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A study on short term treatment response of connective tissue disease related interstitial lung disease

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***Abstract*---**Background: Interstitial lung disease is a major cause of morbidity and mortality in patients suffering from connective tissue diseases. Early detection and prompt recognition of symptoms with appropriate treatment is necessary for effective control of the disease and for better prognosis and long-term survival. Aim: To study the short-term treatment response of patients with connective tissue disease-related interstitial lung disease. Objectives: The purpose of this study was to evaluate the treatment response of connective tissue disease-related interstitial lung disease patients treated with intravenous pulses of cyclophosphamide (CYP) based on improvements in lung function: forced vital capacity (FVC)% predicted, forced expiratory volume in the first second (FEV1)% predicted, dyspnea Borg scale and 6-minute walk test. To determine the factors affecting the treatment outcomes like age, sex, duration of the connective tissue disease, type of connective tissue disease, HRCT type, and presence of PAH. Methods: A cohort study was conducted in the Department of General Medicine, Rheumatology, and Pulmonology at the Amala Institute of Medical Sciences, Thrissur, and Kerala from

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November 2015 to June 2017 that evaluated 74 patients having connective tissue disease-related ILD. A detailed history and a thorough clinical examination were done. Treatment with 6 intravenous pulses of cyclophosphamide was done, and response was assessed after 6 months. Response to treatment and its associations was determined by entering the data in MS Excel and analyzing it by using SPSS software. The methods used for statistical analysis were the Chi-Square test and the paired t test. Results and Discussion: This was a cohort study conducted on 74 patients with connective tissue disease-related interstitial lung disease. Most of the patients were between 50–59 age group (48%). The mean age of the sample was 53.32. Age had no significant influence on the treatment outcome. Out of the 74 patients, 66 were female and 8 were male. Both sexes showed similar treatment responses. Our study showed a better treatment response when the disease was treated earlier. 17 of the 74 patients (23%) had PAH. Our study showed that PAH is a predictor of negative outcomes. Following treatment, there was a definite improvement in the clinical aspects of the patient, which was assessed by the Borg dyspnea score and the cough visual analogue score. Following treatment, there was a definite improvement in PFT (FVC, FEV1), which was also statistically significant. Also, improvement in the 6-minute walk test, assessed by the distance covered in meters in 6 minutes, was seen, which was also statistically significant. There were 2 main patterns of ILD on HRCT-NSIP (62%) and UIP (38%). Patients with NSIP had a better response to treatment than UIP. Conclusion: Our study proves that there was definite improvement in CTD-ILD patients after treatment with cyclophosphamide. Improvement was seen both in clinical and lung function tests. Duration of the disease, HRCT type and presence of PAH were determinants that could predict treatment outcome. The patient's age and the type of CTD were found to have no effect on the treatment outcome. Hence, we conclude that early detection and treatment are of paramount importance in patients with CTD-ILD.Treatment can be provided irrespective of the age and type of CTD. Poor treatment response should be anticipated in those with longer duration of disease and UIP type in HRCT and the presence of PAH.

***Keywords*---**interstitial lung disease, short term treatment, connective tissue disease.

Introduction

Connective tissue diseases can cause a wide variety of pulmonary manifestations. They include interstitial lung disease, bronchiectasis, pleurisies, pleural effusion, and pulmonary artery hypertension (1).Interstitial lung disease (ILD) is characterized by inflammation or fibrosis which causes thickening and distortion of the alveolar wall with consequent impairment of gas exchange. Such individuals typically present with progressive breathlessness and non-productive cough, which frequently causes respiratory failure and death (2).Interstitial lung

diseases are an important cause of disability and death in the working age population. Over the last decade, improvements in therapy for the CTDs have improved the prognosis in individuals with these conditions. For many CTD patients, disease-associated ILD is now the major cause of disability and exercise limitation, while in systemic sclerosis it is now the principal cause of mortality (3). The pathogenesis of CTD-ILD is complex and poorly understood. It is generally accepted that underlying immune system dysfunction and immune-mediated pulmonary inflammation form the basis of the pathology. Abnormalities of cellular and humoral immune function have been described in ILD associated with systemic sclerosis (SSc) and other connective tissue diseases (4). The mechanisms leading to fibrosis are not very well understood, nor are the factors that determine which individuals with CTD develop ILD. Evidence from treatment trials suggests that the modulation of inflammation with immunosuppressant therapies, especially cyclophosphamide, results in some regression of ILD and prevents the development of further fibrosis (5). When deciding on immunosuppressive therapy, we evaluate the following factors: rate of disease progression, severity of lung disease, underlying CTD, patient age, chances of response based on radiographic and histopathology patterns, and finally, the ability to comply with therapy and monitoring. (1). The most common CTDs associated with ILD are systemic sclerosis (SSc), rheumatoid arthritis (RA), polymyositis and dermatomyositis, Sjögren syndrome, and MCTD (mixed connective tissue disease).

Material and methods / experimental details / methodology

Outcome measures

1. Change in lung function (FVC% predicted, FEV1 % predicted)
2. Borg Dyspnoea scale
3. Functional Exercise Tolerance (6-minute walk test)

Methodology

Study design: COHORT study
Study setting: Amala institute of medical sciences
Departments:

- Rheumatology department
- Pulmonology department
- General medicine department

Study period: 2015-2017
Inclusion criteria: Patients diagnosed with connective tissue disorders associated ILD
Exclusion criteria:

- COPD
- Asthma
- Cardiorespiratory failure

Timeline of study: 6 months follow up (0, 6 months)

Treatment given: Monthly doses (750mg/m^2) of intravenous Cyclophosphamide for 6 months.

Statistical Consideration

Sample size

N pairs= $[(Z *1\text{-alpha}/2 + Z* 1\text{-beta})^2 / \text{delta}^2 + (Z*1\text{-alpha}/2)^2 / 2]$
Delta= meu_2-meu_1/S
Meu_2-meu_1= the difference between pre-test mean and post-test mean (TLC %) - 1.2
S=3.6
Alpha- 0.05
Power-80%
N (sample size) = 70 pairs

Sampling procedure: I will be using consecutive sampling technique to undertake my study. All patients who come to rheumatology, pulmonology, general medicine OPD and wards will be taken consecutively after satisfying the inclusion and exclusion criteria.

Method of Data Collection

Study tools

1. I have a Preformat with a questionnaire (attached) To be assessed at 0,6 months
2. Clinical assessment*:* Borg dyspnoea score- which is a subjective grading of Dyspnoea. Dyspnoea according to its severity is graded from 1 to 10 as perceived by the patient. To be performed at 0(before treatment), 6 months (post treatment).
3. 6-minute walk test: maximum distance that can be covered by a person on level ground (metres or feet) in 6 minutes. An increase in 50 metres has been found to be significant. Also, the level of oxygen desaturation is considered both of which tend to correlate with the patient's baseline lung function and mirror the patients clinical course. To be performed at 0(before treatment),6 months (post treatment)
4. Pulmonary function tests: To calculate FVC (forced vital capacity) and FEV1 (Forced expiration velocity at first second).

Restrictive lung disease is characteristic of ILD. It can be easily measured by decrease in both FEV1 and FVC. Ratio is either normal or increased. TLC- total lung capacity- it's the total amount of air in the lung- about 5-6 L is the normal value FVC (forced vital capacity)- is the volume of gas that can be expired forcefully after maximum inspiration FEV1- volume of gas that can be expired forcefully in the first second of expiration. To be performed at 0(before treatment), 6 months (post treatment)

Analysis

Data will be entered in MS Excel and analyzed using SPSS software. Method used for statistical analysis-Chi –Square test and paired t test

Results and Discussion

The present study evaluated 74 patients attending General Medicine, pulmonology and Rheumatology departments' outpatient or inpatient department, who fulfilled the inclusion criteria. They were given the treatment of intravenous cyclophosphamide- 6 cycles and response was assessed after 6 months. Data obtained were coded and entered into Microsoft Excel spread sheet and analyzed using statistical package for Social sciences (SPSS) version 23 for windows**.**

Table .1- Age distribution in ILD patients

Row Labels	Count of Age
20-29	1
30-39	5
40-49	12
50-59	36
60-69	19
70-80	1
Grand Total	74

The above chart consists of the distribution of the number of patients according to their ages. It has been found out that those within the age group 50-59 forms the largest subset among the group (48%) The following chart consists of the distribution of sex in the study.66 of them were females which forms the majority.

Table 2- Sex distribution in ILD patients

Sex	Frequency	Percent
Female	66	89.2
Male	8	10.8
Total	74	100.0

Types of connective tissue disease, autoantibodies, complications, and extra-articular manifestations are all possible.

Connective Tissue Disease Type

The following chart consists of the various connective tissue diseases included in the study. Rheumatoid Arthritis tops the group with 36 patients in them. The most common connective tissue disease was Rheumatoid Arthritis constituting 50% of the cases, followed by MCTD which forms about 32.4 % of the cases.

Table 3- CTD types and their distribution

Connective tissue disease type	Frequency	Percent
Inflammatory polyarthritis	3	4.1
MCTD	24	32.4
Rheumatoid arthritis	37	50.0
Sjogrens	3	4.1
Systemic sclerosis	7	9.5
Total	74	100.0

Autoantibodies

The following chart shows the various auto antibodies that were positive in our study RF; ACCP tops the list being 35 in number.

Table 4- Count of antibody and distribution

Row Labels	*Count of Antibody*
Anti-topoisomerase	7
NIL	3
RF/ACCP	37
Anti-Ro/La	3
Anti U1RNP	24
Grand Total	74

Duration of Disease

The duration from the start of each connective tissue disease to the onset of ILD was calculated and the mean was found to be Tables 5- 5.91 years.

Table 5- Duration of Disease

Time periods	*Mean*	*Std. Deviation*
Duration (years)	5.91	2.517

Pulmonary Artery Hypertension PAH

The following chart shows the number of patients with PAH complicating the disease. Table 6 -17 of the patients had PAH.

Table 6- Count of patients had PAH

Numbers	*NO*	*YES*	*Grand Total*
Count of PAH	57	17	74

Among various diseases RA had- 6 cases (16%) and MCTD had 6 cases (25%), while SSc had 5 cases (71%) with PAH complicating the disease.

Table 7-PAH and distribution among CTD

Connective tissue disease type	PAH		Total
	No	Yes	--
IPA	3	0	3
MCTD	18	6	24
RA	31	6	37
SJOGREN	3	0	3
SSC	2	5	7
Total	57	17	74

Extra-Articular Manifestations

The following chart shows the various extra-articular manifestations found in our patients. Sicca and Raynauds phenomenon was the most common; but majority (53) did not have any manifestations.

Table 8- Count of extra-articular manifestations

NIL	*53*
Raynauds phenomenon (RP)	8
RP, calcinosis, telangiectasia	1
RP, Gastroesophageal reflux disease	2
RP, GERD, calcinosis	2
sicca	8
Grand Total	74

Clinical Assessment

Clinical assessment of the symptoms was done by Borg Dyspnoea score and by a Visual analogue score for cough. Treatment was given, and improvement was assessed for the same.

Table.9-Statistics of clinical assessment scores

Difference	Median	Minimum	Maximum
Dyspnoea Borg score	3	1	4
Cough (visual analogue score)	2.50	1	5

Investigations - HRCT, PFT, and 6 Minute Walk Test

HRCT: The following chart shows the different ILD histological patterns with HRCT. NSIP tops the list with 46 patients and the rest (28) were having UIP pattern.

Table 10- HRCT type and distribution

Row Labels	Count of HRCT
NSIP	46
UIP	28
Grand Total	74

PFT: Following chart shows the distribution of patients according to the value of FEV1 (forced expiratory volume in the first second). Majority of our patients were grouped between 60-69 % of FVC. These values were taken before giving the treatment.

Table11-Count FEV1 and distribution

Row Labels	Count of FEV1
30-39	2
40-49	6
50-59	18
60-69	29
70-80	19
Grand Total	74

Table 12- Count of FVC and distribution

Row Labels	Count of FVC
30-39	6
40-49	4
50-59	18
60-69	31
70-80	15
Grand Total	74

6-Minute Walk Test

The following chart consists of the distance travelled (in metres) by the patients before treatment. Patients were asked to walk the maximum distance they could possibly travel in 6 minutes.

Table 13-count of 6-minute walk test and distribution

Row Labels(m)	*Count of 6-minute walk test (in metres)*
240-259	2
260-279	3

280-299	4
300-319	9
320-339	33
340-359	20

Maximum number of patients came in between 320-339 metres

Treatment Results

FEV1: The following chart shows the improvement of FEV1 post treatment.

1. FEV1 31-50%- Of the total 8 patients in this category,4 patients remained the same, while 4 of them improved to FEV1 group 51-70%
2. FEV1 51-70%-Of the total of 52 patients, 25 remained stable in the same group, 23 improved to 71-90% FEV1 and 4 improved to 91-100% FEV1.
3. FEV1 71-90%- 14 patients were present in this group and they remained stable in the same group post-treatment.

Table 14- count of FEV1 pre-and post-treatment

Count of FEV1	Column Labels				
Row Labels	31-50	51-70	71-90	91-110	Grand Total
31-50	4	4			8
51-70		25	23	4	52
71-90			14		14
Grand Total	4	29	37	4	74

6-Minute Walk Test

1. Group 201-250- 2 patients in number, both the patients improved to group 251-300
2. Group 251-300- 9 in number, 2 remained same, 6 improved to 301-350, 1 improved to 351-400
3. Group 301-350- 60 in number,9 remained same, 51 improved to 351-400
4. Group 351-400- 3 patients, 1 remained same, 2 improved to 401-450

Table 15- count of 6-minute walk test pre- and post-treatment

Count of 6-minute walk test (post therapy-in metres)	Column Labels				
Row Labels	251-300	301-350	351-400	401-450	Grand Total
201-250	2				2
251-300	2	6	1		9

301-350		9	51		60
351-400			1	2	3
Grand Total	4	15	53	2	74

FVC: The following graph shows the improvement of FVC post treatment

1. FVC<41%- 6 patients, all improved to 41-60%
2. FVC 41-60%- total 14 patients, 10remained stable,10 improved to 61-80, 4 improved to 81-100%
3. FVC 61-80%-Total 43 patients, one went to 41-60 group, 31 remained stable in the same group, 12 improved to 81-100.

Table16-count of FVC and pre-and post-treatment

Count of FVC	Column Labels			
Row Labels	41-60	61-80	81-100	Grand Total
<41	6			6
41-60	10	10	4	24
61-80	1	31	12	44
Grand Total	17	41	16	74

Statistics Pertaining to Results

Clinical Parameters

Table 17- statistical significance of clinical scores

	Pre-test			*Post test*			*P value (Wilcoxon Signed)*
	Median	Minimum	Maximum	Median	Minimum	Maximum	Ranks Test)
Dyspnoea Borg score	7	6	8	4	2	6	0.0001
Cough (visual analogue score)	6	4	7	3	1	6	0.0001

The clinical improvement was assessed by Dyspnoea Borg score and a visual analogue score for cough. Responses in these scores were assessed post treatment and found to be statistically significant. (*P*= .0001)

Investigational Parameters: Mean and standard deviation of FVC, FEV1, 6minute walk test, SPO2 was assessed and are as follows

Table 18-SPO2

	Mean	*Std. Deviation*
FVC Diff	9.38	9.386
SPO2 Diff	1.08	.872
6-minute Diff	38.78	15.807
FEV1 Diff	9.01	9.341

Statisticalsignificance

Table 19- statistical significance of investigations-spo2, FVC, FEV1, 6MWT

	Pre-test		*Post test*		*P-value (Paired Samples test)*
	Mean	Std. Deviation	Mean	Std. Deviation	
SPO2	92.19	1.289	93.05	1.204	0.0001
FVC	61.12	10.350	70.36	13.014	0.0001
6-minute walk test (in metres)	324.82	23.987	363.61	30.278	0.0001
FEV1	62.69	10.008	71.70	11.539	0.0001

Response to improvement was assessed by measuring SPO2, PFT- including FVC and FEV1 and 6-minute walk test was assessed, and p value found to be statistically significant (p-0.0001). Hence our treatment has shown good response statistically.

PAH and Treatment Results

1. FEV1 31-50%- 4 patients were in the group, 2 remained same and 2 improved to 51-70%.
2. FEV1 51-70% - 10 patients were in the group, in which 8 remained same and 2 improved to 71-90%
3. FEV1 71-90% -3 patients with PAH remained same after treatment

Table 20- count of PAH pre-and post-treatment

Count of PAH	Column Labels				
Row Labels	31-50	51-70	71-90	91-110	Grand Total
NO					
31-50	2	2			4
51-70		17	21	4	42
71-90			11		11
NO Total	2	19	32	4	57
YES					

31-50	2	2			4
51-70		8	2		10
71-90			3		3
YES Total	2	10	5		17
Grand Total	4	29	37	4	74

Fisher's exact test p value=0.021

Our study shows that PAH is a statistically significant determinant in treatment outcome (P = .02). Those with PAH had a negative prognostic value to treatment outcome.

Connective Tissue Type and Treatment Results

Table 21- Type of CTD and pre-treatment values of FEV1

FEV1 (Pre-therapy) based on type of Connective tissue disease				
Type of CTD	30-49	50-69	70-90	Grand Total
IPA		2	1	3
MCTD	1	16	7	24
RA	6	21	10	37
SJOGREN		3		3
SSc	1	5	1	7
Grand Total	8	47	19	74

The following two graphs gives the improvement in FEV1 depending on the type of connective tissue disease. Our study has found no significance in the type of connective tissue disease and treatment outcome statistically.

Table 22-Type of CTD and post-treatment FEV1 values

Count of Connective tissue disease type	*Column Labels*				
Row Labels	30-49	50-69	70-89	90-110	Grand Total
IPA		2	1		3
MCTD		10	13	1	24
RA	2	9	23	3	37
SJOGREN		1	2		3
SSc		5	2		7
Grand Total	2	27	41	4	74

Relation between Connective tissue disease type and differences – no relation has been found between treatment outcome and type of connective tissue disease.

HRCT Type and Treatment Outcome

Table 23- HRCT type frequency

HRCT	*Frequency*	*Percent*

NSIP	46	62.2
UIP	28	37.8
Total	74	100.0

The following table shows the type of HRCT in relation with the various connective tissue diseases.

Discussion

This was a cohort study conducted on 74 patients with connective tissue disease related interstitial lung disease. The ILD was proven by HRCT. Pre-treatment status was assessed by Dyspnoea Borg score; cough visual analogue scale, PFT-including FEV1 and FVC, 6-minute walk test. Them they were given 6 intravenous pulses 0f cyclophosphamide 1 month apart. Treatment with cyclophosphamide has been proven beneficial in various studies Results were assessed by reviewing Dyspnoea Borg score, cough visual analogue scale, PFT and 6-minute walk test. The patients were from general medicine, pulmonology and rheumatology departments. Our study has found that the treatment produced a positive response by assessing all outcome variables and they were also statistically significant. (P= .0001)

Age: It has been found out that those within the age group 50-59 forms the largest subset among the group (48%). The mean of the age is 53.32. Our statistics show that age has no significant influence on treatment outcome. (P value>0.05, all determinants showed a non-significant p-value). Later age of onset has been shown to be a negative prognostic factor in some the studies like Nihtyanova SI et al (6) Sex: Out of the 74 patients, 66 were female and 8 were male. Both sexes showed similar treatment response. Many studies have more females mostly due to female preponderance in connective tissue diseases (7) (8).

Type of Connective Tissue Disease: The types of connective tissue diseases taken for the study are Rheumatoid arthritis, Progressive Systemic Sclerosis, Mixed connective tissue disease, Sjogren syndrome, and inflammatory polyarthritis. In these patients, autoantibodies have been positive for RA (RF/ACCP), Sjogren (Ro/La), SSc (anti-centromere), MCTD (U1RNP). The most common connective tissue disease was Rheumatoid Arthritis constituting 50% of the cases, followed by MCTD which forms about 32.4 % of the cases.

Prevalence of ILD in various CTD- (105)
Scleroderma- 50 to 70%
RA- 20 to 30 %
Polymyositis/Dermatomyositis- 20 to 54 %
Sjogren- 25 %
SLE- 3 to 8 %
MCTD – 66%
Our study has found no significance in the type of connective tissue disease and treatment outcome statistically (p-value>0.05).

Duration of Connective Tissue Disease: Our graphs show us that as the disease is treated earlier, there is more response towards the treatment. As the duration became 12-15 years, there was only one case, but it remained same as the pre-

treatment status, whereas treatment responses maximum in 0-2 years, 3-5 years and 6-8 years as explained by the previous graphs. Similar studies have proven that earlier treatment has better outcomes. Such an example is a study by Steen et al. (9) Some studies have shown that duration of the disease did not affect disease progression as in an assessment of Scleroderma Lung Study done by Khanna et al (10).

PAH: 17 of the 74 patients had PAH i.e. 23% of the total patients had PAH. 25% of MCTD, 16% of RA, 71% of scleroderma had associated PAH. Our study shows that PAH is a predictor of negative outcome of treatment and does significantly influence the treatment given for ILD. (p value-0.021).Various studies including those of B Chang et al have found PAH to be negative prognostic factor and responsible for causing increased mortality. (11)

Clinical Parameters: Dyspnoea Borg Score & