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【 CASE REPORT 】

Successful Early Immunosuppressive Therapy for Pulmonary Arterial Hypertension Due to Takayasu arteritis: Two Case Reports and a Review of Similar Case Reports in the English Literature

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Abstract:
The efficacy of early immunosuppressive therapy without invasive therapy, such as endovascular or surgical revascularization, for pulmonary hypertension due to Takayasu arteritis (TAK-PH) remains to be elucidated. We herein report two cases of TAK-PH due to pulmonary arteritis successfully treated with early immunosuppressive therapy. A literature review of 42 cases of TAK-PH with pulmonary artery involvement showed that the cases treated with immunosuppressive therapy early after the onset (within 12 months) had a higher erythrocyte sedimentation rate and better outcome without invasive therapy than those treated later. TAK-PH may be successfully treated with immunosuppressive therapy without invasive therapy when diagnosed early with high disease activity.

Key words: Takayasu arthritis, pulmonary hypertension, immunosuppressive therapy, revascularization

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Introduction

Pulmonary hypertension (PH) is an intractable disease, but an early diagnosis and treatment can improve its prognosis (1). PH has various causes, including connective tissue disease (CTD), which accounts for about one quarter of cases (2). According to a report on CTD-related PH from Japan, mixed connective tissue disease (MCTD) was the most common underlying disease, followed by systemic sclerosis (SSc) and systemic lupus erythematosus (SLE), and the 3-year survival rate was 76% (3). Immunosuppressive therapy in addition to vasodilators has been reported to be effective in MCTD- and SLE-related PH, but not in SSc-related PH (1, 4). This may reflect the pathological differences seen in the pulmonary arteries; MCTD- and SLE-related PH show proliferation of endothelial and smooth muscle cell with inflammatory cell infiltration, while SSc-related PH shows obliterative lesions with intimal fibrosis (5, 6).

Takayasu arteritis (TAK) is one rare cause of PH and associated with a poor prognosis. Although most large studies of CTD-related PH have not included TAK-related PH (TAK-PH) (3, 7, 8), 1 report from China showed that TAK accounted for 12% of CTD-related PH (9). TAK is a chronic inflammatory disease that involves the aorta and its major branches (10), 0-17.8% of which are complicated by PH (11-13). Pulmonary arterial hypertension (PAH) is caused by mechanical stenosis of pulmonary arteries due to pulmonary arteritis. Left heart failure and thrombosis also cause PH in TAK (11, 13, 14). Pulmonary artery lesions are found in 5.7-86% (13, 15), and isolated ones are seen in 19.4% of TAK cases (11). PH has been described to occur in 42.2-78.1% of TAK cases with pulmonary arteritis (16). Treatments for TAK-PH include corticosteroids, immunosuppressants, biologics, and vasodilators, as well as invasive therapy, such as interventional and surgical revascularization (15, 17). Although TAK-PH has been reported to have a poor prognosis (11, 14, 18), these reports included many cases in which treatment was started long after the onset and/or who were treated with invasive therapy.

To our knowledge, no reports with a large number of

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TAK-PH cases have documented the impact of early immunosuppressive therapy on the outcome because of its rarity. Whether or not early immunosuppressive therapy can allow for the avoidance of invasive therapy remains to be determined. We herein report two cases of TAK complicated by PAH (TAK-PAH) and review the pertinent literature, on the basis of which we suggest that the early initiation of immunosuppressive therapy soon after the onset can be associated with a good outcome, even without interventional or surgical procedures.

Case Reports

Case 1

A 27-year-old woman was admitted because of a fever, back pain, and palpitation on exertion. Four months before admission, a fever and pain of the posterior neck, shoulders, and back appeared. Three months before admission, shortness of breath and palpitation on exertion developed. On admission, her blood pressure was 99/56 mmHg without laterality. She had dyspnea on exertion [World Health Organization (WHO) functional class II].

