Original Article

Clinical use of macitentan in the treatment of connective tissue disease-associated pulmonary arterial hypertension

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Background: Connective tissue disease (CTD) is the second most common cause of the pulmonary arterial hypertension (PAH). Currently, clinical data concerning CTD-PAH is scarce. Our study aimed to assess the efficacy and safety of macitentan in the treatment of CTD-PAH.

Methods: In this retrospective study, patients diagnosed with CTD-PAH at The First Affiliated Hospital of Soochow University from April 2020 to November 2021 were included. Of the patients, 9 were switched to macitentan monotherapy whereas 23 received initial combination therapy. The mean follow-up time was 24 weeks. Six-minute walking distance (6MWD), World Health Organization functional class (WHO-FC), serum N-terminal pro-brain natriuretic peptide (NT-proBNP), and echocardiography parameters before and after medication were assessed. Adverse reactions were also recorded and compared.

Results: After 24 weeks of treatment, 6MWD, NT-proBNP, systolic pulmonary artery pressure (sPAP) estimated by ultrasound, tricuspid regurgitation pressure gradient (TRPG) and tricuspid annular plane systolic excursion (TAPSE) in the macitentan monotherapy group revealed significant differences (Z=–2.67, Z=–2.67, t=6.20, t=5.60, t=–3.04, P<0.05). There were no statistically significant differences in right ventricular diameter (RVD), right atrial diameter (RAD), ascending aortic root inner diameter (AAO) and left ventricular end-diastolic diameter (LVEDd) (P>0.05). After 24 weeks of medication, the number of patients with WHO-FC grade III/IV symptoms decreased from 6 to 3, 1 to 0 respectively (P<0.05), and that of patients with WHO-FC grade I/II symptoms increased from 0 to 2, 2 to 4 respectively(P<0.05). After 24 weeks of treatment, 6MWD, NT-proBNP, LVEDd, sPAP and TRPG in the macitentan combined with sildenafil treatment group revealed statistically significant differences (Z=–4.11, Z=–3.74, Z=–3.83, t=6.88, t=6.54, P<0.001). Significant differences in RVD, RAD, and TAPSE were found (t=3.46, t=3.69, t=–3.12, P<0.05). There were no statistically significant variances in AAO between the groups (P>0.05). The number of patients with WHO-FC grade III/IV symptoms decreased from 16 to 8, 5 to 0 respectively (P<0.05), and that of patients with WHO-FC grade I/II symptoms increased from 0 to 1, 2 to 14 respectively (P<0.001). There were no statistically significant differences before and after treatment in 6MWD, NT-proBNP, RVD, RAD, AAO, LVEDd, sPAP, TRPG and TAPSE between the two groups (P>0.05). There were no statistically significant differences in alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Scr) and hemoglobin (Hb) between 0 and 24 weeks (P>0.05).

Conclusions: Exercise tolerance and cardiac function in patients with CTD-PAH were significantly

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improved after treatment with macitentan, which was well tolerated. Therefore, macitentan may be an effective and safe targeted drug for CTD-PAH.

Keywords: Connective tissue disease (CTD); pulmonary arterial hypertension (PAH); macitentan; echocardiography

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Introduction

Pulmonary arterial hypertension (PAH), classified as group 1 pulmonary hypertension according to the 2022 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines for the diagnosis and treatment of pulmonary hypertension (PH) (1), is a rapid progressive disorder, mainly characterized by increased pulmonary vascular resistance (2) that can lead to the gradual deterioration of the right heart function and an extremely high mortality. Connective tissue disease (CTD) is the second most common cause of PAH, followed by idiopathic/hereditary PAH (3). Early diagnosis is highly difficult due to its insidious onset. Moreover, patients with CTD-PAH often have a poor prognosis. Systemic lupus erythematosus (SLE)-associated PAH (SLE-PAH) is the most common subtype in China, which differs from Western countries, where systemic sclerosis (SSc) has the highest prevalence and worse prognosis due to its unique pathogenesis. The drugs currently approved for treatment against PAH target three main pathways (2). Macitentan is a second-generation endothelin receptor antagonist (ERA) developed after bosentan and exhibits high receptor affinity, strong tissue penetration, and low potential for drug-drug interaction with other PAH-targeted drugs (4). Macitentan possesses considerable advantages in safety and clinical efficacy as compared to first-generation ERAs. Despite significant advancements in drug therapy for PAH, the long-term outlook for these patients remains suboptimal. Presently, there was limited clinical data on the effectiveness and safety of macitentan in Chinese with CTD-PAH. As a result, this study retrospectively analyzed 32 CTD-PAH patients who were treated with macitentan, with the aim to investigate its efficacy and safety. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-151/rc).

