence in Asiatic than in Western countries. Finally, regarding the SLE-PAH prevalence in Africans (like our patient), no definitive data are available. Even so, a US study of 2967 patients with PAH (24), showed a higher prevalence of SLE-PAH (31.8%) than SSc-PAH (10.9%) in African Americans as opposed to Caucasians, (SSc-PAH, 83.9% *vs.* SLE-PAH, 37.4%), in line with the more aggressive course of SLE in Africans.

The peculiar clinical presentation in this patient parallels that in the patient reported by Kawamura *et al.* (25), who had SLE-PAH with minimal lupus activity at the onset. Both cases are at variance with the majority of large cohort studies, that indicate that PAH commonly occurs after a mean time of 3.2 years following the diagnosis of SLE (6). Another peculiar aspect of the present case is the presence of significant pleural effusions at onset, whereas in SLE-PAH less abundant pleural effusions are most commonly detected (26). On the other hand, our patient's sex, age and NYHA functional class are in line with the data reported in the literature, that describe a strong predilection of PAH for women (89%), a mean age of 34 years at presentation (21) and most commonly the NYHA functional class III at presentation (10).

Pathogenesis of SLE-PAH

The definition of specific PAH pathogenic pathways leading from a reversible to an irreversible vasoconstriction, along with the corresponding key points for therapeutic intervention, are illustrated in Fig. 2. Depending on the SLE clinical setting, different events have been considered to trigger endothelium damage leading to PAH. These include i) autoimmune vasculitides, ii) thromboembolic events, and iii) an increased vasoconstrictors/-dilators ratio.

The prominent role of immunological events in the endothelial damage is supported by the response to immunosuppressive therapy in the earliest phase of SLE-PAH; the presence of an abundant lymphocyte/macrophage infiltrate in the affected vessel walls (9); the higher percentage of anti-RNP Abs (49.2% of SLE-PAH patients *vs.* 20% of SLE patients without PAH) (8); the rheumatoid factor positivity (50% of SLE-PAH patients *vs.* 12.1% of SLE patients without PAH, p=0.02) (6); and/or possibly the presence of anti-endothelial cells Abs (AECA) (27). Thromboembolic events, too, contribute to small-vessel damage (28), as indicated by the common presence of anti-cardiolipin Abs (87.5% of SLE-PAH *vs.* 36.4% of SLE patients without PAH, p=0.008) (6) and anti-phospholipids Abs (80% of SLE-PAH *vs.* 36% of SLE patients without PAH; p<0.05) (29). It should be noted, however, that even anti-phospholipids Abs can trigger an inflammation, regardless of their ability to induce thromboembolic events. Indeed, recent findings have shown that anti-phospholipids Abs/anti-β_2GPI Abs can bind endothelial cells and monocytes by specifically targeting a multiproteins signaling complex composed of toll-like receptor (TLR)-4 and annexin 2 (or by TLR-2 and its co-receptor CD14) (30, 31), which ultimately activate a number of intracellular pathways, namely tumour necrosis factor receptor-associated factors (TRAFs) (32), interleukin-1 receptor-associated kinases (IRAKs) (32), and "nuclear factor kappa-light-chain-enhancer of activated B cells" (NF-κB) (30). These pathways are also involved in the pathogenesis of SLE and are currently being investigated for therapeutic purposes (33). Finally, endothelium damage is favoured by the increased vasoconstrictors/-dilators ratio, as demonstrated by the increased serum levels of endothelin-1 (34).

The above mentioned *noxae* will ultimately lead to irreversible changes in and around small vessels referred to as vascular remodeling (Fig. 2) (1, 35, 36). Some of these histological changes are very similar to those observed in SSc (1), indicating a final pathway leading to a non-responsive PAH either in SLE or SSc. Even so, the intimal fibrous thickening that is frequently de-

tected in SSc-PAH pulmonary biopsies (35) is rarely seen in SLE-PAH, and justifies the different prognosis (10), higher survival (47% in SSc-PAH and 75% in SLE-PAH at 3 years) (37) and response rate to therapy in SLE-PAH than in SSc-PAH (13).

