Lack of correlation of the Health Assessment Questionnaire Disability Index with lung parameters in systemic sclerosis associated pulmonary arterial hypertension

S. Chow, J. E. Pope, S. Mehta

Departments of Rheumatology and Respirology, Schulich School of Medicine, University of Western Ontario, London, Ontario, Canada.

Abstract

Objective

Pulmonary arterial hypertension (PAH) affects the quality of life (QoL) and the ability to perform the activities of daily living (ADLs) in patients with systemic sclerosis (SSc). We determined whether the Health Assessment Questionnaire - Disability Index (HAQ-DI), a self-assessment measure of function, correlates with a patient's PAH status in a population of SSc patients with PAH.

Methods

Forty-one patients from one centre with systemic scleroderma, dyspnea and PAH were included. All patients filled in a HAQ-DI, and underwent evaluation with pulmonary function tests (PFTs), 6-minute walk distance (6MWD), degree of dyspnea (Borg dyspnea index), NYHA functional class, and expert PAH physician global assessment every 6 months. Change in HAQ DI was studied to determine relationship to changes in PAH.

Results

The HAQ-DI scores had no significant correlation with PAH, including NYHA functional class ($r=0.38$, $p=0.39$), Borg dyspnea index ($r=0.60$, $p=0.37$), 6MWD ($r=-0.04$, $p=0.86$), % predicted DLCO ($r=0.31$, $p=0.25$), % predicted FVC ($r=0.02$, $p=0.93$), and expert PAH physician global assessment ($r=0.06$, $p=0.97$).

Conclusion

HAQ-DI is not an adequate measure of PAH status in SSc patients with PAH. Although PAH causes severe morbidity and death, changes in PAH severity were not reflected in an overall functional status change as assessed by the HAQ-DI. Thus, HAQ-DI changes do not reflect PAH status in SSc.

Key words

Systemic sclerosis, pulmonary arterial hypertension (PAH), Health Assessment Questionnaire Disability Index (HAQ-DI).

Shirley Chow, MD
Janet E. Pope, MD, FRCPC
Sanjay Mehta, MD, FRCPC

Dr. Chow's work was supported by the American College of Rheumatology (ACR) Medical Student Summer Clinical Preceptorship and unrestricted educational/research funds from the Department of Medicine, The University of Western Ontario.

Please address correspondence and reprint requests to:
Dr. Janet Pope, St. Joseph's Health Care, 268 Grosvenor St., London, ON, Canada, N6A 4V2.
E-mail: janet.pope@sjhc.london.on.ca

Received on February 19, 2008; accepted in revised form on May 19, 2008.

Conflict of interest: Dr. S. Mehta has received consultancy and speaking fees from Actelion, GSK, Pfizer and United Therapeutics, and clinical investigator fees/research grants from Actelion, GSK, Lilly, Pfizer and United Therapeutics. Drs. S. Chow and J. Pope have declared no competing interests.

Introduction

Systemic sclerosis (SSc, scleroderma) is an autoimmune connective tissue disorder characterized by widespread visceral and cutaneous fibrosis and vascular pathology. One of the severe organ involvements is pulmonary arterial hypertension (PAH). PAH is defined as a mean pulmonary artery pressure greater than 25mmHg at rest in the absence of significant left-sided heart disease, lung disease with hypoxemia or thromboembolic disease (1). PAH is a frequent and serious pulmonary complication affecting 10-20% of SSc patients (2, 3) and is a major cause of death in SSc (4). The median survival if untreated is less than two years after diagnosis and almost all SSc patients affected by PAH die within five years if untreated (5).

Symptoms of PAH include dyspnea, fatigue and impaired exercise tolerance. These symptoms are not specific for PAH and may be due to other lung diseases in scleroderma patients, such as pulmonary fibrosis. Impaired exercise capacity may also be due to other SSc associated morbidity: arthritis, weight loss, deconditioning, cardiomyopathy and myopathy. The diagnosis of scleroderma associated pulmonary arterial hypertension (SSc-PAH) is thus often delayed. Furthermore, many patients with scleroderma develop dyspnea gradually and adapt to it (6). They may presume that their symptoms are part of SSc and unconsciously limit their activities, such that they do not readily recognize that they are short of breath. This is detrimental since survival declines dramatically in SSc patients who are in New York Heart Association (NYHA) Class III and IV at diagnosis (7). It is crucial to identify patients who may have PAH early so they can receive timely adequate treatment (6). Rather than just asking patients if they are short of breath, specific questions about function asked in the Health Assessment Questionnaire Disability Index (HAQ-DI), such as running errands or doing chores, may be helpful to determine whether patients are indeed limited (6).

