

Title:

Pulmonary arterial hypertension therapy in Australian patients with systemic sclerosis related pulmonary arterial hypertension: analysis of the Australian Scleroderma Cohort Study

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1. INTRODUCTION:

This paper has been prepared at the request of the Reference Group for the Post-Market Review of Pulmonary Arterial Hypertension (PAH) Medicines to provide data on PAH medicine utilisation in patients with systemic sclerosis (SSc) related PAH.

The aims of this analysis are to determine:

1. The types of pulmonary hypertension (PH) defined by right heart catheterisation (RHC) by World Health Organisation group in patients in the Australian Scleroderma Cohort Study (ASCS) who were alive during the period July 2016 to June 2017
2. The clinical features and PAH severity of the patients with RHC-defined pulmonary arterial hypertension (PAH) by functional class (FC) who were receiving PBS reimbursed PAH therapies at an index visit between June 2016 and December 2017.
3. The PAH therapies and other therapies used by the patients with RHC-defined PAH by FC who were receiving PBS reimbursed PAH therapies at an index visit between June 2016 and December 2017.
4. The co-morbidities of the patients with RHC-defined PAH by FC who were receiving PBS reimbursed PAH therapies at an index visit between June 2016 and December 2017.

2. BACKGROUND

Systemic sclerosis in Australia:

Systemic sclerosis (SSc, also known as scleroderma) is a multi-organ autoimmune connective tissue disease with potentially devastating consequences and no effective disease modifying agents or cure. Australia has one of the highest prevalences of SSc worldwide estimated to be 23.3/100 000 in 2001 (1) with a total prevalence approaching 6000. It is characterised by the pathological triad of autoimmunity, vasculopathy and fibrosis, typically manifested by autoantibodies, cold-induced colour change of the peripheries (Raynaud's phenomenon) with or without digital ulceration and skin thickening, respectively. In many patients, these pathologic changes also lead to gradual accrual of irreversible damage in organs such as the gastrointestinal tract, lungs, kidneys and heart.

Among the rheumatic diseases, SSc is associated with one of the greatest increases in mortality and morbidity compared with age and sex-matched peers. A meta-analysis in 2012 reported standardised mortality ratios (SMRs) for SSc ranging from 2.5 to 4.5, with a pooled SMR of 3.5 (95% CI: 3.03, 4.11, $p < 0.0001$) (2). In Australia, SSc is associated with an average reduction in life expectancy of 11.3 years for women and 25.8 for men, compared with the general population (3). Furthermore, the chronic nature of the disease and the involvement of multiple organ systems over time, makes SSc one of the most costly rheumatic diseases in terms of health care utilisation. In recent data linkage studies from the Australia Scleroderma Cohort, the average total annual direct and indirect costs were estimated to be \$15,127 per annum per patient (4, 5).

The extent of skin involvement defines two subtypes of disease: limited cutaneous and diffuse cutaneous. Each subtype differs in terms of rate of disease progression and type and severity of internal organ involvement with the diffuse subtype having the most rapid onset, more frequent interstitial lung disease (ILD) and renal crisis and worse outcomes. Collectively, the pulmonary complications of ILD and pulmonary arterial hypertension (PAH) are the leading cause of mortality among patients with SSc (6, 7).

The **Australian Scleroderma Interest Group (ASIG)** is a multidisciplinary collaboration of rheumatologists, immunologists, cardiologists and respiratory physicians from all states and

territories of Australia except the Northern Territory, who have a special interest in improving the outcomes of patients with SSc. In 2007, ASIG established the Australian Scleroderma Cohort Study (ASCS), a multi-centre, longitudinal observational cohort as a framework for the study of cardiopulmonary complications in patients with SSc and the related scleroderma variant, mixed connective tissue disease (MCTD).

Initial research activities focussed on identifying prognostic factors for the cardiopulmonary complications of SSc, ILD and PAH, in order to develop guidelines for systematic detection, monitoring and therapy of patients with these complications. This work has led to numerous publications and peer-reviewed funding, including a NHMRC project grant for a multicentre, randomised controlled trial of a new oral anti-coagulation drug in SSc-related PAH (APP1062638) (8). Multiple national and international collaborations since, have led to an array of research activities covering the full spectrum of organ involvement in SSc.

PAH in systemic sclerosis:

PAH is characterised by restricted flow through the pulmonary arterial circulation due to increased pulmonary vascular resistance i.e. a form of “pre-capillary” pulmonary hypertension (PH) (WHO Type 1) (9). This leads to elevated pressures in the pulmonary circulation, reflected in increased pulmonary arterial pressures (PAP), and eventually in the right heart.

The disease moves through a preclinical phase of early pulmonary vascular disease, where the vascular damage is advanced, but the cardiopulmonary circulation is able to maintain relatively normal function and haemodynamics, through to established and progressive PAH, ultimately compromising right ventricular function and cardiac output. The clinical repercussions of disease progression are increasing symptoms (dyspnoea, reduced exercise tolerance, palpitations, fatigue, dizziness and syncope) and signs (arrhythmia, right heart failure) of PAH resulting in reduced quality of life, increased hospitalisation, consideration for transplantation and the need for palliative measures, such as home oxygen and atrial septostomy and ultimately death.