Whether interstitial lung disease (ILD), in addition to endothelial lesions, might have contributed to PAH in our patient deserves some comment in the light of the ground-glass high-density pattern detected by chest HTC at diagnosis. Firstly, a similar radiological pattern may also be generated by interstitial inflammation or edema, associated to partial alveoli collapse. Secondly, these changes are more likely to occur in this acute phase of the disease. Finally, the disappearance of this radiological pattern after 12 months of therapy makes ILD unlikely, as this usually progresses to pulmonary fibrosis.

Predictor markers in SLE-PAH

Indirect evidence for ongoing endothelial damage in SLE-PAH includes the increased serum expression of vascular endothelial growth factor, endothelin-1, P-selectin and lipoprotein-associated phospholipase A2 (38). Their serum levels and the levels of auto-Abs associated to SLE-PAH, along with clinical manifestations, have been investigated as potential markers of PAH, considering that initial events leading to endothelium damage often occur in asymptomatic patients. As a result of these investigations, the positive predictor factors identified were anti-phospholipids Abs (29), anti-U1-RNP Abs (7), rheumatoid factor (6), high levels of endothelin-1 (34) and the presence of Raynaud phenomenon (7, 29). By contrast, disease duration, ESR and anti-dsDNA titer were not found to be significantly associated with PAH (6).

Thus, the only predictive factor present in our SLE patient was the presence of anti-U1-RNP Abs (240 UI/ml), often observed in MCTD, which is frequently associated to PAH. Indeed, the diagnosis of MCTD was considered but ruled out, because i) the anti-U1- RNP Abs titers were moderately high, ii) hands edema (sausage-like fingers) or acrosclerosis were lacking, iii) there was no clinical and laboratory evidence suggestive for myositis and/or SSc (anti-CENP and anti-topoisomerase Ab were also negative) (39, 40), and iv) there was renal involvement with pericardial and pleural effusions. These organ/tissues involvements have been rarely, if at all, observed in MCTD (41).

Table I. Laboratory data of the PHA-SLE patient at admission.

Analysis		Values (IS)	Normal ranges
Haematochemical	Erythrocytes	4.1 x 10^{12}/L	(4.00-5.20)
	Leukocytes	4.4 x 10^{9}/L	(3.54-9.06)
	Haemoglobin	105.0 g/L	(120-158)
	Hematocrit	0.3	(0.354-0.444)
	Platelet count	136 x 10^{9}/L	(165-415)
	Creatinine	78.6 µml/L	(44-80)
	Urea nitrogen	4.3 mml/L	(2.5-7.1)
	Glucose	5.6 mml/L	(3.6-5.3)
	AST	13 U/l	(15-37)
	ALT	8 U/l	(12-78)
	LDH	227.0 U/l	(84-246)
	Total bilirubin	9.4 µml/L	(5.1-22)
	Albumin	26 g/L	(40-50)
	ESR	78 mm/1h	(1-20)
	CRP	22.2 mg/L	(<10)
	NT-proBNP	1775 ng/L	(<125 up to 75 years)
	Troponin T	<0.015 µg/L	(0-0.01)
	D-dimers	3778ng/mL	(<300)
	PT	12.7 s	(12.7-15.4)
	PTT ratio	28.2 s	(26.3-39.4)
	Fibrinogen	3.8 g/L	(2.33-4.96)
	Gamma-globulins	49.4%	(11.0-20.0)
		46 g/L	(7-17)
	Total protein	93 g/L	(67-86)
	C3	0.9 g/L	(0.83-1.77)
	C4	0.2L	(0.16-0.47)
Urine	pH	6	
	Glucose	0 mg/dl	(0-10)
	Protein	200 mg/dl	(0-0)
	Haemoglobin	1 mg/dl	(0-10)
	Ketones	0 mg/dl	(negative)
	Bilirubin	0 mg/dl	(negative)
	Urobilinogen	0.2 Eu/dl	(negative)
	Leukocytes	75 Leu/ul	(0.2-1.0)
	Urinary sediment	White blood cells carpet. Cylinders with leukocyte inclusions	
	24-hour proteins	2.2 g/d	(<0.15)
Autoimmunity	ANA	1:5120 (homogeneous nuclear pattern)	≤1:40
	Anti-dsDNA antibody	239 IU/ml	(≤25)
	Anti-Sm antibody	>320 IU/ml	(<10)
	Anti-RNP antibody	>240 IU/ml	(<10)
	Anti-SSA	>640 IU/ml	(<10)
	Rheumatoid factor	10 kU/L	(<15)
	Lupus anticoagulant screening	Negative	Negative

Therapeutic perspective

The pathogenic mechanisms described indicate the most appropriate key points for therapeutic intervention (Fig. 2). Cyclophosphamide blocks auto-Abs production and inhibits lymphocytes proliferation; corticosteroids inhibit NF-κB, IRAKs and TRAFs-dependent intracellular signalling; vasodilators (bosentan, sildenafil, prostanoids, calcium antagonists) counteract vasoconstrictors, thus limiting vascular remodeling (36); anticoagulants prevent thrombotic events in the context of an anti-phospholipids syndrome.

In addition to the above-mentioned drugs, preclinical studies report interesting data on the action of mycophenolate mofetil and cyclosporine and their potential mechanisms to counteract PAH. In mice, mycophenolate mofetil

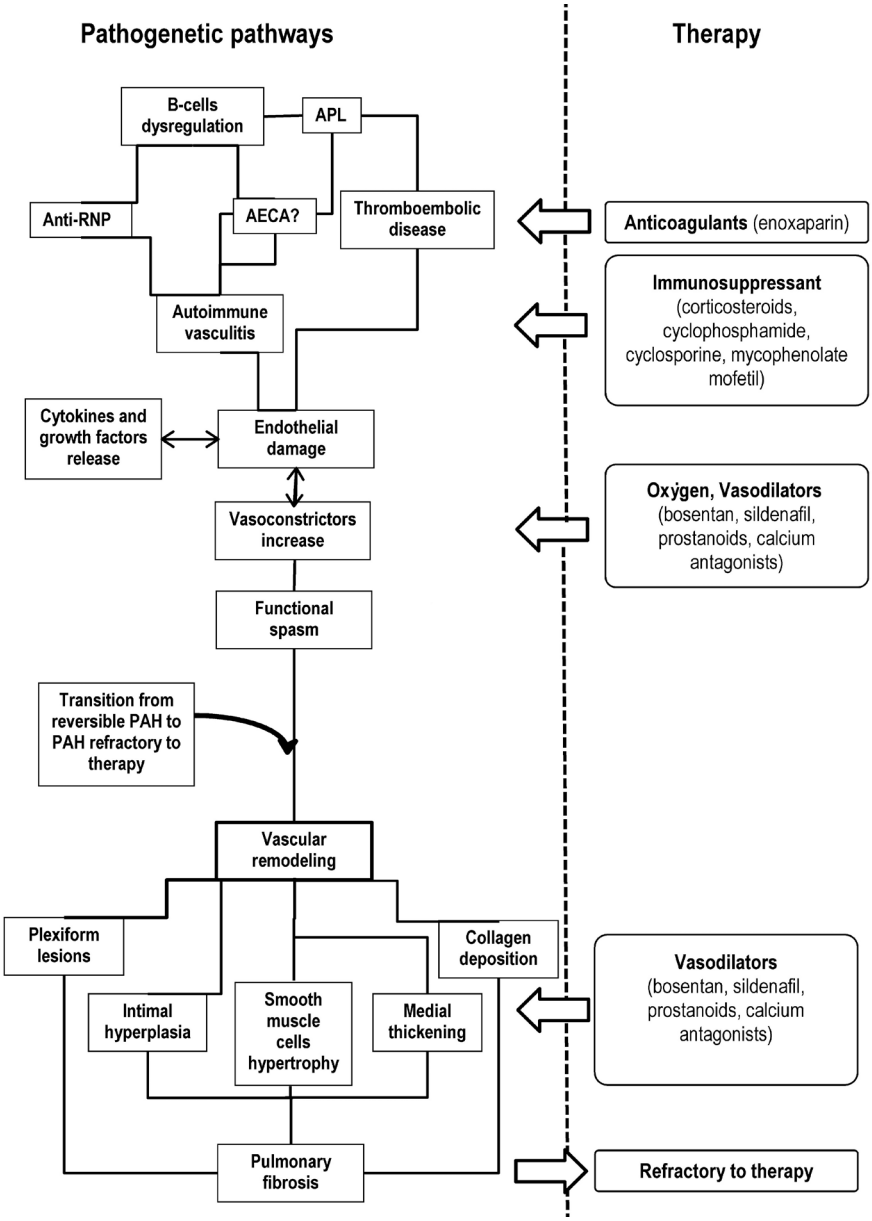


Fig. 2. Schematic representation of therapeutic targets according to the pathogenic pathways of systemic lupus erythematosus - associated pulmonary arterial hypertension (SLE-PAH).
APL: anti-phospholipids antibodies; **anti-RNP**: anti-ribonucleoproteins antibodies; **AECA**: anti-endothelial cell antibodies.

seems to be effective in preventing pulmonary arterial walls thickening, by exerting its anti-proliferative effect either on smooth muscle cells or on "proliferating cell nuclear antigen" (PCNA)-positive cells (42), by inhibiting infiltration of macrophages or decreasing the expression of P-selectin and interleukin-6 (IL-6) (43). Cyclosporine has been demonstrated in rats to inhibit endothelin-1-induced hypoxia-inducible factor-1 production (44, 45) and, in humans, the production of IL-2 by $CD3^+$ activated T lymphocytes (46).

Table II summarises clinical trials reported in the last 10 years on SLE-PAH treatment. In these studies, the response to therapy was evaluated as significant improvements in clinical (NYHA functional class, borg dyspnea index) and haemodynamic parameters (6-minute walking test, mPAP, sPAP, pulmonary vascular resistance and its corresponding index, and cardiac index). Several conclusions can be drawn from the results of these studies: i) SLE-patients account for 24.2% of the total CTD patients analysed (176/728) ii) clinical trials on the treatment of SLE-PAH are few and 4/9 are open non-comparative trials (50, 52-54); iii) more than half (5/9) of the studies focuses on the use of vasodilators only: 3/6 on bosentan (20, 49, 52), 1/6 on prostanoids (48) and 1/6 on sildenafil (51); iv) long-term survival and safety at 3, 5 and/or 6 years are reported only in three studies (50, 53, 54) and 5/9 studies describe the adverse events (20, 47, 48, 52, 53). Overall, the average follow-up timing is 176 weeks, ranging from a minimum of 12 weeks (48, 49, 51) to a maximum of 340 weeks (53), and 6MWT is the parameter most commonly adopted for treatment response evaluation.

Regarding the use of cyclophosphamide, the doses used in the 4 studies (3 open non controlled clinical trials and 1 double blind-controlled clinical trial) are 500 (47, 54) and 600 (50, 53) mg/m^2 intravenous boluses monthly for 3-6 months as first line therapy, associated with a satisfactory long-term survival (92% at 6 years) (54).

These data indicate that no single therapeutic regimen has yet proven to be more effective than others for the treatment of SLE-PHA due to the lack of controlled clinical trials and/or the low number of patients enrolled (36). Even so, vasodilators/steroids/immunosuppressant combination therapy is the most recommended in a high activity setting (55). Among immunosuppressants, monthly intravenous boluses of cyclophosphamide is the preferred choice of most qualified SLE-PAH treatment centers (53, 54, 56), whereas mycophenolate mofetil and azathioprine are suggested for the maintenance phase in certain clinical settings (56, 57).

The case reported here shows that mycophenolate mofetil and cyclosporine (along with steroids and vasodilators) could be an appropriate first-line therapeutic strategy as an alternative to cyclophosphamide, that warrants evaluation in future clinical trials.

Conclusions

The earlier SLE-PAH is diagnosed the better the response to therapy and obviously the prognosis. However, an early diagnosis is hindered by the common

Table II. Clinical trials for the treatment of pulmonary arterial hypertension (PAH) in patients (pts) with connective tissue disease (CTD), including systemic lupus erythematosus (SLE).

