Screening for pulmonary arterial hypertension in patients with scleroderma—a New Zealand perspective

Sanjib K Ghosh, Michael M Corkill, Hamish H Hart, Kristine P Ng

Abstract

Background Pulmonary arterial hypertension (PAH) in scleroderma (SSc) patients is a devastating complication with high mortality if untreated. Early recognition and specific treatment of PAH may improve outcome. Regular interval screening for PAH is generally recommended in scleroderma patients especially with the availability of emerging new therapies. The aim of this study is to determine the self-reported screening and treatment practices for SSc-PAH amongst rheumatologists in New Zealand (NZ).

Methods An anonymous online questionnaire survey was emailed to all rheumatologists in New Zealand.

Results Responses were received from 65% (39/60) of rheumatologists. The majority of patients had limited SSc (lcSSc) (57%) versus diffuse SSc (dcSSc) (34%). Twelve percent of patients had PAH. Eighty-two percent of rheumatologists screened for PAH in all SSc patients regardless of symptoms. The most commonly used screening modalities were pulmonary function tests (PFT) (97%) followed by clinical examination (95%) and echocardiogram (TTE) (92%). The majority of rheumatologists performed screening tests on a yearly basis (80% used PFT and 64% used TTE). A right heart catheter was used to confirm PAH in 70% of patients. Sixty-four percent of rheumatologists extend screening interval time if their patients were clinically stable. The most common PAH-specific therapy used was sildenafil (57%) followed by bosentan (19%). Sixty-four percent of rheumatologists supported a national PAH-SSc screening guideline.

Conclusion This study has shown a wide variability of how NZ rheumatologists screen for PAH in scleroderma patients. The development of a PAH-SSc guideline for screening and diagnosis may help standardise treatment practices in NZ.

Scleroderma is an autoimmune connective tissue disease of unknown aetiology with an estimated prevalence of 19–75 cases per 100,000.1 It has the potential to involve multiple systems. Scleroderma is generally classified into two subgroups; diffuse (dcSSc) and limited scleroderma (lcSSc) depending on the extent of skin involvement and serological pattern. Pulmonary complications are relatively common with reports of up to 26% of patients developing pulmonary arterial hypertension (PAH) and up to 40% developing interstitial lung disease (ILD).2-5

Pulmonary arterial hypertension (PAH) is a devastating complication and leading cause of death in up to 30% of patients in 2 years if left untreated.6-8 The prognosis is worse in patients with ILD associated PAH compared to PAH alone with a five-fold increase in risk of death.8 PAH is often under-recognised because of non-specific symptoms.9

With recent advances in PAH-SSc therapy and evidence that early recognition and treatment reduces disease progression and improves long-term outcomes, it is important to diagnose PAH-SSc early in the course of the disease. Routine screening for PAH, even in asymptomatic patients, has assumed greater importance. Yearly echocardiogram and pulmonary function tests (PFT) with diffusion capacity for carbon monoxide (DLCO) are generally recommended.

The management of PAH in scleroderma patients often requires multidisciplinary coordination between rheumatologists, respiratory physicians and cardiologists. Early intervention with PAH-specific treatment is essential to improve outcome. The prevalence of screening and treatment practices amongst rheumatologists in New Zealand (NZ) for PAH in scleroderma patients is unknown.

This study aims to determine self-reported screening, diagnosis and treatment practices for SSc-PAH amongst rheumatologists in NZ.

Methods

We surveyed 60 rheumatologists in NZ through an online questionnaire using website http://www.surveymonkey.com. The email contacts were obtained from the New Zealand Rheumatology Association membership. We emailed a questionnaire comprising of 10 questions (Figure 1). The results were analysed.

Figure 1. Questionnaire

1. Please estimate the number of SSc patients in your rheumatology practice?

2. How many of your SSc patients have interstitial lung disease? Please state number.

3. How many of your SSc patients have Pulmonary Arterial Hypertension (PAH)? Please state number.

4. Of the patients diagnosed with PAH, how many have had a right heart catheter study? Please state number.

5. Do you routinely screen your SSc patients for PAH? If "No" please omit question 6 & 7.

6. If you do screen, please outline which of the following methods do you use and how often? Please select as many as you like from the following: history & examination, pulmonary function tests (PFT) with diffusion capacity for carbon monoxide (DLCO), transthoracic echocardiogram (TTE), electrocardiogram (ECG) and six minute walk test (6MWT).

7. Do you extend the screening time if your patients are stable clinically? If yes. Please indicate how your screening time is changed.

8. How many of your SSc-PAH patients are treated with a pulmonary vasodilator, anticoagulant or both? Please state number.

9. For those SSc-PAH patients who are on a pulmonary vasodilator please specify number of patients on endothelin receptor antagonists (e.g. Bosentan), sildenafil and prostacycin analogues (Iloprost).

10. Do you feel that a national NZ PAH screening guideline will be helpful? Please specify reason.

Results

Thirty-nine rheumatologists (65%) responded to our survey. The majority of patients had lcSSc (n=301/525, 57%) followed by dcSSc (n=176/525, 34%) and 9% (n=48/525) had overlap of connective tissue diseases. The mean number of patients for an individual rheumatologist was 8 (range 0–20) for lcSSc and 5 (range 0–20) for
dcSSc. Interstitial lung disease was present in 20% (n=106/525) of patients and 12% (n=63/525) had PAH.

Table 1 displays the self-reported screening patterns for PAH in SSc patients depending on symptoms. Eighty-two percent of rheumatologists screened all SSc patients (limited and diffuse) regardless of symptoms. Five percent of rheumatologists screened only symptomatic patients in both groups. Another 5% of rheumatologists screened all dcSSc and symptomatic lcSSc patients only. Two rheumatologists do not screen lcSSc patients at all.

Table 2 demonstrates a wide variability of different investigations and frequency of tests used for PAH screening among rheumatologists. Ninety-seven percent (n=38/39) of rheumatologists preferred PFT with DLCO as a screening test. Of these, 82% of rheumatologists performed this test yearly.

Ninety-five percent (n=37/39) of rheumatologists conducted clinical examination for screening and of these, 59% performed this 6-monthly. Ninety-two percent (n=36/39) of rheumatologists used echocardiogram as a screening method and of these, 64% ordered this test yearly.

Twelve rheumatologists requested yearly electrocardiogram (ECG). Twenty-six percent (n=10/39) of rheumatologists performed the 6-minute walk test (6MWT) for screening, of which 18% ordered this yearly.

Table 1. Screening patterns of rheumatologists in diffuse and limited scleroderma patients depending on symptoms

<table>
<thead>
<tr>
<th>Diffuse scleroderma</th>
<th>Limited scleroderma</th>
<th>Number of rheumatologists (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients regardless of symptoms</td>
<td>All patients regardless of symptoms</td>
<td>32 (82)</td>
</tr>
<tr>
<td>Symptomatic patients only</td>
<td>Symptomatic patients only</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Symptomatic patients only</td>
<td>All patients regardless of symptoms</td>
<td>1 (2)</td>
</tr>
<tr>
<td>All patients regardless of symptoms</td>
<td>Symptomatic patients only</td>
<td>2 (5)</td>
</tr>
<tr>
<td>All patients regardless of symptoms</td>
<td>No patients screened</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Symptomatic patients only</td>
<td>No patients screened</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>
Table 2. Methods and frequency of screening

<table>
<thead>
<tr>
<th>Method of screening</th>
<th>Less than 6 monthly n (%)</th>
<th>6 monthly n (%)</th>
<th>Yearly n (%)</th>
<th>2 yearly n (%)</th>
<th>Range in months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFT with DLCO*</td>
<td>2/38 (5)</td>
<td>31/38 (82)</td>
<td>5/38 (13)</td>
<td></td>
<td>6 to 60</td>
</tr>
<tr>
<td>History &amp; Examination</td>
<td>7/37 (19)</td>
<td>23/37 (62)</td>
<td></td>
<td></td>
<td>2 to 12</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>25/36 (69)</td>
<td>11/36 (31)</td>
<td>1/12 (8)</td>
<td></td>
<td>12 to 24</td>
</tr>
<tr>
<td>ECG**</td>
<td>11/12 (92)</td>
<td>1/12 (8)</td>
<td></td>
<td></td>
<td>12 to 24</td>
</tr>
<tr>
<td>6MWT***</td>
<td>7/10 (70)</td>
<td>2/10 (20)</td>
<td></td>
<td></td>
<td>4 to 24</td>
</tr>
</tbody>
</table>

*PFT with DLCO=Pulmonary function tests with diffusion capacity for carbon monoxide, **ECG=Electrocardiogram, ***6MWT=6-minute walk test

Table 3. Extension of screening interval time

<table>
<thead>
<tr>
<th>Method of screening</th>
<th>Number of rheumatologists extending screening time n=39 (%)</th>
<th>6 to 12 months n=39 (%)</th>
<th>12 to 24 months n=39 (%)</th>
<th>Range (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx &amp; Ex*</td>
<td>23 (59)</td>
<td>12 (30)</td>
<td></td>
<td>3 to 12</td>
</tr>
<tr>
<td>PFT with DLCO**</td>
<td>14 (36)</td>
<td>7 (18)</td>
<td>2 (5)</td>
<td>6 to 36</td>
</tr>
<tr>
<td>ECG§</td>
<td>5 (13)</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td>12 to 72</td>
</tr>
<tr>
<td>6MWT§§</td>
<td>4 (10)</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td>6 to 36</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>14 (36)</td>
<td>8 (21)</td>
<td></td>
<td>12 to 36</td>
</tr>
</tbody>
</table>

* Hx & Ex=History and examination, ** PFT with DLCO=Pulmonary function test with diffusion capacity for carbon monoxide, § ECG=Electrocardiogram, §§6MWT=6-minute walk test

Table 4. Medications used for pulmonary arterial hypertension in scleroderma patients

<table>
<thead>
<tr>
<th>Medications</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>36 (57)</td>
</tr>
<tr>
<td>Bosentan</td>
<td>12 (19)</td>
</tr>
<tr>
<td>Prostacyclin analogue</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>24 (38)</td>
</tr>
<tr>
<td>Both (pulmonary vasodilators and anticoagulation)</td>
<td>24 (38)</td>
</tr>
<tr>
<td>None</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

Sixty-four percent of rheumatologists extended their screening interval time provided their patients were clinically stable. Fifty nine percent of rheumatologists extended their clinical examination interval time and 30% extended the interval period from 6 months to 1 year.

Thirty-six percent of rheumatologists extended screening interval time for PFT with DLCO and half of them changed this interval from yearly to 2-yearly. Thirty-six percent of rheumatologists extended screening interval time for echocardiogram and 21% changed the screening interval from yearly to 2-yearly.
Thirteen percent and 10% rheumatologists extended their screening interval time for ECG and 6MWT respectively and almost half of them changed the interval time from yearly to 2-yearly (Table 3). Seventy percent of SSc-PAH patients were diagnosed by a right heart catheter (RHC) study.

In terms of PAH-specific treatment, 57% patients received sildenafil. Twenty four patients received anticoagulation in combination with other PAH-specific treatment. Only 12 patients and 8 patients received treatment with bosentan and prostacyclin analogue respectively. Five percent of patients did not receive any form of treatment (Table 4).

**Discussion**

Our descriptive study has shown that there is a wide variation of screening and treatment practices of PAH in SSc patients among NZ rheumatologists. Scleroderma patients have an increased risk of cardiopulmonary and other systemic organ involvement.

The mortality from scleroderma renal crisis has improved significantly since the advent of angiotensin converting enzyme\(^ {17}\) but mortality from lung involvement remains very high if untreated.\(^ {18}\) A number of studies recommend regular interval screening for early detection and introduction of specific treatments to improve outcome.\(^ {10-13}\)

Our study revealed that the majority of rheumatologists (82%) screen all their SSc patients for PAH regardless of symptoms using different methods, with no consistent interval between screenings. The number of rheumatologists screening for PAH in SSc patients has increased significantly since a prior audit conducted from 1999 to 2004\(^ {19}\)

The previous audit aimed to look at screening practice of SSc related lung disease in a single rheumatology tertiary centre. In that audit, only 50% of patients had echocardiographs performed. None of the patients in that audit were on specific PAH medications as the drugs were not funded at that time.

Our study has shown that NZ rheumatologists screening practices for PAH have changed with 92% of rheumatologists using echocardiograph as a screening test for PAH.

The screening interval time varied from months to years. The most frequently used screening tests are PFT with DLCO (97%) followed by clinical examination (95%) and echocardiogram (92%). Most rheumatologists are screening six monthly to yearly depending on which investigation is used.

Our study found that lcSSc patients are not screened as routinely compared to dcSSc patients. In the previous audit, limited SSc patients were also not screened as rigorously as diffuse SSc patients for any scleroderma related lung disease (67% versus 90%)\(^ {19}\). The lcSSc patients require regular screening as the prevalence of PAH increases with prolonged duration of disease in lcSSc patients.

This study has highlighted that a small minority of rheumatologists (5%) do not screen for PAH in lcSSc at all.
Current screening recommendations for PAH in SSc patients are largely based on consensus. A variety of screening recommendations have been published by organisations such as the American College of Cardiology Foundation/American Heart Association and the European Society of Cardiology/European Respiratory Society (ESC/ERS).20,21

Most international screening guidelines for PAH in SSc patients recommend yearly echocardiogram and PFT with DLCO15. A recent study observed a better prognosis in patients identified in an active screening programme compared to those in routine clinical practice.22

This study has shown that a significant number of rheumatologists are not following international guidelines in screening for PAH-SSc. There may be a variety of factors for this including lack of resource, in particular constraint to investigations such as echocardiogram, lack of specialised PAH cardiothoracic units in smaller NZ regions and no clear guidelines on screening in the NZ setting.

