

Treatment of pulmonary hypertension in patients with connective tissue disease and interstitial lung disease

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BACKGROUND: Pulmonary hypertension (PH) in patients with connective tissue disease (CTD) can occur in isolation or concomitantly with interstitial lung disease (ILD). Targeted therapies for PH can mitigate clinical deterioration in CTD patients with isolated PH; however, the effect of these therapies in CTD patients with PH and ILD (CTD-PH-ILD) are poorly characterized.

OBJECTIVE: To investigate outcomes following long-term treatment of PH in patients with CTD-PH-ILD.

METHODS: A retrospective evaluation of 13 CTD-PH-ILD patients who were treated with bosentan, sildenafil or bosentan plus sildenafil, was conducted. Immunosuppressants were prescribed as indicated. Patients underwent pulmonary function testing and assessment of 6 min walk distance at the time of treatment initiation and during follow-up. Patients were followed until time of death, lung transplantation or the end of the study. Kaplan-Meier estimates of survival were calculated and log-rank testing was used to analyze survival differences according to CTD subtype.

RESULTS: Thirteen patients (seven with systemic sclerosis [SSc], four with overlap syndrome, and two with rheumatoid arthritis) were followed for a mean (\pm SD) duration of 33.8 \pm 21.7 months. The survival estimate at a median duration of 34 months was 85%; two patients with SSc died. Mortality rates were greater among patients with SSc versus other CTD subtypes ($P=0.04$). No changes from baseline to follow-up in mean forced vital capacity or exercise capacity, and no treatment-related toxicity, were observed.

CONCLUSION: Treatment using PH-specific therapies in patients with CTD, PH and ILD was well tolerated. Further studies to investigate the efficacy of PH-specific therapies in CTD-PH-ILD patients are warranted.

Key Words: *Exercise capacity; Overlap syndrome; Pulmonary function; Rheumatoid arthritis; Survival; Systemic sclerosis*

The term 'connective tissue disease' (CTD) is applied to a heterogeneous group of disorders including systemic sclerosis (SSc), systemic lupus erythematosus (SLE), idiopathic inflammatory myositis (IIM), rheumatoid arthritis (RA), primary Sjögren's syndrome and mixed connective tissue disease (MCTD). A well-known complication of CTD is pulmonary hypertension (PH), which may develop in isolation or in association with interstitial lung disease (ILD) (1-3). CTD-associated PH (CTD-PH) is a leading cause of mortality; patients with this manifestation have an estimated three-year survival rate of 56% (4,5). Less is known about survival among patients with CTD, PH and ILD (CTD-PH-ILD), although reported observations suggest that the prognosis for these patients is particularly poor (2,6). In a recent study by Mathai et al (7), patients with SSc, PH and ILD had an estimated three-year survival rate of 39%, a rate five-times worse than the rate observed in patients with SSc or PH alone (7).

Le traitement de l'hypertension pulmonaire chez des patients ayant une maladie des tissus conjonctifs et une maladie pulmonaire interstitielle

HISTORIQUE : L'hypertension pulmonaire (HP) chez les patients ayant une maladie des tissus conjonctifs (MTC) peut se manifester isolément ou conjointement avec une maladie pulmonaire interstitielle (MPI). Des thérapies ciblées de l'HP peuvent limiter la détérioration clinique de la MTC chez les patients ayant une HP isolée, mais l'effet de ces thérapies sur les patients ayant une MTC accompagnée d'une HP et d'une MPI (MTC-HP-MPI) est mal caractérisé.

OBJECTIF : Examiner les issues après un traitement à long terme de l'HP chez les patients ayant une MTC-HP-MPI.

MÉTHODOLOGIE : Les chercheurs ont procédé à une évaluation rétrospective de 13 patients ayant une MTC-HP-MPI traités au bosentan, au sildénafil ou au bosentan et au sildénafil. Des immunosuppresseurs leur étaient prescrits selon les indications. Les patients ont subi une exploration fonctionnelle respiratoire et une évaluation de la distance de marche en 6 minutes au début du traitement, puis pendant le suivi. Ils ont été suivis jusqu'à leur décès, à une transplantation pulmonaire ou à la fin de l'étude. Les chercheurs ont calculé les évaluations de survie de Kaplan-Meier et ont utilisé le test de Mantel-Haenszel pour analyser les différences de survie selon le sous-type de MTC.

RÉSULTATS : Treize patients (sept ayant une sclérose systémique [ScS], quatre, un syndrome de chevauchement et deux, une polyarthrite rhumatoïde) ont été suivis pendant une période moyenne (\pm ÉT) de 33,8 \pm 21,7 mois. L'évaluation de survie après une période médiane de 34 mois était de 85 %; deux patients atteints de ScS étaient décédés. Le taux de mortalité était plus élevé chez les patients atteints d'une ScS que chez ceux ayant d'autres sous-types de MTC ($P=0,04$). Les chercheurs n'ont observé ni changement entre le point de départ et le suivi pour ce qui est de la capacité vitale forcée moyenne ou de la capacité à l'effort, ni toxicité liée au traitement.

CONCLUSION : Un traitement faisant appel à des thérapies propres à l'HP chez les patients ayant une MTC, une HP et une MPI était bien toléré. D'autres études pour examiner l'efficacité des thérapies propres à l'HP chez des patients atteints de MTC-HP-MPI s'imposent.

Clinical trial data (8-13) show that PH-specific therapies (prostanoids, endothelin receptor antagonists and phosphodiesterase type 5 inhibitors) improve hemodynamic parameters, exercise capacity, health-related quality of life and, possibly, survival in CTD-PH patients. However, patients with CTD-PH and significant ILD were typically excluded from these trials due to concerns regarding worsening ventilation/perfusion mismatch and shunt, and the impact of these physiological changes on outcomes such as exercise capacity and survival (14). As a result, little is known about the impact of PH-specific therapies on survival and exercise capacity in CTD-PH-ILD patients.

The present article reports the results of a retrospective analysis of outcomes in CTD-PH-ILD patients who were treated with long-term, PH-specific therapies at a tertiary referral centre. Using Kaplan-Meier estimates, the outcomes investigated included survival and baseline changes in exercise capacity and pulmonary function.

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METHODS

Study design and patient population

The present study was a retrospective analysis of data from the University of Manitoba Pulmonary Hypertension clinic registry (Winnipeg, Manitoba). Patients with CTD-PH-ILD in the absence of other secondary etiologies, who received bosentan between July 1, 2001, and November 3, 2008, were included in the analysis.

Patients exhibiting SSc, SLE, IIM, RA, primary Sjögren's syndrome and MCTD, diagnosed by a rheumatologist were included in the analysis. The presence of overlap syndrome was recorded among patients diagnosed with more than one CTD, which included patients with MCTD.

PH was defined as a resting mean pulmonary arterial pressure of 25 mmHg or greater, a pulmonary vascular resistance (PVR) of more than 3.0 Wood units/m² and a pulmonary capillary wedge pressure of lower than 15 mmHg on right heart catheterization (RHC). In cases for which a patient refused or could not tolerate RHC, an estimated right ventricular systolic pressure of 45 mmHg or greater, as measured by Doppler echocardiography in the absence of left heart failure, was used to define PH.

The presence of ILD was defined as a forced vital capacity (FVC) of lower than 80% of predicted. The severity of ILD was categorized as mild in patients with an FVC of 70% to 80% of predicted values, and moderate to severe in patients with an FVC of 70% of predicted values or lower (15).

Data collection and assessments

The primary end points for patients in the present study were death or lung transplantation. The follow-up period (survival) in patients who met either primary end point comprised the duration from the initiation of PH-specific therapy until the date of the event. For patients who did not meet either end point, the follow-up period (survival) comprised the duration from date of initiation of PH-specific therapy until the date of the most recent clinic visit.

All patients required a pulmonary function test (PFT) and 6 min walk distance (6MWD) results to be measured within six months of PH-specific treatment initiation (baseline) and at time of follow-up to be included in the present study.

