CHEST Online Supplement

Correlation of Cough With Disease Activity and Treatment With Cyclophosphamide in Scleroderma Interstitial Lung Disease

Findings From the Scleroderma Lung Study

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e-Appendix 1.

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e-Table 1.

SLS Inclusion Criteria

- SSc as defined by the American College of Rheumatology (E1), and classified as either limited or diffuse
- Onset of their first non-Raynaud's manifestationwithin the last 7 years
- FVC >45% and <85% predicted
- Exertional dyspnea > Grade II according to the Magnitude of Task component of the Mahler Baseline Dyspnea Index(BDI)
- Evidence of active alveolitis defined by neutrophilia ($3%) and/or eosinophilia ($2%) on bronchoalveolar lavage (BAL) and/or the presence of any groundglass opacity (GGO; hazy parenchymal opacity through which normal lung markings can be seen) on thoracic HRCT images, irrespective of the additional presence of evidence of fibrosis or honeycombing

SLS Exclusionary Criteria

- Single-breath diffusing capacity of the lung for carbon monoxide (DLCO) <30% predicted
- Forced expiratory volume of the lung during the first second (FEVI)/FVC ratio <65%
- Smoking within the past 6 months
- Significant pulmonary pathology other than interstitial lung disease on HRCT
- Pulmonary hypertension deemed to be clinically significant or requiring drug therapy
- Unexplained hematuria (>10 RBC/hpf; hematologic abnormalities (<4000 WBC/mm3, <150,000 platelets/mm3)
- Serum creatinine > 2.0 mg/dl
- Pregnancy or unwillingness to utilize appropriate contraceptive measures
- Other serious concomitant medical illness
- Medication exclusions included >10 mg/day of prednisone, prior treatment with cyclophosphamide (CYC) that exceeded 4 weeks of oral drug or 2 intravenous doses, or recent use of other potentially disease-modifying medications (azathioprine, methotrexate, D-penicillamine, etc.)

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e-Table 2. **Baseline characteristics of participants randomized into the scleroderma lung study who had 24 month evaluable data*

	All (*n = 145*)	CYC (*n = 73*)	Placebo (*n = 72*)	*P* Value (*CYC vs. Placebo*)
Age, yr	47.9 ± 1.0	47.9 ± 1.3	47.8 ± 1.5	0.9322
Female, %	69.7	76.7	62.5	0.0627
SSc duration, yr	3.2 ± 0.2	3.3 ± 0.3	3.1 ± 0.2	0.5974
With diffuse SSc, %	62.1	63.0	61.1	0.8134
FVC, % predicted	67.9 ± 0.9	67.6 ± 1.3	68.3 ± .5	0.7250
FEV_1/FVC, %	82.9 ± 0.7	82.8 ± 1.0	83.1 ± 0.9	0.8038
TLC, % predicted	69.0 ± 1.1	69.4 ± 1.5	68.7 ± 1.5	0.7308
FRC, % predicted	73.3 ± 1.6	74.6 ± 2.1	71.9 ± 2.3	0.3905
DL_{CO}, % predicted	46.9 ± 1.2	47.1 ± 1.5	45.8 ± 1.5	0.5356
Mahler BDI focal score (0–12)	5.6 ± 0.2	5.6 ± 0.22	5.6 ± 0.23	0.8504
Skin score (range, 0–51)	15.2 ± 0.9	15.9 ± 1.3	14.5 ± 1.2	0.4232
Diffuse SSc	20.9 ± 1.0	21.7 ± 1.5	20.2 ± 1.4	0.4619
Limited SSc	5.9 ± 0.5	6.1 ± 0.7	5.7 ± 0.6	0.6969
HAQ-DI (range, 0–3)	0.82 ± 0.06	0.96 ± 0.08	0.68 ± 0.08	0.0131

The mean time from diagnosis to study entry was 3.2 +/- 0.2 SEM years)

Definition of abbreviations: BDI = baseline dyspnea index; CYC = cyclophosphamide; DL_{CO} = diffusing capacity of carbon monoxide; HAQ-DI = Health Assessment Questionnaire–Disability Index; SSc = systemic sclerosis.

Plus/minus values represent means (±SEM).

*Reprinted with permission from Clements PJ, Roth MD, Elashoff R, et al; Scleroderma Lung Study Group. Scleroderma lung study (SLS): differences in the presentation and course of patients with limited versus diffuse systemic sclerosis. Ann Rheum Dis 2007; 66(12):1641-7.

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e-Table 3. *Correlation of phlegm production with other baseline variables*

		None (n =41)		Occasional (n = 63)		Frequent (n = 10)		p value*
		Mean	S.D.	Mean	S.D.	Mean	S.D.	
PFTs	FVC	67.22	13.19	69.04	12.66	61.52	12.72	0.71
	TLC	69.68	13.07	70.04	11.89	66.7	15.35	0.62
	DlCO	43.31	13.27	47.41	13.29	43.63	11.8	0.26
Health Perception	PCS	31.64	9.8	31.76	11.2	29.59	7.17	0.57
	MCS	51.84	9.66	49.07	10.22	44.67	10.65	0.06
	BDI	6	1.77	5.89	1.73	5.7	1.7	0.67
	HAQ	0.87	0.71	0.86	0.71	0.75	0.65	0.82
HRCT	MaxFib	1.97	1.03	2.18	0.99	2.2	1.03	0.39
	MaxGG	0.61	0.72	0.79	0.84	0.3	0.67	0.85
	MaxHC	47%		38%		10%		
BAL	PMN	5.2	5.72	6.37	5.61	16.01	15.52	**0.01**
	Eos	2.58	2.98	2.76	4.58	3.11	2.72	0.94
Clinical	Rodnan	15.34	10.26	12.6	10.73	13.3	10.11	0.13
	Diffuse	63%		49%		40%		0.82
	GERD	50%		57%		67%		0.93
	PPI use	54%		52%		40%		0.59

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e-Table 4. *Changes in Cough severity, frequency and phlegm production at 12 and 18 months in patients with and without GERD at baseline*

Cough	GERD	N	variable	N	mean	stdev	p-value
Severity	1. YES	106	d12	89	-0.08	0.84	0.84
			d18	66	-0.15	0.88	0.36
	2. NEW	7	d12	6	-0.17	0.41	
			d18	6	0.17	1.17	
	3. NO	44	d12	30	-0.17	0.91	
			d18	19	0.16	0.83	
Frequency	1. YES	106	d12	88	-0.07	0.88	0.86
			d18	65	-0.2	0.96	0.35
	2. NEW	7	d12	6	0	0.63	
			d18	6	0	1.1	
	3. NO	44	d12	29	-0.21	1.05	
			d18	18	0.11	0.76	
Phlegm	1. YES	106	d12	89	-0.03	0.97	0.83
			d18	66	-0.09	1.05	0.42
	2. NEW	7	d12	6	0	0.63	
			d18	6	-0.33	1.86	
	3. NO	44	d12	30	-0.2	1.06	
			d18	19	0.21	1.18	

'YES' includes subjects with GERD at baseline, 'NEW' includes subjects developed GERD, and 'NO' includes subjects without GERD throughout the study. The variable d12 gives change from baseline to 12 months, and d18 gives change from baseline to 18 months. The p-values are for the comparison among 3 GERD groups for 12 months change and 18 months change in severity, frequency and phlegm cough score.

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e-Table 5. *Association between ACE inhibitors and ARB agents and cough at baseline*

	Cough	p value*
ACE use (n =26, 16.5%)	69 %	0.62
No ACE use (n= 131, 83.5%)	74 %	
ARB use (n = 17, 11%)	71.5 %	0.8
No ARB use (n=140, 89%)	73.5 %	

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