The HAQ-DI has been used to measure disease status changes in patients with SSc (8). It is a patient oriented functional assessment tool used to measure functional status by assessing the activities of daily living over the past week. It is self-administered and validated in many rheumatic diseases. It questions 8 dimensions including dressing and grooming, arising, eating, walking, hygiene, reach and grip. Difficulty is rated on a 4 point scale (0-3) as none, mild, much or inability to perform. The HAQ-DI is a good predictor of future disability.

The HAQ-DI has been validated in SSc (9-17) and is used in SSc clinical trials (18). HAQ-DI scores have demonstrated sensitivity over time, paralleling SSc disease activity/severity over the duration of follow-up (11. 13). Change in the HAQ-DI and change in the total skin score were the only 2 variables that were significantly predictive of physicians' global assessments at 24 months in early diffuse SSc, thus indicating the importance of functional disability in physician assessment of early diffuse SSc (13). Although scores are variable, the mean scores are close to 1.0 and thus indicate moderate disability.

A decline in PAH is often accompanied by a decline in ability to perform daily activities. The purpose of our study was to determine whether changes in HAQ-DI correlate with the severity of PAH in a population of SSc patients with PAH.

A secondary aim was to correlate functional status and disability using the HAQ-DI before and after treatment with bosentan (Tracleer), an endothelin receptor antagonist used for the treatment of PAH including in SSc. Bosentan has been shown to prevent deterioration in 6-minute walking distance, significantly improving symptoms including functional class and reducing the risk of clinical worsening at 24 weeks in SSc patients with advanced PAH (19).

Materials and methods

SSc patients followed at the St. Joseph's Health Care Rheumatology Clinic complete a HAQ-DI at every visit. Patients included in the study required a diagnosis of SSc, as defined by the American College of Rheumatology classification criteria, or CREST syndrome

(calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias) if they did not meet ACR criteria (20).

PAH was diagnosed according to the Venice criteria (21), and these were reviewed every 6 months to assess PAH severity. Severity of PAH was assessed by: 1) New York Heart Association (NYHA) functional class, which has 4 categories (Class I has no limitation of physical activity, Class II has limitation with strenuous physical activity, Class III has limitation with mild physical activity, and Class IV is when the patient is unable to carry out any physical activity without symptoms); 2) 6-minute walk distance (6MWD), which is a non-invasive method for assessment of severity as well as for serial monitoring and is related to PAH morbidity (22, 23); 3) Borg Dyspnea Index, which is a numerical scale for assessing perceived dyspnea (breathing discomfort) with a scale of 0=no breathlessness at all, 0.5=very very slight (just noticeable), 1=very slight , 2=slight breathlessness, 3=moderate, 4=somewhat severe, 5=severe Breathlessness, 7=very severe breathlessness, 9=very, very severe (almost maximum) and 10=maximum; 4) changes in global status from 1 - marked clinical improvement, 2 - no change, and 3 - clinical worsening, as rated by the physician; and 5) Pulmonary function tests (PFTs), specifically pulmonary diffusing capacity for carbon monoxide (DLCO) and forced vital capacity (FVC). Impaired DLCO is common in symptomatic PAH in SSc patients due to obliteration of the small pulmonary arteries (24). It is non-specific and can be impaired in PAH (correlating with severity of PAH, but also abnormal in interstitial lung disease, smoking and other causes of impaired gas exchange).

Demographic and clinical data were collected retrospectively by chart review. The correlation between HAQ-DI and initial PAH parameter measurements done within 3 months of HAQ-DI was studied. Changes in HAQ-DI were compared with changes in PAH outcomes. In general, aside from PAH, other SSc treatment was stable, for example immunosuppressants (rarely used), PPI's and RP treatment with calcium channel blockers.

JMP 4 statistical software was used to analyze data. Bivariate fit analysis was used to compare continuous variables such as 6MWD and PFT measurements. Univariate analysis tests were used for dichotomous variables including NYHA class, Borg dyspnea index, and changes in global status. We plotted a one-way ANOVA and linear fit to find the r square and *p*-values. A *p*-value of <0.05 was considered statistically significant. Results were given in mean±SD where appropriate.

Table I. Baseline characteristics of subjects.