Clinical trial*	CTD pts no. (SLE no.)	Drug¶	Dose; interval; duration (mo.)**	Time at evaluation (weeks)	Response to treatment§			Pts survival (%); year	Adverse events (%)	Reference
					6MWT (meter improv.)	Changes in mPAP, sPAP, PVR, PVR-I, CI o BDI.	NYHA improv. (Pts.%)			
DBC	213 (16)	BOS	250-500 mg/day; NR; 3 mo.	16	44	↓ BDI: 0,6	12	NR	Headache (21), Syncope (9), Flushing (9), Liver toxicity (9)	(20)
DBC	34 (34)	ivCTX	500 mg m^{-2}; monthly; 6 mo.	24	NR	↓ sPAP: 15	NR	NR	Infection (87), Nausea and vomiting (81), Leukopenia (6)	(47)
DBC	90 (25)	TRE	8.4 ng/kg/min; NR 3 mo.	12	25	↓ PVR-I: 4; ↑CI + 0.2 ; ↓ BDI	NR	NR	Infusion site pain (NR), PGE-related adverse event (NR)	(48)
DBC	66 (N.R.)	BOS	NR; N.R.; 18 mo.	12 and 16	19.5	NR	NR	85.9; 1 73.4; 2	NR (NR)	(49)
R-ONC	28 (12)	ivCTX/CTS	600 mg m^{-2}; monthly; 3 mo.	48	NR	NR	NR	NR	NR (NR)	(50)
DBC	189 (64)	SIL	20 mg/day; NR 40 mg/day; NR 80 mg/day; NR	12	42 36 15	↓ mPAP and PVR	20-42	NR	None	(51)
P-ONC	53 (5)	BOS	125 mg/day; 1 mo. 250 mg/day; 11 mo.	16 48	NR	NR	24 27	92; 1	Peripheral edema (17), Increased liver enzymes (17), Diarrhoea (13), Increased dyspnea (13), Nausea (13), Pneumonia (8)	(52)
R-ONC	23 (13)	ivCTX/CTS or ivCTX/CTS +BOS or EPO or TRE	600 mg m^{-2}, monthly; 6 mo./ 0.5-1 mg/kg/ day; 1 mo.,then tapering	4-340 24-272	Improved Improved	↓ mPAP, PVR and CI ↓ mPAP, PVR and CI	Improved Improved	100; 1; 95.1; 2; 87.2; 3; 87.2; 5	CYC-related minor complications (neutropenia, thrombocytopenia, nausea, vomiting) (NR)	(53)
R-ONC	32 (7)	ivCTX/CTS	500 mg; monthly, first 3 mo. Then once every 3 mo. / 1mg/kg/die;1 mo.	48-72	NR	↓ mPAP and PVR ; CI stable	NR	92.3; 6	NR (NR)	(54)

*DBC: Double blind, controlled clinical trial; ONC: Open non controlled clinical trial; R: Retrospective; P: Prospective.
¶ BOS: Bosentan; CTS: Corticosteroids; EPO: Epoprostenol; ILO: Iloprost; ivCTX: Intravenous cyclophosphamide; SIL: Sildenafil; TRE: Treprostinil.
**mo.: month; NR: Not reported.
§ BDI: Borg dyspnea index score; CI: Cardiac index (l/min/m^2); mPAP: Mean pulmonary arterial pressure (mm Hg); 6MWT: Six minute walking test (meter); PVR: Pulmonary vascular resistance (mmHg/l/min) (dyne*s*cm5) ; PVR Index: Pulmonary vascular resistance (U x m^2); sPAP: Systolic pulmonary arterial pressure (mm Hg).

asymptomatic presentation with initial vascular injuries. The identification of specific predictive markers with a higher specificity and sensitivity than those currently available, is urgently needed. Such biomarkers, in association to echo doppler echocardiography, should also ideally allow a certain diagnosis to be made without the aid of right heart catheterisation, which is still the gold standard despite its invasive nature.

Besides the rarity of SLE-PAH, three additional reasons have hindered the development of homogeneous controlled clinical studies, namely the heterogeneous management of SLE-PAH patients in different geographic areas, the ethnic differences and the failure to make an appropriate diagnosis because of either reluctance to perform cardiac catheterisation or the continuous evolvement of the sPAP cut-off criteria to establish PAH. Therefore, clinical trials for therapeutic assessment are limited, and produce poorly comparable results. Even so, vasodilators-steroids-cyclophosphamide boluses combination therapy is the preferred choice in a high activity setting.

Although no solid conclusions can be drawn from the present case, the patient's rapid and persistent response to mycophenolate mofetil and cyclosporine (with steroids) suggests that these drugs, along with vasodilators, should be considered as alternatives to cyclophosphamide in future clinical trials aimed at assessing the most effective therapy for SLE-PAH at presentation.

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