Highlight box

Key findings

- Exercise tolerance and cardiac function in patients with connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) were significantly improved after treatment with macitentan, which was well tolerated. Therefore, macitentan may be an effective and safe targeted drug for CTD-PAH.

What is known and what is new?

- Macitentan was found to improve exercise tolerance and cardiac function in patients with CTD-PAH.
- This study conducted a retrospective analysis of 32 patients with CTD-PAH, preliminarily concluded macitentan may be an effective and safe targeted drug for CTD-PAH in short time.

What is the implication, and what should change now?

- Our study provides a clinical data on the effectiveness and safety in Chinese with CTD-PAH.

Methods

Selection of patients

This study was conducted in the Department of Rheumatology and Immunology at The First Affiliated Hospital of Soochow University from April 2020 to November 2021 (from China), the medical records of 42 CTD-PAH patients were reviewed, among them, 6 cases had incomplete data, and 4 cases were not followed up regularly in our hospital, finally 32 patients diagnosed with CTD-PAH were enrolled in inpatient and outpatient settings. Among the 32 patients, 9 who had an insufficient response to phosphodiesterase type 5 (PDE5i) inhibitors (these patients were diagnosed with CTD-PAH and experienced no significant improvement in risk stratification after standard treatment with PDE5i for 3–6 months) received macitentan monotherapy (specific medication regimen: macitentan once a day, 10 mg each time), and 23 patients received combination with macitentan and PDE5i (specific medication regimen: macitentan once a day, 10 mg

each time; sildenafil 3 times a day, 25 mg each time, both are oral preparations). The diagnostic standard for PAH was based on the observation of pulmonary artery segment widening and tricuspid regurgitation on cardiac color Doppler ultrasound. The systolic pulmonary artery pressure (sPAP) was estimated using a simplified Bernoulli equation (sPAP = square of 4V plus right atrial pressure, V represents tricuspid regurgitation peak velocity), and sPAP ≥5.33 kPa (40 mmHg) (1 mmHg =0.133 kPa) considered PAH. The exclusion criteria were other possible causes of PAH, including other forms of arterial pulmonary hypertension such as idiopathic PAH and congenital heart disease, PAH caused by left heart disease, PAH caused by lung diseases such as severe obstructive pulmonary disease and restrictive pulmonary disease, pulmonary embolism or chronic thromboembolic PAH, and other causes. The follow-up period for this study was 24 weeks.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethical committee of The First Affiliated Hospital of Soochow University [No. (2024) Ethical Research Approval No. 130], and the informed consent of the patients was collected.

Clinical characteristics of patients

The clinical characteristics of inpatients and outpatients were reviewed, and the patients were followed up through telephone consultations. The following data were collected: the demographic characteristics and types of CTD at baseline; functional assessment indicators at baseline and 24 weeks after treatment, including World Health Organization functional class (WHO-FC) proposed by the World Health Organization; 6-minute walking distance (6MWD) conducted under the guidance and supervision of specialist doctors; serological markers including serum N-terminal pro-brain natriuretic peptide (NT-proBNP) tested by the laboratory using immunoassay; echocardiographic parameters, including the right ventricular diameter (RVD), right atrial diameter (RAD), ascending aortic root inner diameter (AAO), left ventricular end-diastolic diameter (LVEDd), sPAP estimated by ultrasound, tricuspid regurgitation pressure gradient (TRPG), and tricuspid annular plane systolic excursion (TAPSE); serum liver and kidney function indexes; and hemoglobin values tested by the laboratory before and after treatment. Additionally, the therapeutic dose of macitentan, presence or absence of combination therapy, changes in treatment regimens, and adverse events were recorded.

Statistical analysis

Continuous variables with a normal distribution were presented as mean ± standard deviation, while continuous variables with a skew distribution were presented as median (interquartile range). Group comparisons were conducted using the *t*-test and the Mann-Whitney U test. Count data were expressed as cases (%), and the χ^2 test or Fisher's exact test was used according to the actual situation. Paired design measurement data were compared using the paired *t*-test or Wilcoxon rank sum test. A two-sided P value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS 25.0 software.

Results

Patients and baseline characteristics

The medical records of 42 CTD-PAH patients were reviewed, among them, 6 cases had incomplete data, and 4 cases were not followed up regularly in our hospital. In the end, a total of 32 patients with CTD-PAH were included in this study. The macitentan monotherapy group comprised 9 patients, with 6 females (66.7%) and an average age of (46.44±17.05) years. Additionally, there were 5 patients with SLE, 1 patient with Sjogren's syndrome, 2 cases of mixed CTD, and 1 case of SSc in this group. In the macitentan combined with sildenafil treatment group, there were 23 individuals, with 20 (87.0%) being females and an average age of (41.65±12.57) years. This group included 11 cases of SLE, 3 cases of Sjogren's syndrome, 4 cases of mixed CTD, 3 cases of SSc, and 2 cases of rheumatoid arthritis. At baseline, there were no statistically significant differences in gender, age, etiology, WHO-FC composition, 6MWD, NT-proBNP, RVD, RAD, AAO, LVEDd, sPAP, TRPG, TAPSE, ALT, AST, Scr, Hb, etc. between the two groups (P>0.05). The results are shown in *Table 1*. The follow-up time was 24-week.

Efficacy

Analysis of the efficacy of macitentan monotherapy group

Statistical analysis comparing 6MWD, NT-proBNP, sPAP,

Table 1 Baseline data, functional assessment and echocardiographic indicators of patients grouped based on medication regimen

Parameters	Macitentan (n=9)	Macitentan+ Sildenafil (n=23)	Statistic	P
Age (years)	46.44±17.05	41.65±12.57	t=0.88	0.39
Female	6 (66.7)	20 (87.0)	χ^2=1.75	0.31
Etiology			χ^2=0.98	0.97
SLE	5 (55.6)	11 (47.9)		
SS	1 (11.1)	3 (13.0)		
RA	0 (0)	2 (8.7)		
MCTD	2 (22.2)	4 (17.4)		
SSc	1 (11.1)	3 (13.0)		
WHO-FC			Z=−1.078	0.28
I	0	0		
II	2	2		
III	6	16		
IV	1	5		
6MWD (m)	280.00 (185.00, 362.50)	290.00 (180.00, 328.00)	Z=−0.08	0.93
NT-proBNP (mmHg)	1,605.00 (719.45, 2,275.05)	1,127.00 (269.30, 2,736.00)	Z=−0.36	0.72
RVD (mm)	43.78±8.35	42.30±4.42	t=0.50	0.63
RAD (mm)	44.78±8.79	45.09±5.56	t=−0.10	0.92
AAO (mm)	33.00±4.06	31.43±4.42	t=0.92	0.37
LVEDd (mm)	45.00 (35.00, 61.00)	42.00 (39.00, 44.00)	Z=−0.40	0.69
sPAP (mmHg)	76.11±20.67	85.04±19.82	t=−1.13	0.27
TRPG (mmHg)	72.11±21.35	80.30±20.98	t=−0.99	0.33
TAPSE (mm)	16.28±2.59	17.72±3.36	t=−1.15	0.26
ALT (U/L)	23.60 (10.10, 32.25)	16.60 (10.50, 26.10)	Z=−0.48	0.63
AST (U/L)	19.00 (17.45, 29.80)	19.70 (14.90, 29.70)	Z=−0.89	0.43
Scr (μmol/L)	59.80 (54.20, 64.35)	59.70 (51.20, 75.60)	Z=−0.19	0.85
Hb (g/L)	130.00 (115.50, 144.00)	123.00 (113.00, 138.00)	Z=−0.82	0.41

Data are presented as n (%), mean ± standard deviation or median (interquartile range). SLE, systemic lupus erythematosus; SS, Sjogren's syndrome; RA, rheumatoid arthritis; MCTD, mixed connective tissue disease; SSc, systemic sclerosis; WHO-FC, World Health Organization functional class; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; RVD, right ventricular diameter; RAD, right atrial diameter; AAO, ascending aortic root inner diameter; LVEDd, left ventricular end-diastolic diameter; sPAP, systolic pulmonary artery pressure; TRPG, tricuspid regurgitation pressure gradient; TAPSE, tricuspid annular plane systolic excursion; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine; Hb, hemoglobin.

TRPG and TAPSE in the macitentan monotherapy group at 0 and 24 weeks revealed significant differences (Z=−2.67, Z=-2.67, t=6.20, t=5.60, t=−3.04, P<0.05). However, no statistically significant differences were observed in RVD, RAD, AAO and LVEDd between the two groups (P>0.05). At the beginning of the study, 2, 6 and 1 patients had class II, III, and IV symptoms, respectively. After 24 weeks of medication, the number of patients with WHO-FC grade III/IV symptoms decreased from 6 to 3, 1 to 0 respectively (P<0.05), and that of patients with WHO-FC grade I/

Table 2 Functional assessment and echocardiographic indicators at week 0 and 24 in the macitentan monotherapy group

Parameters	Baseline	After treatment	Statistic	P
WHO-FC			Z=−2.33	0.02
I	0	2		
II	2	4		
III	6	3		
IV	1	0		
6MWD (m)	280.00 (185.00, 362.50)	450.00 (327.50, 482.50)	Z=−2.67	0.008
NT-proBNP (mmHg)	1,605.00 (719.45, 2,275.05)	328.60 (55.19, 658.60)	Z=−2.67	0.008
RVD (mm)	43.78±8.35	36.89±6.83	t=1.98	0.08
RAD (mm)	44.78±8.79	37.89±6.23	t=2.03	0.08
AAO (mm)	33.00±4.06	33.33±4.18	t=−0.76	0.47
LVEDd (mm)	45.00 (35.00, 61.00)	48.00 (41.50, 51.00)	Z=−1.01	0.31
sPAP (mmHg)	76.11±20.67	47.22±28.06	t=6.20	<0.001
TRPG (mmHg)	72.11±21.35	44.11±28.62	t=5.60	0.001
TAPSE (mm)	16.28±2.59	18.61±2.29	t=−3.04	0.02
ALT (U/L)	23.60 (10.10, 32.25)	14.50 (8.10, 28.00)	Z=−0.89	0.37
AST (U/L)	19.00 (17.45, 29.80)	20.70 (17.85, 25.60)	Z=0.001	>0.99
Scr (μmol/L)	59.80 (54.20, 64.35)	63.00 (46.75, 79.40)	Z=−1.01	0.31
Hb (g/L)	130.00 (115.50, 144.00)	110.00 (93.50, 142.00)	Z=−1.24	0.21

Data are presented as numbers, mean ± standard deviation or median (interquartile range). WHO-FC, World Health Organization functional class; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; RVD, right ventricular diameter; RAD, right atrial diameter; AAO, ascending aortic root inner diameter; LVEDd, left ventricular end-diastolic diameter; sPAP, systolic pulmonary artery pressure; TRPG, tricuspid regurgitation pressure gradient; TAPSE, tricuspid annular plane systolic excursion; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine; Hb, hemoglobin.

II symptoms increased from 0 to 2, 2 to 4 respectively (P<0.05). The results are shown in *Table 2*.

Analysis of the efficacy of macitentan combination group

Statistically significant differences were observed in 6MWD, NT-proBNP, LVEDd, sPAP and TRPG among the macitentan combined with sildenafil treatment group between 0 and 24 weeks (Z=−4.11, Z=−3.74, Z=−3.83, t=6.88, t=6.54, P<0.001). Additionally, significant differences in RVD, RAD, and TAPSE were found between the two groups (t=3.46, t=3.69, t=−3.12, P<0.05). However, there were no statistically significant variances in AAO between the groups (P>0.05).

At the beginning of the study, 2, 16 and 5 patients had class II, III, and IV symptoms, respectively. After 24 weeks of medication, the number of patients with WHO-FC grade III/IV symptoms decreased from 16 to 8, 5 to 0 respectively (P<0.05), and that of patients with WHO-FC grade I/II symptoms increased from 0 to 1, 2 to 14 respectively (P<0.001). The results are shown in *Table 3*.

Comparison the efficacy between macitentan monotherapy and combination group

There were no statistically significant differences before and after treatment in 6MWD, NT-proBNP, RVD, RAD, AAO, LVEDd, sPAP, TRPG and TAPSE between the two groups (P>0.05). The results are shown in *Table 4*.

Safety

There were no statistically significant differences in ALT,

Table 3 Functional assessment and echocardiographic indicators at week 0 and 24 in the macitentan combination group

Parameters	Baseline	After treatment	Statistic	P
WHO-FC			*Z*=−3.76	<0.001
I	0	1		
II	2	14		
III	16	8		
IV	5	0		
6MWD (m)	290.00 (180.00, 328.00)	400.00 (300.00, 465.00)	*Z*=−4.11	<0.001
NT-proBNP (mmHg)	1,127.00 (269.30, 2,736.00)	205.00 (65.27, 524.80)	*Z*=−3.74	<0.001
RVD (mm)	42.30±4.42	38.22±6.05	*t*=3.46	0.002
RAD (mm)	45.09±5.56	40.30±5.80	*t*=3.69	0.001
AAO (mm)	31.43±4.42	32.26±3.06	*t*=−1.12	0.28
LVEDd (mm)	42.00 (39.00, 44.00)	46.00 (42.00, 48.00)	*Z*=−3.83	<0.001
sPAP (mmHg)	85.04±19.82	61.17±23.73	*t*=6.88	<0.001
TRPG (mmHg)	80.30±20.98	57.17±23.53	*t*=6.54	<0.001
TAPSE (mm)	17.72±3.36	19.54±2.76	*t*=−3.12	0.005
ALT (U/L)	16.60 (10.50, 26.10)	17.40 (9.60, 22.00)	*Z*=−1.00	0.32
AST (U/L)	19.70 (14.90, 29.70)	19.20 (17.30, 22.60)	*Z*=−0.82	0.41
Scr (μmol/L)	59.70 (51.20, 75.60)	62.40 (54.00, 69.80)	*Z*=−0.23	0.82
Hb (g/L)	123.00 (113.00, 138.00)	119.00 (112.00, 128.00)	*Z*=−0.62	0.54

Data are presented as numbers, mean ± standard deviation or median (interquartile range). WHO-FC, World Health Organization functional class; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; RVD, right ventricular diameter; RAD, right atrial diameter; AAO, ascending aortic root inner diameter; LVEDd, left ventricular end-diastolic diameter; sPAP, systolic pulmonary artery pressure; TRPG, tricuspid regurgitation pressure gradient; TAPSE, tricuspid annular plane systolic excursion; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine; Hb, hemoglobin.

Table 4 Comparison of efficacy between the monotherapy group of macitentan and the combination group of macitentan and sildenafil

Parameters	Macitentan (n=9)	Macitentan + sildenafil (n=23)	Statistic	P
Δ6MWD (m)	−120.00 (−210.00, −95.00)	−70.00 (−165.00, −20.00)	*Z*=−1.70	0.09
ΔNT-proBNP (mmHg)	867.10 (181.55, 1,995.54)	729.00 (91.53, 1,676.00)	*Z*=−0.36	0.72
ΔRVD (mm)	6.89±10.43	4.09±5.67	*t*=0.76	0.46
ΔRAD (mm)	6.89±10.17	4.78±6.21	*t*=0.58	0.57
ΔAAO (mm)	−0.33±1.32	−0.83±3.55	*t*=0.57	0.57
ΔLVEDd (mm)	−3.00 (−8.00, 2.50)	−4.00 (−6.00, −2.00)	*Z*=−0.40	0.69
ΔsPAP (mmHg)	28.89±13.99	23.87±16.64	*t*=0.80	0.43
ΔTRPG (mmHg)	28.00±15.00	23.13±16.95	*t*=0.75	0.46
ΔTAPSE (mm)	−2.33±2.30	−1.83±2.81	*t*=−0.48	0.63

Data are presented as mean ± standard deviation or median (interquartile range). Δ refers to the difference between the indicator before and after treatment. 6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; RVD, right ventricular diameter; RAD, right atrial diameter; AAO, ascending aortic root inner diameter; LVEDd, left ventricular end-diastolic diameter; sPAP, systolic pulmonary artery pressure; TRPG, tricuspid regurgitation pressure gradient; TAPSE, tricuspid annular plane systolic excursion.

AST, Scr and Hb between 0 and 24 weeks (P>0.05). The results are shown in *Tables 2,3*.

Discussion

PAH is a progressive disorder, characterized by a progressive pulmonary vasculopathy (5), leading to a gradual decrease in right heart function and even death. The symptoms of PAH are nonspecific especially for PAH associated with CTD, so its early diagnosis is particularly difficult.

2022 ESC/ERS Guidelines for the diagnosis and treatment of PH (1) advised that resting transthoracic echocardiography should be employed as the main method for screening PAH. Ghio *et al.* (6) found that the TAPSE measured by echocardiography, left ventricular eccentricity index, and degree of tricuspid regurgitation could effectively evaluate the prognosis of patients with idiopathic PAH, reflecting right ventricular function. Although RHC is still the gold standard for the diagnosis of PAH, noninvasive tests such as echocardiography are often used as an alternative evaluation method to RHC due to its invasiveness and high limitation in clinical practice. In this study, multiple echocardiographic parameters before and after treatment were used as the main indicators for assessing clinical efficacy. 2022 ESC/ERS Guidelines also proposed that the four-strata model was recommended as a basic risk-stratification tool at follow-up, but additional variables including haemodynamics should be considered as needed (1). Guidelines recommended that clinicians should make treatment strategies based on risk stratification according to presence or absence of cardiopulmonary comorbidities. Specifically, for symptomatic patients with PAH, without cardiopulmonary comorbidities, initiating oral combination therapy (ERA and PDE5i) rather than monotherapy was suggested despite the low certainty of evidence. For patients with cardiopulmonary comorbidities, there was no evidence-based treatment recommendations as they were under-represented. Moreover, they responded less well to PAH medication or lack of tolerability. In our study, although patients were diagnosed with CTD-PAH, we couldn't rule out the possibility that they had the left heart phenotype or cardiopulmonary phenotype. We included nine patients receiving macitentan monotherapy who had an insufficient response to PDE5i for 3–6 months.

In this study, multiple indicators before and after treatment were comprehensively assessed in 32 patients. WHO-FC, 6MWD, and NT-proBNP showed significant improvements after treatment with macitentan once daily at 10 mg for 24 weeks, indicating that it could improve exercise tolerance in patients. Echocardiographic parameters including RVD, RAD, LVEDd, sPAP, TRPG and TAPSE were all significantly improved in CTD-PAH cases after 24 weeks of treatment with macitentan compared with baseline values (P<0.05). The apparent changes of echocardiographic parameters reached statistical significance, suggesting that macitentan could delay the progression of cardiac remodeling to some extent.

It is currently believed that immune and/or inflammatory mechanisms play an important role in the occurrence and development of PAH. A previous study on its pathogenesis (7) showed a marked inflammatory status accompanied by immune cell infiltration in the lungs of patients with PAH regardless of the etiology and type of PAH, especially for CTD-PAH. Therefore, the inflammatory concept for the pathogenesis of CTD-PAH appears to be supported by the evidence. Inflammation causes endothelial cell dysfunction and smooth muscle cell and fibroblast proliferation, which is an initial trigger for pulmonary vascular remodeling (8). The inflammatory process constitutes the link between CTD and PAH, and therefore, anti-inflammatory and immunotherapies might become new strategies for preventing or even reversing the development of PAH. Anti-inflammatory therapy can improve clinical outcome via reducing pulmonary vascular remodeling (9). Immunosuppressive therapy mainly consisting of glucocorticoids and other immunosuppressive agents can significantly improve symptoms and inhibit or even reverse multiple organ damages and is considered the most basic treatment strategy for patients with CTD (10). Zhao *et al.* (11) put forward the dual concept of treat-to-target first, emphasizing that immunosuppressive therapy of CTD and PAH-specific therapy should be administered equally. Zhao *et al.* investigated the efficacy of PAH-specific drugs and found that the treatment regimen for primary CTD remained unchanged in all enrolled patients.

Endothelial cell dysfunction caused the occurrence and development of CTD-PAH. In the study, the impaired production of vasoactive mediators and excess production of vasoconstrictors such as thromboxane A2 (TXA2) and endothelin-1 (ET-1) (12) and proliferative mediators promoted vascular remodeling.ET-1, an endogenous peptide produced by vascular endothelial cells, exerts a potent vasoconstrictor effect and can induce the smooth muscle cell division. ET-1 was found to figure prominently in the pathogenesis of CTD-PAH (13). ERAs treat PAH by interfering with the endothelin signaling pathway. The

drugs currently used in clinical practice are mainly divided into the first and second-generation ERAs. Compared with ambrisentan and bosentan, macitentan exhibits stronger tissue penetration and long-lasting binding of receptors, which in turn inhibits ET to the greatest extent. In addition, few adverse reactions in patients who received macitentan have been found. Several randomized controlled trials have confirmed that macitentan significantly improved cardiac function and exercise tolerances in patients with PAH with no obvious adverse reactions, regardless of it being used as monotherapy or in combination therapy. The prospective, multicenter, single-arm, open-label, phase IV OPTIMA trial (14) examined initial combination therapy with macitentan and tadalafil for 16 weeks in patients with newly diagnosed PAH. This study reported that initial macitentan and tadalafil combination therapy was well tolerated in patients with PAH and resulted in hemodynamic improvement as well as improvements in functional parameters and risk profile. SERAPHIN trial (15), a double-blind, placebo-controlled, event-driven phase III trial, the first completed long-term trial in patients with PAH and provided evidence that combination therapy with macitentan is effective and well-tolerated in the management of PAH. Macitentan was shown to improve cardiopulmonary function, hemodynamic indicators, and health-related quality of life and contributed to a reduced risk of morbidity/mortality and rehospitalization for heart failure. The SERAPHIN-OL trial (16), open-label extension study of SERAPHIN, provided the longest follow-up for safety and survival published to date for any PAH therapy and the safety profile of macitentan was in line with SERAPHIN. Recently, a multicenter, double-blind, adaptive phase 3 A DUE study (17) investigated the efficacy and safety of macitentan/tadalafil fixed-dose combination *vs.* macitentan 10 mg and *vs.* tadalafil 40 mg monotherapies in PAH patients and concluded that macitentan and tadalafil FDC significantly improved pulmonary vascular resistance *vs.* monotherapies with a safety and tolerability profile consistent with the individual components. Above studies included patients with CTD-PAH accounted for a part of enrolled patients, but data on real-world clinical practice and outcomes of patients with CTD-PAH were scarce. The OPUS/OrPHeUS studies (18) enrolled patients newly initiating macitentan, including those with CTD-PAH and described patient characteristics, treatment patterns, outcomes, and safety profiles of patients in the US using OPUS/OrPHeUS. This study demonstrated the safety and tolerability profile of macitentan in patients with CTD-PAH was comparable to that of I/HPAH patients.