Baseline variables	All patients (n=41)	Diffuse cutaneous SSc (n=12)	Limited cutaneous SSc (n=29)
Age, years (±SD)	59.8±12.5	56.7±12.0	61.0±12.4
% overall of SSc-PAH	100	29	71
% female	80	71	83
SSc Duration, years (±SD)	14.4±11.2	11.4±7.1	16.4±12.1
Died during follow-up (%)	15	25	10
Medications(n)			
Calcium channel blocker	3	0	3
Vasodilator	8	2	6
Sildenafil	2	0	2
Bosentan	14	3	11

Results

The baseline demographics of SSc subjects with PAH are summarized in Table I. Forty-one SSc patients had dyspnea and PAH (from Class I to IV at PAH diagnosis; 70% in Class III). Patients ranged in age from 38 years to 84 years, with a mean age of 59

Table II. Changes in HAQ-DI, PAH, and pulmonary physiologic parameters in SSc patients over 6 months.

	All Patients		Diffuse SSc (n=14)		Limited SSC (n=28)	
	Baseline	Change over 6m	Baseline	Change over 6 m	Baseline	Change over 6 m
HAQ-DI (0-3)	1.35 ± 0.75	0.22 ± 0.48*	1.22 ± 0.69	0.01 ± 0.41*	1.41 ± 0.78	0.34 ± 0.48*
NYHA class (1-4)	2.65 ± 0.58	0 ± 0.67	2.5 ± 0.76	0 ± 0.87	2.60 ± 0.63	0.13 ± 0.74*
NYHA Class						
% Class I	4	0	0	0	7	0
% Class II	26	39	25	33	27	50
% Class III	70	57	75	60	67	50
% Class IV	0	4	0	7	0	0
6MWD (meters)	387 ± 79	-18 ± 76*	387 ± 111	-38 ± 138*	389 ± 72	-11 ± 41*
Borg Dyspnea Index (0-10)	4.00 ± 2.09	0.39 ± 1.79*	4.4 ± 1.67	0.60 ± 1.52*	3.92 ± 2.35	0.33 ± 2.01*
FVC (% predicted)	89.4 ± 24.7	-2.47 ± 14.7*	98.5 ± 18.6	-6.33 ± 9.75*	85.2 ± 26.6	-0.69 ± 16.5*
DLCO (% predicted)	52.1 ± 25.9	-2.67 ± 12.1*	39.0 ± 20.4	6.33 ± 12.35	62. 6 ± 26.7	-8.10 ± 7.49*
PAH expert global assessment (1- better; 2 - same; 3 - worse)	2.10 ± 0.64	0 ± 0.64*	2.29 ± 0.76	-0.43 ± 0.53	2.00 ± 0.60	+0.17 ± 0.72*

*worsening.

Table III. Changes in NYHA Class in SSc patients with PAH over 6 months.

	Total patients		Diffuse SSc		Limited SSc	
	Baseline	Change over 6 m	Baseline	Change over 6 m	Baseline	Change over 6 m
NYHA all classes (n)	23		8		15	
Better n (%)		4 (17)		2 (25)		2 (14)
Same n (%)		16 (70)		6 (75)		10 (66)
Worse n (%)		3 (13)		0		3 (20)
NYHA class I n (%)	1 (4)		0		1	
Better n (%)		0				0
Same n (%)		0				0
Worse n (%)		1 (100)				1 (100)
NYHA II n (%)	6 (26)		2		4	
Better n (%)		0		0		0
Same n (%)		5 (83)		2 (100)		3 (75)
Worse n (%)		1 (17)		0		1 (25)
NYHA III n (%)	16 (70)		6		10	
Better n (%)		4 (25)		2 (33)		2 (20)
Same n (%)		11 (69)		4 (66)		7 (70)
Worse n (%)		1 (6)		0		1 (10)

No patients in Class IV were studied for this analysis.

Table IV. Changes in HAQ-DI in SSc patients with PAH over 6 months.

	Total patients		Diffuse SSc		Limited SSc	
	Baseline	Change over 6 m	Baseline	Change over 6 m	Baseline	Change over 6 m
HAQ-DI change	32		10		22	
>0.2 better (%)		8 (25)		4 (40)		4 (18)
Same (%)		7 (22)		2 (20)		5 (23)
>0.2 worse (%)		17 (53)		4 (40)		13 (59)

years. Thirty-three (80%) were women and 28 (68%) had limited disease. The mean±SD duration of SSc prior to study enrollment was 14.4±11.2 (SD) years and 6 died during follow-up.