According to a meta-analysis in 2010, the prevalence of PAH in both subtypes of SSc is similar at around 9% (10). Since the inception of the ASCS, a new diagnosis of WHO Group I PAH has

been made in 160 of 1636 patients as a result of active risk assessment, with a prevalence of 11.8% [10.3% in lcSSc, 8.5% in dcSSc and 12.0% in the scleroderma variant, mixed connective tissue disease (MCTD)] (11). The annual incidence of PAH was 0.9% (1.4% in lcSSc, 0.9% in dcSSc, 1.4% in MCTD). SSc-PAH has a significant impact on functional capacity and health-related quality of life (HRQoL). In the ASCS, HRQoL scores are lower at PAH diagnosis across a number of domains of the SF-36, particularly in physical functioning, role-physical, general health and vitality, compared with the US normative mean, and lower than SSc patients without PAH (12). In the ASCS data linkage studies, PAH was a determinant of median hospitalisation, ambulatory care and medication costs with odd ratios of 2.3 (1.2-2.8), 2.8 (1.4-5.7) and 7.8 (3.4-18.3) respectively in multivariable logistic regression analysis (4). It was also a significant risk factor for unemployment and reduced productivity (5).

Importantly, patients with SSc who develop PAH during their lifetime have a worse prognosis than those with PAH due to other causes such as idiopathic PAH, with a mortality rate of 50% at one year without therapy (13). Advanced pulmonary vasodilator therapies for PAH including endothelin-receptor antagonists (bosentan, ambrisentan and macitentan), phosphodiesterase-5 inhibitors (sildenafil and tadalafil) and prostacyclins (inhaled iloprost and intravenous epoprostenol) are funded as monotherapy by the Pharmaceutical Benefits Scheme (PBS) and since February 2017, soluble guanylate cyclase stimulator (riociguat). There is RCT evidence that these improve functional class, haemodynamics and HRQoL and evidence for improved survival in longitudinal cohorts(14). With the advent of these therapies, the establishment of centres with expertise in PAH and a focus on early detection, there has been considerable improvement in survival. Nonetheless, survival is still poor with one-, two-, three- and five-year survival of 87.8%, 78.3%, 61.7% and 32.2%, respectively, in Australia (12).

Among 132 SSc-PAH patients in the ASCS, over a median follow-up from time of diagnosis and initiation of therapy of 3.8 years, 60 (45.5%) patients died with a median survival time from PAH diagnosis of 4.0 years (12). The SMR for patients with SSc-PAH was 5.8 (95%CI 4.3-7.8). Kaplan-Meier survival curves and proportional hazards regression showed a survival benefit with reduced mortality (hazard ratio 0.28, 95% CI 0.1-0.7), with combination PAH therapy and anticoagulation compared with monotherapy alone.

Diagnosis of PAH in patients with systemic sclerosis:

A definitive diagnosis of PAH can only be made by finding pre-capillary PH at right heart catheterisation (RHC). RHC is also used to determine eligibility for advanced pulmonary vasodilator therapies for PAH. This is now defined as a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest with a pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg (previously PAWP < 18 mmHg was permitted) and pulmonary vascular resistance (PVR) of > 3 Wood units, in the absence of significant lung disease and chronic thromboembolic pathology (9).

Not all PH in SSc is WHO group I PAH and other therapeutic strategies may be necessary. Patients should be assessed for other forms of pre-capillary PH including hypoxaemic lung disease such as end stage interstitial lung disease (WHO group 3) and pulmonary veno-occlusive disease (WHO group 1') as well as chronic thromboembolic PH (WHO group 4). Post-capillary PH due to left heart disease (WHO group 2) may be caused by myocardial microvascular changes and fibrosis due to SSc (9).

Potential reasons for poor outcomes in patients with systemic sclerosis related PAH:

1. Delay in diagnosis:

Despite one in ten SSc patients being likely to develop PAH, diagnosis and institution of therapy is commonly delayed which may contribute to poor outcome. At diagnosis, the majority of patients with SSc-related PAH in the ASCS are in WHO functional class III (59.9%) (12).

To encourage earlier detection of PAH in SSc, pulmonary hypertension guidelines from the American College of Cardiology Foundation/American Heart Association, ESC/ERS (15) and the National Pulmonary Hypertension Centres of the UK and Ireland recommend an annual transthoracic echocardiogram (TTE) for **all patients with systemic sclerosis not already diagnosed with PH**. TTE can provide an estimate of the systolic pulmonary arterial pressure (sPAP), based on the peak tricuspid regurgitant velocity (TRV) of the regurgitant jet of blood at the tricuspid valve, and taking into account the right atrial pressure as described by the simplified Bernoulli equation. Regular measurement of diffusing capacity for carbon monoxide (DLCO), corrected for haemoglobin (DLCOcorr) on PFTs is often recommended also. A gradual decline

in the DLCO_{corr} to a level that is disproportionately low compared with lung volumes such as forced vital capacity (FVC) on PFTs, is characteristic of pulmonary vascular disease such as PAH (16) although the DLCO_{corr} is often reduced to some extent in patients with SSc and not all patients with PAH have a reduced DLCO_{corr} at the time of diagnosis. Neither of these tests alone or in combination with other assays, reliably identify patients with PH. They can only provide an indication of the likely risk of PH and hence help select patients who should have a RHC.