Limited clinical research evidence currently exists on the use of macitentan for treating PAH associated with CTD. Many clinical studies had strict inclusion criteria, making it challenging to generalize findings to broader patient populations. In this retrospective observational study, 32 patients were evaluated to assess the short-term efficacy and safety of macitentan in treating CTD-PAH. Patients were divided into two groups based on their medication status: macitentan monotherapy group and macitentan combined with sildenafil treatment group. The study compared patients' exercise tolerance, WHO-FC, biochemical markers and echocardiographic indicators before and after 24 weeks of treatment. The analysis revealed significant improvements in exercise tolerance, cardiac function, biomarkers and certain echocardiographic indicators after 24 weeks of treatment, aligning with findings from the aforementioned studies.

This study did not observe any difference between macitentan combination and monotherapy, which contradicted the results of a multicenter, double-blind, adaptive phase 3 A DUE study referenced earlier. This study demonstrated that treatment with the single-tablet combination of macitentan and tadalafil was superior to either monotherapy alone in reducing PVR. In addition, another study found that combination therapy was also benefit for CTD-PAH compared to monotherapy, with a 51.7% risk reduction of clinical failure in CTD-PAH except SSc (19). However, this study did not find any significant differences between the two treatment groups, possibly due to the limited follow-up period and small sample size of participants.

In our study, 32 patients with CTD-PAH who were treated with macitentan were followed up for 24 weeks, and the changes in multiple indicators in patients before and after treatment were retrospectively analyzed. Based on the findings, we can preliminarily conclude that macitentan improved exercise capacity and cardiac function in patients with CTD-PAH, with no adverse reactions such as obvious anemia and liver and kidney damage.

This study had some limitations. First, we employed a single-center, retrospective study design, with no controls, and thus our findings represent a lower level of evidence compared to randomized controlled trials. Second, RHC failed to be generally carried out among all patients due to the state of illness and operative invasiveness; therefore, we were unable to evaluate the hemodynamic indicators of patients with CTD-PAH. We thus conducted the illness condition assessment and curative effect observation in

patients with CTD-PAH according to the other three aspects from the guideline. Third, the number of samples in this study was small, and the differences in some indicators before and after treatment were not statistically significant. Fourth, the follow-up time of this study was 24 weeks, and thus the long-term efficacy and long-term prognosis of patients with CTD-PAH who were treated with macitentan could not be determined.

The potential impact of SARS-CoV on patients with chronic diseases was of great concern, particularly those with PAH, as the viral infection represents a common triggering factor (20). Although this study was conducted during the peak of COVID-19 pandemic, no significant deterioration of pulmonary hypertension, death, or readmission to heart failure due to COVID-19 infection was observed during follow-up. Furthermore, PAH targeted drugs such as ambrisentan, are under research based on potential protective role (21). In the background of the COVID-19 epidemic, effective management of CTD-PAH necessitates patient self-care practices such as self-protection, careful monitoring of antipyretic medication dosages, timely receiving the COVID-19 vaccination, and limiting fluid intake to prevent exacerbation of cardiac function during infection.

Conclusions

In summary, macitentan was found to improve exercise tolerance and cardiac function in patients with CTD-PAH which instead of and may be considered a safe and effective targeted drug for CTD-PAH in short term. It is worthy of clinical promotion and application, but its long-term efficacy still needs further clinical research to evaluate.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethical committee of The First Affiliated Hospital of Soochow University [No. (2024) Ethical Research Approval No. 130], and the informed consent of the patients was collected.

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