Table II shows the HAQ-DI, PAH, and lung function measurements at baseline and 6 months. SSc patients with PAH had an average HAQ-DI at baseline of 1.4±0.8, indicating a moderate amount of functional disability. Over six months their HAQ worsened by an average of 0.2±0.5.

The patients' NYHA class was 2.6±0.6 at baseline and did not change appreciably after 6 months. At baseline 6MWD was 387±79 meters, and over 6 months this deteriorated by an average of 18±76 meters. Patients with diffuse disease had a greater decline, 38±138 meters, than limited disease, 11±41 meters. The Borg Dyspnea Index, a subjective measure of exertional dyspnea, showed that patients on average had very low dyspnea at baseline and this worsened slightly over 6 months. Mean FVC and DLCO both showed worsening over 6 months. There was a mild decrease in FVC. Diffuse SSc had a higher FVC than limited. At baseline, SSc patients with PAH had a low % predicted DLCO of 52.1±25.9. Patients with diffuse SSc had a lower DLCO of 39±20.4 % compared to patients with limited (% predicted DLCO was 62.6±26.7), which may have reflected that patients with severe ILD at this time were not eligible for coverage of PAH patients and thus not referred to the PAH clinic. There was no change in the average PAH expert global assessment over 6 months, although those with diffuse SSc on average improved and those with limited SSc worsened.

Table III shows SSc subjects with HAQ-DI separated by NYHA class at baseline and after 6 months. The large majority of patients stayed the same over 6 months. Of the 23 SSc subjects with PAH with a documented NYHA class at 6 months, 70% had no change in NYHA class after 6 months. Table IV shows SSc subjects with HAQ changed by >0.20 over 6 months, as this is the minimal change for significance. Half of the subjects had a worsened HAQ over 6 months, and a quarter of the subjects improved. Global assessment of SSc subjects are shown in Table V. Over 6 months, the majority of physician-rated global assessment did not change.

Using the bivariate and univariate analysis, we looked for correlations between change in HAQ with change in PAH measurements (Table VII). Change in HAQ-DI scores were compared with change in NYHA (r=0.38, p=0.39), Borg dyspnea (r=0.60, p=0.37), expert PAH physician global assessment (r=0.06, p=0.97), 6MWD (r=-0.04, p=0.86), % predicted DLCO (r=0.31, p=0.25) and % predicted FVC (r=0.02, p=0.93). Thus, the HAQ-DI scores had no meaningful clinical or

Table V. Changes in PAH expert global assessment in SSc patients with PAH over 6 months.

	Total patients		Diffuse SSc		Limited SSc	
	Baseline	Change over 6 m	Baseline	Change over 6 m	Baseline	Change over 6 m
PAH expert global assessment n	20		7		13	
Better n (%)		5 (25)		2 (29)		3 (23)
Same n (%)		9 (45)		4 (57)		5 (38)
Worse n (%)		6 (30)		1 (14)		5 (38)

statistically significant correlation with all measurements of PAH.

We studied a subset of subjects with SSc and PAH treated with bosentan (n=8) (Table VI). Although measure of PAH severity improved or stabilized, HAQ was unchanged. The NYHA class, PAH expert global assessment, 6MWD, and DLCO showed improvement after treatment with bosentan. Borg Dyspnea Index remained low and thus did not improve. There were no significant correlations between HAQ-DI change and other parameters in this small exploratory analysis.

Discussion

Pulmonary arterial hypertension (PAH) can be a disabling condition in patients with systemic sclerosis (SSc). In this study we determined whether changes in HAQ-DI correlate with the severity of PAH in a population of SSc patients with PAH. We found that HAQ-DI is not influenced by PAH in subjects with SSc-PAH including at baseline or change over 6 months.

The HAQ-DI is a musculoskeletal targeted instrument to assess function. It is used in SSc patients to capture SSc disease activity and severity. Although PAH causes severe disability and death, changes in commonly used measures of PAH severity were not reflected by changes in the HAQ-DI. This is different from the Scleroderma Lung Study which looked at HAQ-DI in SSc patients with interstitial lung disease randomized to either treatment with cyclophosphamide or placebo. Cyclophosphamide improved HAQ-DI and dyspnea, but the mechanisms may have been different. For instance, cyclophosphamide slightly improved DLCO% and dyspnea scores and also had an improvement in skin involvement, and the latter may have influenced the HAQ-DI score. This is more likely an explanation of the differences between ILD and PAH trials in SSc and their effects on HAQ, as dypnea improved in some patients in both trials but HAQ-DI only improved in the cyclophosphamide ILD SSc trial.

As the HAQ-DI is a self-administered disability index, the increase must be related to a sudden modification of the quality of life, which is rare in systemic sclerosis respiratory history. It is thus possible that this index is not well correlated with the usually gradual increase in pulmonary vascular resistance in early PAH.

PAH causes dyspnea and decreased function in SSc patients. In our study, patients with SSc-PAH had moderate functional impairment. This is reflected in the high HAQ-DI at baseline and worsening over time. They also had a high NYHA class at baseline. Indeed, many patients have historically been diagnosed at more advanced stages of their PAH. They may not have had the potential for reversibility in HAQ-DI (*i.e.*, damage with little or no disease activity), and may have had long SSc disease duration which worsens HAQ-DI over time.

PAH not only increases morbidity but it can also increase mortality in SSc patients. From our data at one centre, SSc patients with PAH were mostly older women with limited cutaneous disease, of whom 6 died during follow-up. This is consistent with previous literature that compared patients with idiopathic PAH to PAH associated with connective tissue diseases and showed that CTD-PAH patients were mainly older women with a significantly lower cardiac output and showed a trend toward

Table VI. Effects of bosentan on HAQ-DI, PAH, and pulmonary physiologic parameters in SSc patients (pre- and post-bosentan).

n=8	Pre-bosentan	Post-bosentan	Change
HAQ-DI (0-3)	1.1 ± 0.8	1.1 ± 0.8	0.0 ± 0.6
NYHA class (1-4)	3.0 ± 0.0	2.9 ± 0.4	-0.1 ± 0.4
6MWD (m)	318 ± 65	350 ± 45	32 ± 60
Borg Dyspnea Index (0-10)	0.3 ± 0.3	0.9 ± 1.2*	0.6 ± 1.4
FVC (%)	99.8 ± 24.7	99.7 ± 21.7	-0.2 ± 7.4
DLCO (%)	29.7 ± 11.3	39.6 ± 11.1	9.2 ± 10.4
PAH expert global assessment (1-3)	2.7 ± 0.5	1.3 ± 0.8	-1.3 ± 0.8

*worse.

Table VII. Change in HAQ-DI vs. change in PAH parameters in SSc subjects.

	r-value	*p*-value
NYHA class	0.38	0.39
6MWD	-0.04	0.86
Borg Dyspnea Index	0.60	0.37
% predicted FVC	0.02	0.93
% predicted DLCO	0.31	0.25
PAH expert global assessment	0.06	0.84

a shorter survival (3). In a UK registry, the average time between diagnosis of systemic sclerosis and PAH was 14 years (3). This is also consistent with our results, which show that our patients had scleroderma disease duration of 14.4 years.

In a sub-analysis, we compared the HAQ-DI and lung function tests pre and post treatment with the oral endothelin receptor antagonist bosentan. The NYHA class, 6MWD, PAH expert global assessment, and DLCO showed average improvement after treatment with bosentan. Although this is a small number of patients, it is consistent with previous studies that showed improved exercise capacity with bosentan after 20 weeks (5). We did not see improvement in the Borg dyspnea index or HAQ-DI. However there is a large standard deviation and it is conceivable that with a larger number of patients there could be a difference. We doubt that we have missed a relevant relationship in HAQ-DI as it did not improve in a large observational study of Class III-IV CTD-PAH, the majority of whom had SSc (25)

This is the first study to specifically examine whether there is a correlation between the HAQ-DI score and PAH measurements in SSc-PAH. The TRUST study looked at quality of life (by SF-36) in SSc-PAH and did not find a correlation between the HAQ and NYHA class (25). The strengths of our study include a relatively large SSc-PAH sample and the variability in our data, thus a correlation should have been found if one existed. For instance, some of SSc-PAH got better, some worsened and some stabilized. The limitations of our study were that the data were from one referral clinic, and there were some missing data. Also, some patients were not eligible for treatment to be reimbursed if they presented in Class I or II, so earlier interventions may have made treatment look more favorable in NYHA class and other parameters. Patients with significant limitations in functional class did not rate their dyspnea very high, thus demonstrating that SSc patients with PAH may adapt and not report significant dyspnea.

We conclude that the HAQ-DI is of no value as an outcome measurement or marker for SSc-PAH. Physicians who see patients with scleroderma should not rely on the HAQ-DI to reflect presence of symptoms of PAH, and should always carry a high index of suspicion for PAH.

References

1. HATANO S, STRASSER T: Primary pulmonary hypertension. World Health Organization 1975, *WHO*: Geneva, 1975.
2. GALIE N, MANES A, FARAHANI KV *et al.*: Pulmonary arterial hypertension associated to connective tissue diseases. *Lupus* 2005; 14: 713-7.
3. MUKERJEE D, ST. GEORGE D, COLEIRO B *et al.*: Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension" Application of a registry approach. *Ann Rheum Dis* 2003; 62: 1088-93.
4. ALTMAN RD, MEDSGER TA JR, BLOCH DA *et al.*: Predicators of survival in systemic sclerosis (scleroderma). *Arthritis Rheum* 1991, 34: 403-19.
5. STUPI AM, STEEN VD, OWEN GR *et al.*: Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. *Arthritis Rheum* 1986; 29: 515-24.
6. STEEN VD: The lung in Systemic Sclerosis. *J Clin Rheumatol* 2005; 11: 40-6.
7. RUBIN LJ: Primary pulmonary hypertension. *Chest* 1993; 104: 236-50.
8. MORITA Y, MURO Y, SUGIURA K *et al.*: Results of the Health Assessment Questionnaire for Japanese patients with systemic sclerosis--measuring functional impairment in systemic sclerosis versus other connective tissue diseases. *Clin Exp Rheumatol* 2007; 25: 367-72.
9. POOLE JL, STEEN VD: The use of the Health Assessment Questionnaire (HAQ) to determine physical disability in systemic sclerosis. *Arthritis Care Res* 1991; 4: 27-31.
10. MERKEL PA: Measurement of functional status, self-assessment and psychological well-being in scleroderma. *Curr Opin Rheumatol* 1998; 10: 589-94.
11. STEEN VD, MEDSGER TA JR: The value of the health assessment questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. *Arthritis Rheum* 1997; 40: 1984-91.
12. CLEMENTS PJ, WONG WK, HURWITZ EL *et al.*: Correlates of the disability index of the health assessment questionnaire: a measure of functional impairment in systemic sclerosis. *Arthritis Rheum* 1999; 42: 2372-80.
13. CLEMENTS PJ, WONG WK, HURWITZ L *et al.*: The Disability Index of the Health Assessment Questionnaire is a predictor and correlate of outcome in the high-dose versus low-dose penicillamine in systemic sclerosis trial. *Arthritis Rheum* 2001; 44: 653-61.
14. MERKEL PA, HERLYN K, MARTIN RW *et al.*: Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. *Arthritis Rheum* 2002; 46: 2410-20.
15. MOSER DK, CLEMENTS PJ, BRECHT M *et al.*: Predictors of psychosocial adjustment in systemic sclerosis. *Arthritis Rheum* 1993; 36: 1398-405.
16. ROCA RP, WIGLEY FM, WHITE B: Depressive symptoms associated with scleroderma *Arthritis Rheum* 1996 Jun; 39: 1035-40.
17. MALCARNE VL, GREENBERGS HL: Psychological adjustment to systemic sclerosis. *Arthritis Care Res* 1996; 9: 51-9.
18. HOCHBERG MC, SILMAN AJ, SMOLEN JS, WEINBLATT ME, WEISMAN MH, (Eds.): *Rheumatology* (Vol. 2), Toronto: Elsevier Limited (Mosby), 2003.
19. RUBIN LJ, BADESCH DB, BARST RJ *et al.*: Bosentan therapy for PAH. *N Engl J Med* 2002; 346: 896-903.
20. LEROY EC, BLACK C, FLEISHMAJER R *et al.*: Scleroderma: classification, subset and pathogenesis. *J Rheumatol* 1988; 15: 202-5.
21. BADESCH DB, ABMAN SH, AHEARN GS *et al.*: Medical Therapy For Pulmonary Arterial Hypertension: ACCP Evidence-Based Clinical Practice Guidelines. *Chest* 2004; 126: 35S-62S.
22. GUYATT GH, SULLIVAN MJ, THOMPSON PJ *et al.*: The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *CMAJ* 1985; 132: 919-23.
23. BARST MD, LEWIS JR, WALKER AL *et al.*: A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *NEJM* 1996 334: 296-301.
24. VARGA J: Pulmonary hypertension in systemic sclerosis: bete noire no more? *Curr Opin Rheumatol* 2002; 14: 666-70.
25. DENTON CP, POPE JE, PETER HH *et al.*: Long-term effects of Bosentan on quality of life, survival, safety and tolerability in pulmonary arterial hypertension related to connective tissue diseases. *Ann Rheum Dis* 2008; 67: 1222-8.