PFTs included spirometry, measurements of lung volume and single-breath carbon monoxide diffusing capacity (DLCO); measurements were standardized to reference data reported by Gutierrez et al (16). The PFT results measured closest to bosentan initiation (baseline) and the most recently available PFT results (follow-up) were used for analysis. Progressive decline in lung function was defined as a decrease in FVC of 10% of predicted or greater from baseline to follow-up assessment.

Measurement of 6MWD was performed using a standardized protocol among patients breathing room air. The total distance walked (in m), oxygen saturation, fraction of inspired oxygen, and reason(s) for early termination (when applicable) were recorded. Reference equations from Enright and Sherrill (17) were used for assessment. The assessment of 6MWD was performed approximately every four to six months in patients treated with PH-specific therapies; the assessment of 6MWD conducted closest to bosentan initiation (baseline) and the most recently available assessment of 6MWD (follow-up) were used in the analyses.

Other clinical variables quantified at baseline included demographics, concomitant medications and WHO functional class. Hemodynamic parameters obtained during RHC included mean pulmonary arterial pressure, pulmonary capillary wedge pressure, calculated PVR and cardiac index. Alanine and aspartate aminotransferase levels were monitored weekly for the first eight weeks of bosentan therapy, and monthly thereafter.

Statistical analysis

Analyses were performed using Stata Statistical Software release 9 (StataCorp, USA). The duration of follow-up, and results of cardiac hemodynamics, FVC (% predicted), DLCO (% predicted) and 6MWD (m) are expressed as mean \pm SD. Paired *t* tests were used to determine differences in FVC or 6MWD at baseline and at follow-up. Kaplan-Meier analysis was used for investigation of survival. A log-rank test was used to analyze survival differences according to CTD subtype.

RESULTS

Study population

In total, 13 CTD-PH-ILD patients who were treated with bosentan were identified and included in the study. Baseline characteristics and demographics are presented in Table 1. Six patients exhibited mild ILD and seven had moderate to severe ILD. Twelve patients were Caucasian and one was a First Nations person. The mean DLCO at baseline for the study group was 37.2 \pm 9.8% of predicted values.

Hemodynamic measurements from 12 patients who underwent RHC for diagnosis of PH are presented in Table 2. One patient was diagnosed with PH using Doppler echocardiography. This patient exhibited an estimated right ventricular systolic pressure of 48 mmHg and an oxygen saturation of 91% on room air.

Treatment

All patients received initial monotherapy with bosentan 62.5 mg twice daily for four weeks, up-titrated to 125 mg twice daily thereafter. Patients were followed at least every three months and switched to sildenafil – a phosphodiesterase 5 inhibitor – if their 6MWD fell below 350 m or their New York Heart Association functional class remained at class III. Four patients eventually required a combination of bosentan plus sildenafil. Sildenafil 25 mg was administered three times daily. PH-specific treatment was well tolerated, and no episodes of treatment-related toxicity were observed.

In addition to specific PH-therapies, nine patients (69%) received a diuretic, five (38%) were taking warfarin, five (38%) were on supplemental oxygen, four (31%) were taking a calcium channel blocker and two (15%) were taking digoxin. Concomitant immunosuppressant therapy was ongoing in 10 patients at baseline (Table 1).

Survival during follow-up

Patients were followed for a mean duration of 33.8 \pm 21.7 months (range three to 75 months). The Kaplan-Meier survival estimates for all patients in the study population are illustrated in Figure 1. Eleven patients (85%) survived a median of 34 months from bosentan initiation. No patients required a lung transplant.