Echocardiography has important limitations. sPAP cannot be measured on TTE in 20% to 39% of patients because of absent tricuspid regurgitation and/or insufficient image quality, including up to 29% of patients subsequently found to have pulmonary hypertension at RHC (false negative test). The National Echo Database of Australia (NEDA) group reported in 2016 that among 302,746 TTEs performed on 174,229 patients, 33.2% had an insufficient TR jet to measure sPAP (17). If the TR jet is absent, there is a tendency for clinicians to be inappropriately reassured by interpreting the TTE as negative for PH, rather than inconclusive.

We performed a systematic review of nine studies of algorithms for identifying increased risk of PAH in unselected SSc patients (18). All were based on TTE and the total population was 3,504. In studies of patients with prevalent (existing) PAH, the positive predictive value (PPV) was 20.4%-87%. In studies of patients with incident (new-onset) PAH, the PPV was 20.0%-30.7%. PPV of algorithms using ECHO with/without other tests was the same. No study enabled accurate determination of negative predictive value (NPV), sensitivity or specificity as none assessed performance in an unselected population with every patient undergoing the gold standard diagnostic test, a RHC. It is likely that reliance on TTE for identifying patients at high risk of PAH also delays diagnosis.

There is evidence that regular active risk assessment will identify patients in the early stages of PAH before symptoms are established and when prognosis is more favourable, and can improve outcomes. In the ASCS, patients with PAH diagnosed as a result of active risk assessment were more likely than patients in whom PAH was diagnosed at first presentation, to be in a better WHO Functional Class at PAH diagnosis ($p=0.01$) and have less advanced PAH as evinced by

higher mean six minute walk distance ($p=0.03$), lower mean pulmonary arterial pressure ($p=0.009$), lower mean pulmonary vascular resistance ($p=0.006$) and fewer non-trivial pericardial effusions ($p=0.03$) (11). The survival of patients presenting in better functional classes (I and II) is better in registries such as the UK CTD-PAH registry (19). Correspondingly, in the ASCS, worse WHO functional class ($p=0.03$) and higher mean pulmonary arterial pressure at PAH diagnosis ($p=0.001$), older age at PAH diagnosis ($p=0.03$), mild co-existent ILD ($p=0.01$), and digital ulcers ($p=0.01$) were predictive of mortality (12). The impressive 8-year survival rate of 64% in a group of SSc-PAH patients in whom PAH was detected as a result of active strategies compared with 17% for patients diagnosed with PAH in the course of routine care, published by Humbert *et al.*, suggests the improved survival in patients detected earlier is due to more than just lead time bias (20).

2. Limiting therapy to functional class III and IV:

The cost-effectiveness of early identification and treatment has not been formally assessed but a number of factors suggest that, in addition to the clinical benefits of improved HRQoL and survival, earlier therapy is cost-effective. The funding of advanced PAH therapies is managed under the Highly Specialised Drug Scheme. Only patients in functional classes III and IV are eligible under this scheme, but functional class II PAH is not a benign state. In the placebo arm of a randomised controlled trial of bosentan, 14% of 92 patients in functional class II declined by six months (21). Patients in functional classes I and II can access therapy via non-PBS avenues including self-funding and special access schemes or can obtain the least costly drug, sildenafil, via public hospitals. Furthermore, the additional costs of treatment for patients in functional class IV in particular, are substantial.

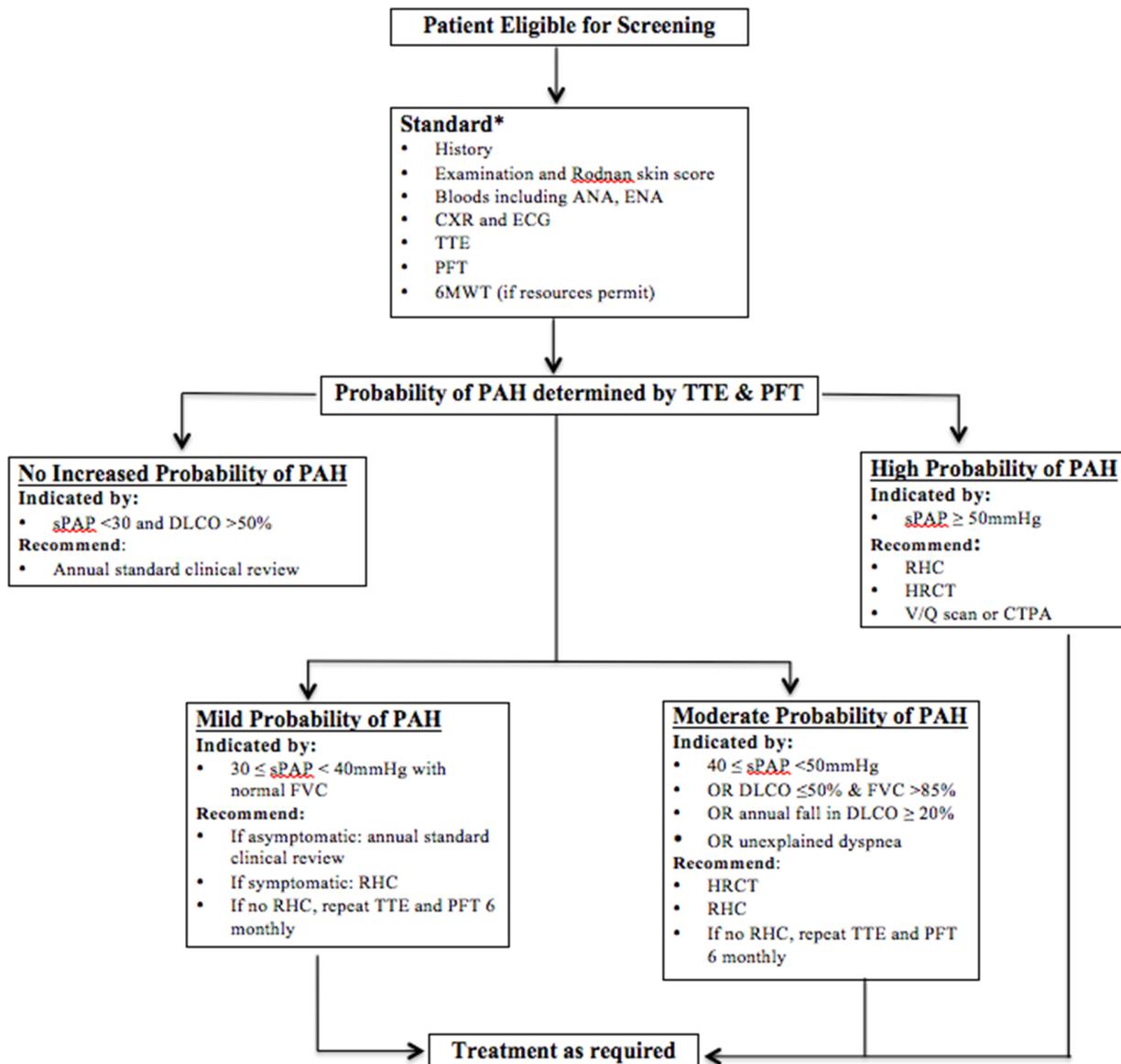
3. Use of monotherapy

The 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines (9) recommend more intensive therapy for patients in worse functional classes such as early use of more than one advanced PAH therapy in combination, first-line use of the most costly drug, intravenous epoprostenol and listing for heart-lung transplantation. These patients use more health resources due to higher rates of co-morbidities and hospitalisations (22).

The Australian Scleroderma Cohort Study program for identifying patients with systemic sclerosis related PAH.

All patients in the ASCS undergo annual screening for PAH that comprises a clinical assessment, TTE and PFTs (Figure 1) (11). RHC is recommended for any patient identified as having possible PAH (sPAP by TTE ≥ 40 mmHg and/or DLCOc $\leq 50\%$ predicted with FVC $> 85\%$, and/or fall in DLCOc $\geq 20\%$ compared with the previous year], especially in the presence of symptoms and without adequate explanation on further investigations of the lungs. At the time of implementation, this approach was very similar to the ESC/ERS guidelines of 2009(23) in which a TRV on TTE of more than 3.4 m/s or $2.8 < \text{TRV} \leq 3.4$ m/s with symptoms (defined as at least one of the following: current dyspnoea, current syncope/near syncope, presence of peripheral oedema) or TRV less than 2.8 m/s with these symptoms and an additional suggestive echocardiographic variable (eg right ventricular or right atrial dilatation) were an indication for RHC referral. The ESC/ERS guidelines updated in 2015 are still dependent on echocardiography with similar criteria for TRV and echocardiographic parameters of PH (9).

Figure 1: Australian Scleroderma Cohort Study algorithm for assessing risk for pulmonary hypertension



All SSc patients, defined according to ACR/EULAR criteria(24) or Leroy/Medsger criteria(25) and mixed connective tissue disease (MCTD), as originally described by Sharp et al.(26), are eligible for annual screening. Abbreviations: antinuclear antibody (ANA), extractable nuclear antibody (ENA), chest radiograph (CXR), electrocardiogram (ECG), diffusing capacity of the lung for carbon monoxide corrected for haemoglobin (DLCO), six minute walk test (6MWT), pulmonary function test (PFT), pulmonary arterial hypertension (PAH), systolic pulmonary arterial pressure (sPAP) determined using the standard method of adding 5mmHg as the right atrial pressure, forced vital capacity (FVC), high resolution chest computed tomography (HRCT), right heart catheterisation (RHC), transthoracic echocardiogram (TTE), ventilation perfusion (V/Q) scan, computed tomography pulmonary angiography (CTPA). Subsequent to the baseline assessment, autoantibodies, a CXR or a 6MWT need only be repeated if clinically indicated. The time period for a fall in DLCO and/or FVC was defined as one year. Both FVC and DLCO were taken into consideration when considering the underlying aetiology (PAH versus interstitial lung disease (ILD) (ie in patients with a significant reduction in DLCO (>20% in one year) or significantly reduced DLCO (<50% predicted), the FVC was used to determine increased risk of ILD (<85% predicted) and HRCT chest was used to confirm it. Pulmonary hypertension (PH) was attributed to ILD in the presence of extensive ILD on HRCT and hypoxemia at rest. PH due to left heart disease was defined according to the ESC/ERS criteria: PAWP>15 mmHg and DPG< 7 mmHg with PVR<3 Wood Units(9).

Respiratory investigations, including a CXR, HRCT and potentially a V/Q scan, are indicated in the following situations: FVC<85% predicted, reduced exercise tolerance, declining six minute walk distance, and /or fine crepitation noted on respiratory examination.

3. USE OF PAH THERAPY BY PATIENTS WITH SSc-RELATED PAH

METHODS:

Patients

Patients diagnosed with PH in the ASCS were eligible for this cross-sectional analysis. This registry recruits consecutive prevalent and incident patients with SSc, and records clinical data annually. Comprehensive demographic and disease-related data, patient reported outcomes (PROs) by questionnaire and the results of investigations are recorded in a single secured web-based online database. Each of the 15 centres has the approval of their local ethics committee, according to local regulations. Patients provided written informed consent at recruitment for collection of de-identified data.

Inclusion criteria for this analysis were: 1. patients with SSc according to ACR/EULAR criteria (24) or Leroy/Medsger criteria (25) and patients with MCTD as originally described by Sharp et al. (26); 2. PH confirmed on RHC with mean PAP \geq 25mmHg; 3. patients who were alive between July 2016 and June 2017.

Data collection

The index visit was defined as the last visit between June 2016 and Dec 2017. Not all tests were done on the same date as the index visit. For patients with multiple tests within the above date range, the last test was used.

The WHO group of PH was determined according to the physician's judgement following RHC. Group 1 (PAH) included patients with PAWP $<$ 18mmHg as eligibility for PBS-funded PAH initially included these patients. Group 2 (left heart disease) was defined as PAWP $>$ 18mmHg or elevated mPAP with transpulmonary gradient $<$ 12 mmHg. Group 3 was defined as PH with moderate to severe ILD based on extent of disease on high resolution CT (HRCT) chest scan with forced vital capacity on pulmonary function tests of $<$ 70% predicted. Group 4, chronic thromboembolic PH (CTEPH) was based on evidence of widespread mismatched defects on ventilation:perfusion scan and/or pulmonary angiogram.

PAH duration was defined as the time elapsed from the first RHC with PAH until December 2017 rather than the date of index visit because some patients had their PAH RHC done after their index visit.

WHO functional class (FC) was assessed by the treating physician at the index visit. FC at the index visit was missing for two patients so FC at the last visit was used.

Sex and age at time of index visit were determined. Disease subtype (lcSSc or dcSSc) was determined according to physician judgement. PBS-reimbursed PAH drugs included: bosentan, ambrisentan, sitaxentan, macitentan, sildenafil, tadalafil, epoprostenolol, inhaled iloprost and riociguat. The only non-PBS reimbursed PAH therapy identified was selexipag. Drugs and other therapies were recorded annually. Six minute walk tests (6MWT) and TTE were recorded annually.

Disease-manifestations were defined as present if they were evident at any time before the index visit. These included digital ulcers, digital amputation, synovitis and myositis based on proximal weakness and raised creatine kinase, electromyographic or biopsy evidence of myositis. A diagnosis of ILD was based on characteristic changes on HRCT chest where available. Physician's best judgment was used for defining scleroderma renal crisis (SRC). Gastrointestinal features included reflux requiring treatment with proton pump inhibitor, symptoms and/or radiographic evidence of oesophageal stricture, and faecal incontinence not due to other causes. Gastric antral vascular ectasia (GAVE) was defined by endoscopy. Information about treatment with corticosteroids, immunosuppressive therapy, invasive hyperalimentation and other co-morbidities such as cardiovascular disease, diabetes and chronic obstructive airways disease (COAD) were also recorded.

Hospitalisation in the 12 months before therapy was commenced and before the index visit was recorded.

Statistical analysis:

Data for those patients for whom the variable was available are presented as numbers

(percentages) for categorical variables, and mean \pm standard deviation (SD) for continuous variables. Differences in frequencies of characteristics between functional class I/II and III/IV were compared using Chi-square test for categorical variables and independent samples t-test for continuous variables. A two-tailed p value ≤ 0.05 was used to indicate statistically significant differences. All statistical analyses were performed using STATA 14.2 (Statacorp, College Station, TX, USA).

RESULTS

Since its inception in 2007, 209 patients with SSc or MCTD and RHC-defined PAH have been enrolled in the ASCS, of whom 32 were diagnosed before enrolment. In addition, 10 patients with exercise-induced PAH, 19 with PH due to left heart disease, 6 due to ILD and none due to CTEPH have also been identified.

The total number of patients with any form of PH with an index visit between June 2016 and December 2017 was 116 (Table 1). The majority of these had PAH (104), ten had PH due to left heart disease and 2 had PH due to ILD. All the patients with PAH were receiving PAH vasodilator therapy at the index visit as were two of the patients with PH due to left heart disease.

At the time of diagnosis/first visit where PAH drugs were given, 80 (76.9%) of the 104 patients, were classified as functional class III and 11 (10.6%) were classified as functional class IV (Appendix I). There were 13 patients (12.5%) missing data for functional class at this time because the database captures data based on annual visits. Some patients were diagnosed between visits, so functional class was not recorded at the time of diagnosis.

Table 1: ASIG patients with SSc or MCTD with any form of pulmonary hypertension with an index visit June 2016 to December 2017

WHO group	No. of patients n = 116	Patients receiving any PAH therapy at index visit* n (%)	Reason for no treatment
PAH (PAWP up to <18mmHg)	104	104 (100%)	
CTEPH	0	N/A	
PH due to left heart disease	10	2 (20%)	PAH therapy not indicated or reimbursed
PH due to lung disease	2	0	PAH therapy not indicated or reimbursed

PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; CTEPH, chronic thromboembolic pulmonary hypertension; PH, pulmonary hypertension; N/A, not applicable

* including investigational drugs for PAH e.g. selexipag

Among the 104 patients with PAH, 25 (25%) were in FC I/II and 79 (76%) were in FC III or IV at the index visit (Table 2). The majority of patients were female and the mean age was around 67 years in both groups. There was no difference in the duration of PAH since RHC diagnosis, which was around 5 years. Most patients had limited SSc and most patients were living in Victoria.