A physical examination revealed widespread systolic murmur in her chest. Blood tests showed elevation of the serum C-reactive protein (CRP) level (8.2 mg/dL) and erythrocyte sedimentation rate (ESR, 76 mm/h) as well as mild anemia [hemoglobin (Hb), 9.6 g/dL]. Chest X-ray showed cardiomegaly (cardio-thoracic ratio, 56%). Transthoracic echocardiography (TTE) showed a normal left ventricular ejection fraction (LVEF, 65%) and inferior vena cava (IVC) size (14 mm), but mild tricuspid regurgitation (TR) with an estimated right ventricular systolic pressure (eRVSP) of 76 mmHg, transtricuspid pressure gradient (TRPG) of 0.6 mmHg, flattening of the interventricular septum by an enlarged right ventricle and pericardial effusion were noted. Right heart catheterization (RHC) showed a pulmonary artery pressure (PAP) of 73/7 mmHg (mean 31), pulmonary arterial wedge pressure (PAWP) of 5 mmHg, and pulmonary vascular resistance (PVR) of 496 dyn·s·cm^{-5}. Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) showed enhanced wall thickening and stenosis of bilateral pulmonary arteries without thrombosis. Fluorodeoxyglucose (FDG)-positron emission tomography demonstrated an increased FDG uptake in the bilateral pulmonary arteries, ascending aorta, and right ventricular myocardium (Fig. 1a-e). Based on these findings TAK-PAH was diagnosed.

After 2 weeks of treatment with corticosteroid of 40 mg/day (0.8 mg/kg/day) and beraprost, her symptoms improved, and her serum CRP level became negative. TTE showed normalization of eRVSP. Four weeks later, each imaging abnormality showed improvement (Fig. 1f-j), and the 6-minute walking distance increased (from 405 to 490 m). Three months later, RHC showed normalization of the PAP [34/0 mmHg (mean 10)]. Beraprost was discontinued. After tapering of corticosteroids with methotrexate and tacrolimus, the ascending aortitis flared up temporarily. However, pulmonary arteritis with PH was not observed. Tocilizumab was added, and remission was achieved for more than five years.

Case 2

A 49-year-old woman was admitted because of a 3-month-history of a low-grade fever, dyspnea on exertion, and systemic edema. On admission, her blood pressure was 100/70 mmHg without laterality. Systolic murmur was noted at the second left sternal border. Blood tests showed elevation of the serum CRP level (4.4 mg/dL) and ESR (86 mm/h) as well as mild anemia (Hb 11.1 g/dL).

TTE showed an LVEF of 73%, eRVSP of 81 mmHg, flattening of interventricular septum by an enlarged right ventricle, and pericardial effusion (Fig. 2a-b). RHC showed bilateral pulmonary artery stenosis, a PAP of 77/5 mmHg (mean 34), PAWP of 3 mmHg, and PVR of 780 dyn·s·cm^{-5}. Contrast-enhanced CT and MRI showed enhanced wall thickening and stenosis of bilateral pulmonary arteries without thrombosis (Fig. 2c). Based on these findings, TAK-PAH was diagnosed.

After 2 weeks of treatment with corticosteroid of 30 mg/day (0.6 mg/kg/day), serum CRP became negative, and eRVSP decreased (37 mmHg). Although TAK without PH relapsed after tapering of corticosteroid, cyclosporine and mizoribine were added, with remission achieved for 15 years. Vasodilators were never administered during her course.

Literature Review

We searched MEDLINE/PubMed for reports on TAK-PH written in English from 1970 to 2020 using the following keywords: "Takayasu arteritis", "pulmonary hypertension" and "pulmonary artery hypertension". We included literature that contained sufficient clinical information, such as the period from the onset of symptoms to the diagnosis, presence/absence of pulmonary artery involvement (PAI), treatment, and prognosis. The prognosis was determined according to the description of each report and classified into improvement and unchanged/exacerbation of symptoms and/or examination results of PH, and death. We excluded cases without PAI. We ultimately identified 40 cases of TAK-PH with PAI (12, 14, 19-46) (Table 1). We divided the 42 total patients, including our cases, into 2 groups: the early treatment group (A; within 12 months from the onset) and late treatment group (B; longer than 12 months from the onset) (Table 2). We used the Mann-Whitney U-test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Continuous variables were expressed as the median [interquartile range (IQR): 25 th-75th percentiles]. Group A included 18 cases (42.9%). The age was similar between the groups. Group A had more women than group B. The period from the onset of symptoms was 5.5 (3.3-7.8) months in group A. The ESR was higher in group A than in group B [76.0 (40.0-87.5) vs. 13.0 (6.3-47.5) mm/h, p=0.003]. More patients in group A

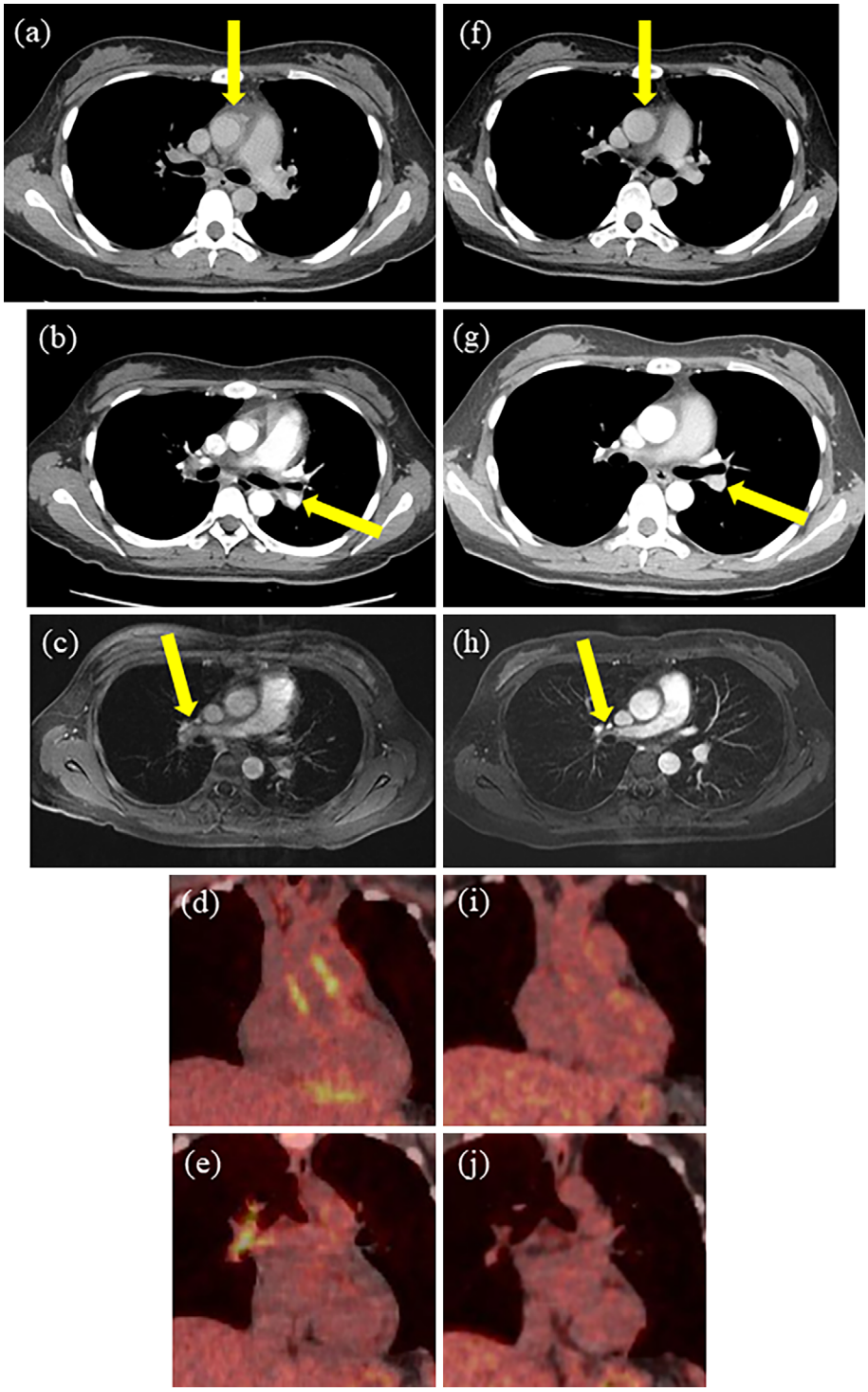

Figure 1. **Imaging findings of Case 1. (a, b) Contrast-enhanced computed tomography showed enhanced wall thickening and stenosis of the ascending aorta and left pulmonary artery without thrombosis (arrows). (c) Contrast-enhanced magnetic resonance imaging (MRI) showed enhanced wall thickening of the right pulmonary artery without thrombosis (arrow). (d-e) Fluorodeoxyglucose (FDG) -positron emission tomography demonstrated an increased FDG accumulation in the ascending aorta, right ventricular myocardium, and right pulmonary artery. (f-j) After four weeks of treatment, all imaging abnormalities were improved.**

received immunosuppressive therapy than in group B [17/18 (94.4%) vs. 15/24 cases (62.5%), p=0.026]. Furthermore, more patients in group A received only medical treatment with immunosuppressive therapy than in group B [12/18 (66.7%) vs. 7/24 cases (29.2%), p=0.028]. There were no significant differences in the use of PAH-specific therapy (endothelin receptor antagonist; phosphodiesterase type 5 inhibitor; prostacyclin analogue) or the observation period af-

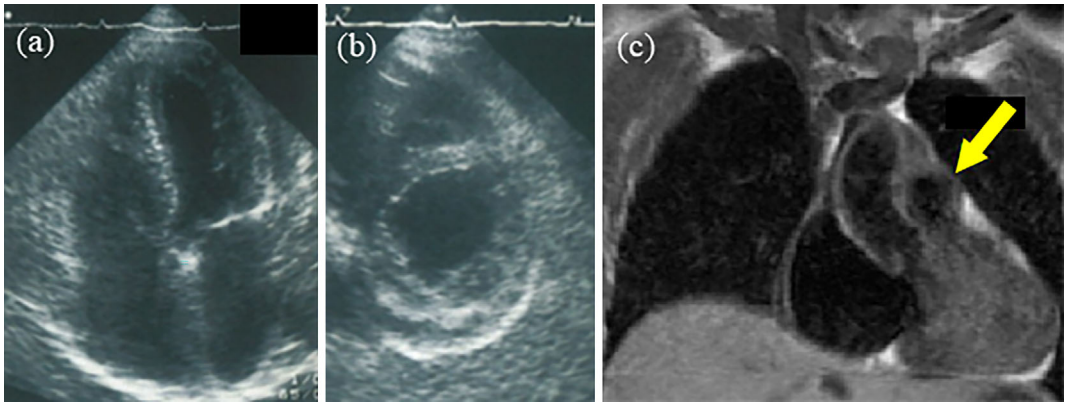

Figure 2. Imaging findings of Case 2. (a, b) Transthoracic echocardiography showed flattening of the interventricular septum by an enlarged right ventricle, along with pericardial effusion. (c) Contrast-enhanced MRI showed enhanced wall thickening and stenosis of the left pulmonary artery without thrombosis (arrow).

ter treatment between groups A and B [6.0 (4.0-24.0) vs. 12.0 (6.0-33.3) months, p=0.391]. Regarding outcome, there were no marked differences in the proportions of cases showing improvement or unchanged/exacerbation of symptoms and/or examination results of PH, or death between the groups. However, among patients who received only medical treatment with immunosuppressive therapy, more improved in group A than in group B [10/12 (83.3%) vs. 2/7 cases (28.6%), p=0.045]. These results showed that the early cases had a higher disease activity and improved to a greater extent with immunosuppressive therapy without invasive treatment than did the late cases.

Discussion

We presented two cases of TAK-PAH that were successfully treated with immunosuppressive therapy from early after the onset without invasive therapy, such as endovascular or surgical procedures. The literature review of 42 TAK-PH with PAI cases showed that ESR and the frequency of improvement with immunosuppressive therapy without invasive therapy were higher in those treated within 12 months from the onset than in those treated later. These results suggest that TAK-PH may be successfully treated with immunosuppressive therapy without endovascular or surgical revascularization when diagnosed in the early stage with high disease activity.

Most previous reports on TAK-PH included many cases that were treated long after the onset, and no reports on a large number of cases have documented the efficacy of early treatment. Yang et al. reviewed 566 TAK cases whose period from the initial symptoms to the diagnosis of TAK was 7.6±0.4 years. Thirty-one of them were complicated by PH with PAI. During 4.5±3.2 years of observation, 7 patients died of cor pulmonale, and 12 patients showed an exacerbated or unchanged course (16). Wang et al. investigated 36 cases of TAK-PH due to PAI. The period from the onset of PH symptoms to the diagnosis was 31.0±28.3 months. For 36.0 ±13.2 (12.0-65.0) months, 33 cases were followed, 3 of whom died of heart failure (9). Gong et al. examined TAK patients with PAI and reported that the period from the onset of symptoms to the diagnosis was significantly longer in patients with PH (33 cases) than in those without it [median 24 (6-72) months vs. 6 (3-24) months, p=0.020] (47). In the present cases and the literature review, we showed that when immunosuppressive therapy was started early from the onset, especially within 12 months, more cases improved with immunosuppressive therapy alone without invasive treatment.

Some case reports of TAK-PH have suggested that immunosuppressive therapy is effective in the early stage but not in the late stage, when invasive treatment is required. It was surmised that the cases in the present report and literature review that were diagnosed within 12 months from the onset responded well to immunosuppressive therapy because of their high disease activity and high ESR. In particular, some of these case reports suggested the efficacy of early immunosuppressive therapy for TAK-PH (14, 19, 23, 30, 32, 37). Pathological inflammatory changes in the pulmonary artery were found in a case of TAK-PH in the early phase (26). In contrast, the main principle of treatment for TAK in the chronic phase is revascularization of stenotic vessels (17). Qin et al. and Dong et al. reported that percutaneous transluminal angioplasty improved the pulmonary artery pressure of patients with TAK-PH four years after the onset of symptoms. (15, 25). Predominant fibrosis in pulmonary arteries was detected pathologically in the late phase of TAK (26, 40, 48). Medical treatment alone becomes ineffective when irreversible changes occur in the affected vessels over time. Therefore, an early diagnosis and treatment in the active phase are important for TAK-PH.

The indications and efficacy of PAH-specific therapy for TAK-PH remain to be elucidated. Although no such hard evidence has become available, Wang et al. reported 7 TAK-PH cases with severe PH (mean PAP >60 mmHg) caused by PAI that were improved by the combination of PAH-specific therapy (bosentan or sildenafil) with corticosteroids (11). As

Table 1. Cases of Takayasu Arteritis Complicated by Pulmonary Hypertension with Pulmonary Artery Involvement.