Two patients (15%) died from end-stage PH during the study period – both were on a combination of bosentan and

TABLE 1
Baseline characteristics of patients included in the study

Patient ID	Sex	Smoking status*	Age, years	WHO class	FVC, % predicted	DLco, % predicted	FEV ₁ /FVC	mPAP, mmHg	PVR, Wood	RAP, mmHg	6MWD, m	IT	
		pack-years							CTD				units
1	Female	N	Ov	68	III	54	39	88	33	4.3	1	260	P/A
2	Male	25	SSc	68	III	76	33	74	33	3.8	5	360	–
3	Female	3	Ov	34	III	32	21	89	28	5.0	7	520	P/CYC
4†	Female	N	SSc	67	II	77	46	82	55	11.2	–	363	A
5	Female	36	SSc	59	IV	72	38	69	63	12.1	–	360	–
6	Male	30	RA	56	IV	64	40	64	55	14.0	8	190	T
7†	Female	2	SSc	75	III	73	44	82	52	15.3	4	335	P
8	Male	N	SSc	58	II	74	28	79	28	4.1	4	416	–
9	Female	N	SSc	66	III	35	22	66	39	5.0	6	295	P
10	Female	N	RA	48	II	61	56	85	45	6.8	4	505	P/T/L
11	Male	68	Ov	47	II	56	33	78	–	–	–	300	P/H
12	Female	15	SSc	64	II	72	43	68	29	6.8	18	510	MTX
13	Female	N	Ov	26	IV	40	40	97	30	5.4	1	280	P/A/H
Mean	–	–	–	56.6	2.9	60.5	37.2	78.5	40.8	7.8	5.8	361.1	–
SD	–	–	–	14.3	0.8	16.0	9.8	10.0	12.6	4.2	4.8	102.5	–

*All patients were nonsmokers at the time of assessment; †Patient died. 6MWD 6 min walk distance; A Azathioprine; CTD Connective tissue disease; CYC Cyclophosphamide; DLco Carbon monoxide diffusing capacity; FEV₁ Forced expiratory volume in 1 s; FVC Forced vital capacity; H Hydroxychloroquine; IT Immunotherapy; L Leflunomide; mPAP Mean pulmonary arterial pressure; MTX Methotrexate; N Never smoker; Ov Overlap; P Prednisone; PVR Pulmonary vascular resistance; RA Rheumatoid arthritis; RAP Right atrial pressure; SSc Systemic sclerosis; T Tumour necrosis factor-alpha inhibitor

TABLE 2
Baseline hemodynamic parameters in patients who underwent right heart catheterization

Parameter	Mean ± SD
Pulmonary arterial pressure, mmHg	40.8±12.6
Pulmonary capillary wedge pressure, mmHg	10.0±3.6
Cardiac index, L/min/m ²	2.5±0.9
Pulmonary vascular resistance, Wood units/m ²	7.8±4.2

sildenafil at time of death. The first death occurred 27 months following PH-specific treatment initiation. In this patient, the most recently available measurements of FVC and 6MWD were 65% of predicted values and 85 m, respectively. The second death occurred 17 months following initiation of PH-specific therapy, with the most recent available measurements of FVC and 6MWD being 67% of predicted values and 310 m, respectively. Intravenous epoprostenol therapy was considered to be an appropriate alternative treatment for these patients; however, ultimately, it was not prescribed because both patients exhibited an inability to self-administer.

All survivors exhibited a CTD other than SSc (four patients had overlap syndrome and two patients had RA); both patients who died had SSc. Using log-rank testing, a significantly greater mortality rate was observed among patients with SSc (n=7) compared with other CTD (n=6) (P=0.04).

Change in FVC

The first assessment of PFT results was performed at a mean of 3.3 months (range zero to 23 months) from bosentan initiation. The final assessment of PFT results was at a mean duration of 32.1 months (range 11 to 76 months) following the first assessment. With the exception of two patients who died, the final assessment of PFT results occurred on the same date as the most recently recorded follow-up visit. Of the two patients who died, the most recently available assessments of PFT results were conducted five days before death in one patient and five months before death in the other.

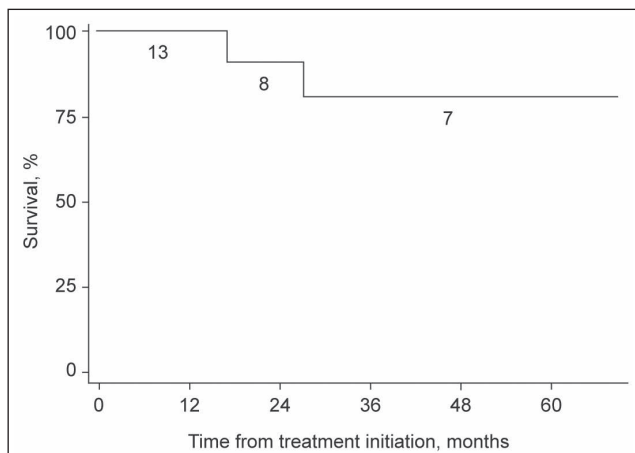


Figure 1) Kaplan-Meier survival estimates for patients with connective tissue disease, pulmonary hypertension and interstitial lung disease who were treated with pulmonary hypertension-specific therapies

The mean and per-patient measurements of FVC at baseline and at the time of follow-up assessment are reported in Figure 2. The mean FVC at baseline was 60.5±16.0% of predicted values and the mean FVC at follow-up was 62.1±13.9% of predicted values. While no significant differences were observed between the two means, three patients exhibited a decline in lung function (defined by a decrease in FVC of 10% of predicted or greater) between their baseline and follow-up assessments.

Change in 6MWD

The first assessment of 6MWD was performed at a mean of 2.3 months (range zero to 23 months) from bosentan initiation. The final assessment of 6MWD was conducted at a mean duration of 36.1 months (range seven to 70 months) following the first assessment. The 6MWD was assessed in all patients within a mean period of one month (range zero to four months) from their most recent follow-up date.

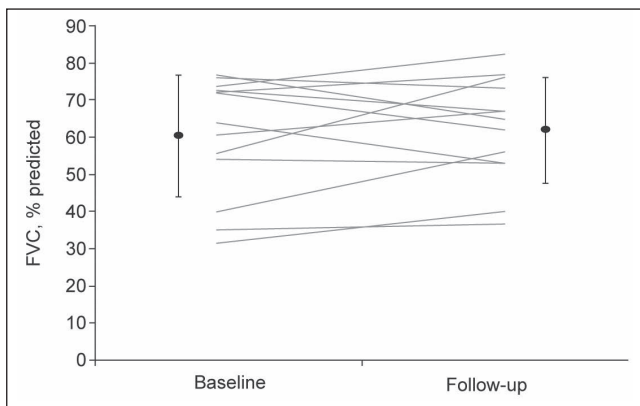


Figure 2) Mean and per-patient forced vital capacity (FVC) at baseline and at follow-up. Data presented as mean \pm SD

The mean and per-patient measurements of 6MWD at baseline and at time of follow-up assessment are illustrated in Figure 3. At baseline, the mean 6MWD was 361.1 ± 102.5 m. At follow-up, the mean 6MWD was 353.0 ± 127.0 m. One patient exhibited a notable decline in 6MWD between baseline and follow-up assessment.

DISCUSSION

PH and ILD are prevalent, and lead the causes of mortality in CTD patients (5). In CTD, PH may develop either as a consequence of progressive ILD or as a complication of the disease. In the present study, we observed a median 34-month Kaplan-Meier survival estimate of 85% among CTD-PH-ILD patients treated with PH-specific medications. A significantly greater mortality was observed among patients with SSc compared with other CTDs. No significant changes in mean FVC or 6MWD were observed during the treatment period – a maintenance of clinical status that may be considered to be a success. PH-specific treatment was well tolerated in this population.