Table 2: Clinical features of patients with RHC-defined PAH for which PAH drugs are PBS reimbursed, according to functional class (at the index visit)

	PAH n = 104		p value
	FC I/II n = 25 (24%)	FC III/IV n = 79 (76%)	
Female n (%)	23 (92.0%)	62 (78.5%)	0.127
Age (mean +/- SD)	67.6 ± 10.7	66.9 ± 9.1	0.724
Duration of PAH since RHC diagnosis (years mean +/- SD)	5.2 ± 3.5	4.6 ± 3.5	0.482
SSc subset n (%)*			
limited	20 (80.0%)	49 (64.5%)	0.174
diffuse	5 (20.0%)	19 (25.0%)	
MCTD	0	8 (10.5%)	
State of origin n (%)			
SA	7 (28.0%)	19 (24.1%)	0.414
Vic	13 (52.0%)	49 (62.0%)	
WA	4 (16.0%)	5 (6.3%)	
NSW	1 (4.0%)	6 (7.6%)	

RHC, right heart catheter; PAH, pulmonary arterial hypertension; FC, functional class; SSc, systemic sclerosis; MCTD, mixed connective tissue disease

*Sample size differs from heading: FC I/II n = 25, FC III/IV n = 76

Chi² test for categorical variables and t-test for continuous variables

As expected, patients in FC III/IV had more severe PAH with shorter 6MWT distance and higher estimated systolic PAP than patients in FC I/II at the index visit (Table 3).

Table 3: Assessment of PAH severity in patients with RHC-defined PAH on any PAH specific therapy according to functional class (at the index visit)

Variable	FC I/II n = 19	FC III/IV n= 69	p value	Samples sizes (if different from n in table heading)
6MWT (m, mean +/- SD)	444.8 ± 121.2	328.9 ± 107.4	<0.001	FC I/II n = 18, FC III/IV n = 59
SaO2 pre- (mmHg, mean +/- SD)	97.3 ± 2.6	96.1 ± 3.5	0.192	FC I/II n = 18, FC III/IV n = 56
SaO2 post- (mmHg, mean +/- SD)	91.9 ± 6.1	89.6 ± 6.9	0.209	FC I/II n = 18, FC III/IV n = 54
TTE parameters				
Est. systolic PAP (mmHg, mean +/- SD)	43.5 ± 21.0	57.8 ± 23.8	0.021	FC I/II n = 19, FC III/IV n = 65
TR severity - n (%)				
Trivial	8 (42.1%)	24 (34.8%)	0.896	
Mild	6 (31.6%)	22 (31.9%)		
Moderate	3 (15.8%)	16 (23.2%)		
Severe	2 (10.5%)	7 (10.1%)		
RV function - n (%)				
Normal	18 (94.7%)	46 (68.7%)	0.132	FC I/II n = 19, FC III/IV n = 67
Mild	1 (5.3%)	9 (13.4%)		
Moderate	0	6 (9.0%)		
Severe	0	6 (9.0%)		
RV size- degree of enlargement n (%)				
Normal	14 (73.7%)	41 (59.4%)	0.345	
Mild	3 (15.8%)	12 (17.4%)		
Moderate	2 (10.5%)	6 (8.7%)		
Severe	0	10 (14.5%)		

RHC, right heart catheter; PAH, pulmonary arterial hypertension; FC, functional class; 6MWT, six minute walk test; SaO2, oxygen saturation; TTE, transthoracic echocardiogram; Est. systolic PAP, estimated systolic pulmonary arterial pressure; TR, tricuspid regurgitation; RV, right ventricle
Chi² test for categorical variables and t-test for continuous variables

In patients who were in FC I/II at the first visit, bosentan was most commonly prescribed as first PAH drug (44.0%) but by the index visit, this had fallen to 20.0% and 52.0% were prescribed macitentan (Table 4). Monotherapy was the first therapy in 76% of patients but 32.0% were receiving dual therapy at the index visit.

In patients who were in FC III/IV at the index visit, macitentan was the most commonly prescribed as first PAH drug (40.5%), this increasing to 55.7% by the index visit. (Table 4). Monotherapy was the first therapy in 77.2% of patients but 44.3% were receiving dual therapy and 6.3% were receiving triple therapy at the index visit. The PAH specific drugs used as monotherapy, dual therapy and triple therapy by patients according to functional class at the index visit are demonstrated in Appendices II-IV. Dual therapy typically comprised an endothelin receptor antagonist and a phosphodiesterase-5 inhibitor and triple therapy entailed the addition of a prostanoid eg epoprostenol.

Anti-coagulation, was used in 19% of FC III/IV by the time of the index visit. Supportive therapy was used by both groups, such as diuretics (32% in FC I/II and 53.2% in FC III/IV at the index visit) but supplementary oxygen was only used in FC III/IV (12.8% at the time of first therapy increasing to 26.6% by the time of the index visit). A range of other therapies for other manifestations of SSc were used by all patients at both the first therapy and index visits.

Approximately one third of patients in FC I/II were hospitalised in the 12 months before the first visit when PAH therapy was commenced and also in the 12 months before the index visit (Table 4). In contrast, these figures were around 50% in the FC III/IV patients.