Case	Age	Gender	Period from onset (months)	ESR (mm/hour)	Treatments				Follow up time (months)	Outcome	Refs
					Immunosuppressive therapy (dose)	Specific anti-PH medication	Other medications	Invasive therapy			
1	19	F	11	44	PSL (NA)	-	-	-	5	Died	[21]
2	25	M	14	NA	-	-	-	-	NA	Unchanged	[22]
3	15	F	36	NA	PSL (NA), immunosuppressive agent (NA)	-	-	+	5	Improved	[39]
4	15	F	60	6	mPSL (1 g/12h for 3 days), PSL (60 mg/day)	-	-	-	1	Died	[20]
5	60	F	12	91	PSL (NA)	-	-	+	6	Improved	[40]
6	56	F	60	79	-	-	+	-	24	Improved	[35]
7	44	M	288	4	-	-	+	-	NA	Improved	[29]
8	31	F	5	NA	PSL (NA)	-	+	+	2	Unchanged	[26]
9	42	F	12	52	PSL (NA), CYC (NA)	-	+	-	36	Improved	[26]
10	31	F	60	46	PSL (NA), CYC (NA)	-	-	-	12	Unchanged	[26]
11	25	F	4	15	PSL (1 mg/kg/day)	-	-	-	1	Died	[23]
12	37	F	3	110	PSL (40 mg; 0.85 mg/kg/day)	+	+	-	4	Improved	[28]
13	57	M	48	11	-	-	-	+	NA	Improved	[41]
14	33	F	48	6	PSL (NA), MTX (NA), AZA (NA)	-	+	+	24	Improved	[27]
15	26	M	24	13	-	-	+	-	3	Improved	[24]
16	34	F	2	NA	PSL (NA)	-	+	+	15	Improved	[24]
17	49	F	156	4	-	-	+	-	12	Improved	[24]
18	67	F	9	36	-	-	-	+	3	Improved	[36]
19	73	F	6	66	PSL (625 mg/day for 3 days following 40 mg/day)	-	-	-	5	Improved	[37]
20	34	F	72	13	PSL (60 mg/day), MTX (20 mg/week)	+	+	-	2	Died	[46]
21	30	F	48	7	PSL (NA)	-	-	+	48	Exacerbated	[25]
22	30	M	24	15	PSL (NA)	-	-	+	39	Improved	[25]
23	34	F	24	1	PSL (NA)	-	-	+	12	Improved	[25]
24	40	F	96	8	PSL (NA)	-	-	+	36	Improved	[25]
25	51	F	48	48	-	+	+	-	6	Improved	[31]
26	19	F	72	86	mPSL (1000 mg), PSL (1 mg/kg), MTX (25 mg/week)	-	+	-	NA	Died	[14]
27	22	F	2	76	mPSL (NA), PSL (1 mg/kg), MTX (15 mg/week), IFX (5 mg/kg/8 weeks)	-	-	-	24	Improved	[14]
28	9	F	6	20	mPSL (NA), MTX (NA)	-	+	-	3	Improved	[19]
29	54	F	36	100	PSL (30 mg/day)	-	-	-	12	Improved	[34]
30	52	F	6	77	PSL (NA), MTX (NA)	+	-	-	NA	Improved	[32]
31	51	F	72	34	-	-	+	+	30	Improved	[43]
32	53	F	36	50	PSL (NA), AZA (NA)	-	-	+	NA	Improved	[33]
33	25	F	3	36	PSL (NA), AZA (NA), MTX (15 mg/week)	-	+	+	24	Improved	[42]
34	18	F	8	89	PSL (30 mg/day)	-	+	+	42	Improved	[38]
35	22	F	7	NA	PSL (NA), CYC (NA)	+	-	-	6	Improved	[12]
36	39	M	96	NA	PSL (NA), CYC (NA), AZA (NA), ADA (NA), TCZ (NA)	-	-	-	12	Improved	[12]
37	52	F	96	NA	PSL (NA), CYC (NA)	+	+	-	96	Exacerbated	[12]
38	50	F	2	89	mPSL (NA), PSL (40 mg/day) CYC (IVCY 500 mg/4 weeks), TCZ (162 mg/2 weeks), IFX (6 mg/kg/4 weeks), MTX (8 mg/week)	-	-	-	10	Improved	[30]
39	50	F	24	NA	-	-	+	+	6	Improved	[45]
40	48	F	252	NA	mPSL (500 mg), PSL (NA)	+	-	+	96	Improved	[44]
41	49	F	4	86	PSL (30 mg/day; 0.6 mg/kg/day), CyA (100 mg/day), MZR (150 mg/day)	-	-	-	228	Improved	
42	27	F	5	76	PSL (40 mg/day; 0.8 mg/kg/day), MTX (6 mg/week), TAC (3 mg/day), TCZ (162 mg/week)	+	-	-	60	Improved	

Cases 41 and 42 are our cases.

F: female, M: male, ESR: erythrocyte sedimentation rate, PH: pulmonary hypertension, Refs: references, PSL: prednisolone, mPSL: methylprednisolone, MTX: methotrexate, IFX: infliximab, CYC: cyclophosphamide, IVCY: intravenous cyclophosphamide, TCZ: tocilizumab, AZA: azathioprine, CyA: cyclosporin, TAC: tacrolimus, MZR: mizoribine, ADA: adalimumab, NA: not available

Table 2. Comparison between Early Treatment Group (within 12 Months from the Onset: Group A) and Late Treatment Group (Longer than 12 Months from the Onset: Group B).

	Group A	Group B	p
Patients, n (%)	18 (42.9)	24 (57.1)	
Age, years old	32.5 (22.8-49.8)	39.5 (30.0-51.0)	0.476
Female, n (%)	18 (100)	18 (75.0)	0.029
The period from the onset of symptoms to the diagnosis, month	5.5 (3.3-7.8)	54.0 (36.0-78.0)	<0.001
Erythrocyte sedimentation rate, mm/hour	76.0 (40.0-87.5)	13.0 (6.3-47.5)	0.003
Medication			
Medical treatment			
Immunosuppressive therapy, n (%)	17 (94.4)	15 (62.5)	0.026
Glucocorticoid, n (%)	17 (94.4)	15 (62.5)	0.026
Immunosuppressants, n (%)	9 (50.0)	8 (33.3)	0.348
PAH specific therapy*, n (%)	4 (22.2)	4 (16.7)	0.706
Other medical treatment**, n (%)	7 (38.9)	11 (45.8)	0.757
Only medical treatment with immunosuppressive therapy, n (%)	12 (66.7)	7 (29.2)	0.028
Invasive treatment			
Endovascular treatment, n (%)	2 (11.1)	8 (33.3)	0.147
Surgery, n (%)	4 (22.2)	4 (16.7)	0.706
Only endovascular therapy or surgery, n (%)	1 (5.6)	3 (12.5)	0.623
Endovascular therapy or surgery with immunosuppressive therapy, n (%)	5 (27.8)	8 (33.3)	0.748
No treatment, n (%)	0 (0)	1 (4.2)	1
Prognosis			
Follow up time, month	6.0 (4.0-24.0)	12.0 (6.0-33.0)	0.391
Improvement, n (%)	15 (83.3)	17 (70.8)	0.473
Improvement by only medical treatment with immunosuppressive therapy, n (%)	10/12 (83.3)	2/7 (28.6)	0.045
No change/exacerbation, n (%)	1 (5.6)	4 (16.7)	0.371
Death, n (%)	2 (11.1)	3 (12.5)	1

*Bosentan, tadalafil, sildenafil, beraprost, epoprostenol

**Diuretics, warfarin, anti-platelet agents, digoxin, nitric oxide, molsidomine, renin-angiotensin-aldosterone system inhibitors, calcium channel blocker, beta blocker

PAH: pulmonary arterial hypertension

the concomitant use of anti-PH agents with immunosuppressant is recommended for severe cases of SLE- and MCTD-related PH (4, 49), it can also be applied for TAK-PH. Further studies are needed to address the therapeutic benefit of anti-PH agents in patients with TAK-PH.

It should be noted that the first symptoms of PH due to TAK may be non-specific, thereby delaying the diagnosis. In TAK cases, dyspnea, hemoptysis, cough, a fever, chest pain, and other issues may be symptoms of PH due to pulmonary arteritis (11, 16, 27). In these cases, the diagnosis can be delayed due to the non-specificity of the symptoms (14). Furthermore, some TAK-PH cases are difficult to differentiate from chronic thromboembolic pulmonary hypertension (CTEPH) (26, 31). One case report described cases that were misdiagnosed with CTEPH and administered only anticoagulants (27). Although an elevated ESR is useful in differentiating between entities, it should be also noted that TAK does not necessarily cause an elevated ESR (23). In addition, some cases of TAK are diagnosed when ischemic symptoms of the involved organs appear after burn-out of the inflammation (50). Therefore, in young women with unexplained respiratory symptoms, pulmonary artery obstruction, unexplained PH, and right heart failure, TAK should be included in the differential diagnosis (12, 16, 31).

Since this literature review was based on case reports, there were some limitations. Some cases diagnosed with PH by only echocardiography were included. As some information on other prognostic factors, including the WHO functional class (3, 51), was not available in most reports, a multivariate analysis with these factors could not be performed. Further studies including a larger number of TAK-PH cases are needed to clarify the optimal treatment in the active/inactive phases.

In conclusion, TAK-PH may be successfully treated with immunosuppressive therapy without endovascular or surgical procedures when diagnosed in the early stage with high disease activity. To achieve an early diagnosis with a good outcome, TAK should be included in the differential diagnosis of the causes of PH.

The patients presented in this report gave their written informed consent prior to their inclusion.

The authors state that they have no Conflict of Interest (COI).

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