Little is known about the survival of CTD-PH-ILD patients on PH-specific therapies. In one single-centre study from the United States, Mathai et al (7) observed a three-year survival rate of 39% among patients with SSc, PH and ILD who received PH-specific treatment. In this study, 15 of 20 SSc patients with PH and ILD received an endothelin receptor antagonist, but still experienced a poor outcome. In a multi-centre observational study from the United Kingdom (18), patients diagnosed with CTD-PH and significant ILD exhibited a three-year survival rate of only 28% despite PH treatment. Furthermore, SSc patients may fare worse than patients with another CTD (2,18). The survival rate we report was higher than in previous reports and may be explained by the fact that several patients in this population exhibited a CTD other than SSc. Condliffe et al (18) reported three-year survival estimates among patients with PH associated with SLE, MCTD, RA and IIM of 74%, 63%, 66% and 100%, respectively. The authors also observed that patients with SLE and IIM exhibited significantly better survival than patients with SSc undergoing PH treatment (18). In another study of 12 SLE-PH patients treated with PH-specific medications (19), there were no deaths or need for lung transplantation observed at a mean follow-up period of 41 months.

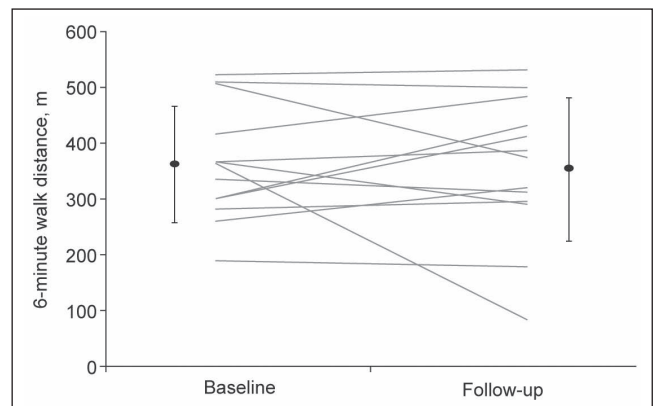


Figure 3) Mean and per-patient 6 min walk distance at baseline and at follow-up. Data presented as mean \pm SD

The clinical characteristics and demographics of our patient population also differ from previous reports. With the exception of one First Nations patient, our study group was comprised of Caucasian patients only. Mathai et al also showed that a low per cent predicted DL_{CO} and high PVR index were significantly associated with mortality in SSc patients with PH and ILD (7). In contrast, our study population exhibited a greater mean DL_{CO} and a lower PVR than the SSc patients with PH and ILD studied by Mathai et al (7).

Notably, our study group was not treated with an endothelin-receptor antagonist as monotherapy. In accordance with the treatment regimen, patients could receive sildenafil or epoprostenol monotherapy; four patients received combination bosentan and sildenafil therapy. Using combinations of PH-specific therapies may improve survival in CTD-PH patients. Condliffe et al (18) observed that two-year survival (71%) was greater among SSc-PH patients treated with combination therapy versus patients on endothelin receptor antagonist monotherapy (51%). Furthermore, 10 patients (77%) in our study population received concomitant immunosuppression for ILD. PH in patients with some CTD may respond well or even reverse following immunosuppressive medications (20-24). However, mean pulmonary arterial pressure in SSc patients with PH and ILD does not typically improve with immunosuppressive treatment, suggesting that PH, at least in SSc, should be treated with PH-specific therapies. This is particularly important given that PH is independently associated with mortality in SSc-PH patients with ILD (25). An additional benefit to patients in our study population may have resulted from the use of anticoagulation therapy in the non-SSc patients with PH (7,26).

We acknowledge several limitations in the present observational, retrospective study. While data collection was detailed, the patient population was small and the study was not powered to detect differences in survival according to clinical features. In addition, our patient population represented a selected group who were referred for PH evaluation at a tertiary care hospital in Canada, and may not be representative of the broader CTD-PH-ILD patient population. We cannot ascribe the observed survival rate merely to treatment with PH-specific therapies; this survival rate may reflect lead time bias or concomitant treatment with immunosuppressants.

CONCLUSION

A Kaplan-Meier survival estimate of 85% at 34 months was observed among CTD-PH-ILD patients who were treated with PH-specific therapies and immunosuppressants. The treatment regimens were well tolerated. Controlled trials to investigate the efficacy of PH-specific therapies in this CTD patient population are warranted.

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