Table 4: PAH specific and other therapies used by patients with RHC-defined PAH according to functional class (at the index visit)

PAH Therapy	FC I/II at index visit n = 25 (24%)		FC III/IV at index visit n = 79 (76%)	
	Therapy at first visit where PAH drugs were given, n (%)	Therapy at index visit n (%)	Therapy at first visit where PAH drugs were given, n (%)	Therapy at index visit n (%)
Bosentan	11 (44.0%)	5 (20.0%)	29 (36.7%)	19 (24.1%)
Ambrisentan	5 (20.0%)	5 (20.0%)	9 (11.4%)	10 (13.0%)
Sitaxentan	0	0	2 (2.5%)	0
Macitentan	9 (36.0%)	13 (52.0%)	32 (40.5%)	44 (55.7%)
Sildenafil	4 (16.0%)	6 (24.0%)	21 (26.6%)	36 (45.6%)
Tadalafil	2 (8.0%)	4 (16.0%)	4 (5.1%)	9 (11.4%)
Epoprostenol	0	0	0 (1.3%)	3 (3.8%)
Inhaled iloprost	0	1 (4.0%)	0	0
Selexipag	0	1 (4.0%)	0	2 (2.5%)
Riociguat	0	0	0	1 (1.3%)
Combination therapy				
Monotherapy	19 (76.0%)	16 (64.0%)	61 (77.2%)	39 (49.4%)
Dual therapy	6 (24.0%)	8 (32.0%)	17 (21.5%)	35 (44.3%)
Triple therapy	0	1 (4.0%)	1 (1.3%)	5 (6.3%)
Other therapies				
Warfarin	2 (8.0%)	3 (12.0%)	10 (12.7%)	12 (15.2%)
NOAC	1 (4.0%)	1 (4.0%)	1 (1.3%)	3 (3.8%)
Diuretics	8 (32.0%)	8 (32.0%)	29 (36.7%)	42 (53.2%)
Supplementary oxygen ¹	0	0	10 (12.8%)	21 (26.6%)
Proton pump inhibitor	22 (88.0%)	25 (100%)	63 (79.8%)	66 (83.5%)
Calcium channel blocker	13 (52.0%)	14 (56.0%)	33 (41.8%)	29 (36.7%)
PGE infusion (intermittent)	0	0	0	0
Corticosteroids (prednisolone)	1 (4.0%)	2 (8.0%)	19 (24.1%)	23 (29.1%)
Conventional immunosuppressive ²	2 (8.0%)	3 (12.0%)	22 (27.9%)	30 (38.0%)
bDMARD ³	0	0	0	1 (1.3%)

Dialysis	0	0	0	0
Renal transplant	0	0	0	0
Heart lung transplant	0	0	0	0
Bone marrow transplant	0	0	0	0
Pacemaker	0	1 (4%)	0	0
Implantable defibrillator	0	0	0	0
Hospital admissions in the 12 months before index visit*	8 (32.0%)	7 (33.3%)	37 (53.6%)	29 (49.2%)

RHC, right heart catheter; PAH, pulmonary arterial hypertension; FC, functional class; NOAC, new oral anticoagulants; PGE, prostaglandin E; bDMARD, biologic disease-modifying anti-rheumatic drug

¹22 patients were missing data for index visit so data from previous visit were used

²methotrexate, leflunomide, azathioprine, penicillamine, hydroxychloroquine, mycophenolate, cyclophosphamide, calcineurin inhibitors, IV immunoglobulin

³TNF inhibitor, anti-CD20, tocilizumab, abatacept, B cell modulators

*Sample size differs from heading: FC I/II n = 25, FC III/IV n = 69 (first PAH visit). FC I/II n = 21, FC III/IV n = 59 (index visit)

These patients had a range of other co-morbidities, such as ILD, gastro-oesophageal disease, faecal incontinence, digital ulcers, synovitis, cardiovascular disease and COAD (Table 5).

Table 5: Co-morbidities of patients with RHC-defined PAH according to functional class (at the index visit)

	FC I/II n = 25	FC III/IV n = 79	p value	Samples sizes, (if different from n in table heading)
Interstitial lung disease	9 (39.0%)	30 (38.0%)	0.859	
Osesophageal disease (GOR, dysmotility, stricture and/or Barret's)	13 (52.0%)	38 (48.1%)	0.734	
GAVE	4 (16.0%)	9 (11.4%)	0.544	
IV TPN or PEG feeding	1 (4.0%)	1 (1.3%)	0.386	
Anal incontinence	12 (48.0%)	29 (38.2%%)	0.417	FC I/II n = 25, FC III/IV n = 76
Renal crisis	0	2 (2.5%)	0.422	
Digital ulcers	18 (72.0%)	43 (55.1%)	0.135	
Gangrene/autoamputation	1 (4.0%)	13 (16.9%)	0.104	FC I/II n = 25, FC III/IV n = 77
Synovitis	8 (32.0%)	35 (45.5%)	0.237	FC I/II n = 25, FC III/IV n = 77
Myositis	0	3 (3.8%)	0.323	
Coronary artery stent/plasty or CABG or valvular surgery	4 (16.0%)	15 (19.0%)	0.736	
Myocardial infarction	4 (16.0%)	13 (16.4%)	0.428	
Peripheral vascular disease	0	11 (14.7%)	0.042	FC I/II n = 25, FC III/IV n = 75
TIA/CVA	1 (4.0%)	4 (5.3%)	0.499	FC I/II n = 25, FC III/IV n = 75
Diabetes	1 (4.0%)	4 (5.3%)	0.499	FC I/II n = 25, FC III/IV n = 75
COAD	5 (20.0%)	10 (13.3%)	0.370	FC I/II n = 25, FC III/IV n = 75

RHC, right heart catheter; PAH, pulmonary arterial hypertension; FC, functional class; GOR, gastro-oesophageal reflux; GAVE, gastric antral vascular ectasia; IV, intravenous; TPN, total parenteral nutrition; PEG, percutaneous enteric gastrostomy; CABG, coronary bypass graft; TIA, transient ischaemic attack; CVA, cerebrovascular accident; COAD, chronic obstructive airways disease.

DISCUSSION

Since the inception of the ASCS in 2007 to 2016, a new diagnosis of WHO Group I PAH has been made in 160 of 1636 patients with SSc or MCTD as a result of active risk assessment, with a prevalence of 11.8% (11). By December 2017, 244 patients have been diagnosed with PH by RHC, of whom 209 had Group I PAH. During the period of July 2016 to June 2017, 116 patients with PH were alive, of whom 104 had PAH. At an index visit between June 2016 and December 2017, 79 were in FC III or IV. These patients had more severe disease based on estimated systolic PAP on TTE and 6MWT distance. Approximately half were on dual or triple therapy at the index visit compared with 36% of those in FC I/II at the index visit. Only two patients with PH due to other causes (left heart disease) were receiving PAH therapy, funded from non-PBS sources.

Although assessment of outcomes is beyond the scope of this analysis, PBS-reimbursed PAH therapy is limited to patients in FC III and IV, but approximately a quarter of patients were in FC I/II at the time of the index visit suggesting improvement in FC since initiation of PAH therapy. The mean follow up was approximately 5 years which is substantially longer than the prognosis of untreated PAH. Being a cross-sectional analysis, this cohort included some with longstanding disease. It is well-recognised that patients with prevalent PAH have a survival bias that can skew outcome analyses (12). Although all the patients included in this analysis had been followed from the time of diagnosis, this bias cannot be excluded.

The number of patients with RHC demonstrated PH due to left heart disease or ILD is quite low in this cohort. This may reflect low rates of referral for RHC of patients suspected to have PH due to these indications for which PAH vasodilator therapy is not PBS reimbursed, rather than low rates of these forms of PH in this cohort.

Note that the ASCS is a dynamic registry with data collected in a real-life setting and hence not all annual visits occur at the scheduled time. Hence the longer period over which an index visit was identified ensured that at least one representative visit was included for each patient. Drug use is recorded annually at which time it is possible to determine when two or more drugs are

taken concurrently but not at which stage they were commenced e.g. for how long monotherapy continued before another drug was added. Nor is it possible to identify the exact sources of these drugs. Anecdotally, most patients on an ERA receive it from the PBS and the second drug, usually a PDE5 inhibitor is obtained from a local hospital, a Special Access Scheme or is self-funded.

It is also worth noting that following publication of the ECS/ERS guidelines in 2015, the uptake of initial combination has increased. It is not possible to draw conclusions about changes in prescribing patterns in this cross-sectional analysis. Finally, patients seen at ASCS centres are not recruited to the Registry of the Australian New Zealand Pulmonary Hypertension Society (PHSANZ) in order to avoid duplicate reporting.

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APPENDICES

Appendix I: Functional class of patients with RHC-defined PAH at the time of diagnosis/first visit where PAH drugs were given.

Functional class	No. of patients n = 104
I	0
II	1 (1.0%)
III	80 (76.9%)
IV	11 (10.6%)
Missing	12 (11.5%)

Appendix II: PAH specific therapies used by patients on monotherapy with RHC-defined PAH, according to functional class at the index visit

PAH Therapy	FC I/II at index visit n = 16	FC III/IV at index visit n = 39
Bosentan	5 (31.3%)	9 (23.1%)
Ambrisentan	3 (18.8%)	5 (12.8%)
Macitentan	7 (43.8%)	19 (48.7%)
Sildenafil	1 (6.3%)	4 (10.3%)
Tadalafil	0	2 (5.1%)

Appendix III: PAH specific therapies used by patients on dual therapy with RHC-defined PAH, according to functional class at the index visit

PAH Therapy	FC I/II at index visit n = 8	FC III/IV at index visit n = 35
Bosentan Sildenafil	0	7 (20.0%)
Ambrisentan Sildenafil	0	5 (14.3%)
Macitentan Sildenafil	5 (62.5%)	15 (42.9%)
Ambrisentan Tadalafil	2 (25.0%)	0
Macitentan Tadalafil	1 (12.5%)	7 (20.0%)
Macitentan Riociguat	0	1 (2.9%)

Appendix IV: PAH specific therapies used by patients on triple therapy with RHC-defined PAH, according to functional class at the index visit

PAH Therapy	FC I/II at index visit n = 1	FC III/IV at index visit n = 5
Bosentan Sildenafil Epoprostenol	0	2 (40.0%)
Bosentan Sildenafil Selexipag	0	1 (20.0%)
Ambrisentan Tadalafil Selexipag	1 (100%)	0
Macitentan Sildenafil Epoprostenol	0	1 (20.0%)
Macitentan Sildenafil Selexipag	0	1 (20.0%)