The first evidenced based PAH detection study was published recently using a two-step internally validated algorithm. The algorithm uses simple clinical data and non-invasive tests to determine the likelihood of PAH and cut-off points for decision to refer a patient to echocardiograph and subsequent RHC.23 The DETECT algorithm may optimise the use of already limited resources by identifying the appropriate high risk patient for echocardiograph and RHC. The application of classic screening criteria such as the Wilson and Jungner criteria will be more applicable in the future as more evidence based data is available to guide the principles of screening24.

The 6-minute walk test (6MWT) is an outcome measure that is used in most PAH studies. Some groups suggest that it is a highly reproducible test in SSc-ILD patients, used as a primary outcome measure in the management of PAH in scleroderma patients.25 However, this test has never been validated in the SSc population and the interpretation of this test can be difficult in SSc patients. SSc patients have other factors such as arthritis and a low fitness level that will affect the reproducibility of this test.

Furthermore, it is difficult to obtain a good measure of oxygen saturations with a finger probe in SSc patients due to poor peripheral circulation. Wilsher and colleagues have suggested using forehead probe to measure oxygen saturations26. In our study only 26% of rheumatologists are performing the 6MWT and 18% of rheumatologists are requesting this test annually.

The 6MWT is often not available in peripheral regions of NZ where there is no specialised respiratory unit. We suspect this is one of the main reasons as to why this test is under-utilised.

The RHC study is the gold standard for diagnosing PAH. Only 70% patients are reported as being diagnosed with PAH by RHC study. This may be due to the difficult access of this specialised test. Another possible explanation is that patients with mild to moderate PAH with good exercise tolerance have yet to proceed to confirmatory RHC study.

Our study has found no consistency with regards to increasing screening interval time amongst rheumatologists if their patients are clinically stable. Two thirds of
rheumatologists extended the screening interval time for their patients if they are clinically well. However there was a huge variability of increasing screening interval time depending on which investigation is used – range from few months to years.

A number of studies have clearly demonstrated that early intervention with specific treatment for SSc-PAH patients improves outcome.\textsuperscript{15,16} The EULAR recommendations for treatment of systemic sclerosis emphasise the benefit of PAH-specific treatment.\textsuperscript{27} PAH-specific treatment is currently funded by PHARMAC (via an expert panel) and available in NZ.

Sildenafil is a phosphodiesterase 5 inhibitor, is funded for PAH patients with New York Heart Association (NYHA) class III and IV symptoms. Bosentan, an endothelial receptor antagonist (ERA) is available for those who have not responded to sildenafil. In our study, the majority of patients (57\%) received sildenafil and followed by bosentan (19\% of patients) which reflects the local funding criteria guidelines.

Our questionnaire had a good response rate from NZ rheumatologists compared to a similar study in Australia.\textsuperscript{9} We feel that this study has highlighted a wide variability of how SSc patients are screened for PAH amongst NZ rheumatologists and provides a snapshot of current PAH-SSc practices in NZ.

One of the limitations of our study is that this is a small study and it was not designed to identify barriers to performing screening and diagnostic tests. It is also likely (although not addressed in the study questionnaire) that stricter criteria for PAH-SSc patients to qualify for treatment (compared to many overseas countries) may influence NZ Rheumatologists’ screening practices.

Resource constraint is a major issue revealed from the comments made by rheumatologists. The majority (64\%) of rheumatologists believe a national screening guideline for PAH-SSc would be valuable and in line with international recommendations. PAH-specific medications are currently only funded for symptomatic patients in NZ. Therefore, screening asymptomatic patients would not be cost effective.

The application of a validated breathless assessment questionnaire may be useful to identify the patients that will need further tests to screen for PAH.\textsuperscript{28} One of the difficulties in setting up a national screening guideline is the variability of access for tests such as PFT and echocardiograph in NZ regions. Some regions of NZ have no or very limited access to these investigations (personal communication).

In summary our study recognises the wide variability of screening and treatment practices for PAH-SSc patients amongst NZ rheumatologists. There may be a role for national screening guideline to standardise our approach in the management of PAH-SSc patients.

\textbf{Competing interests:} Nil.

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References:


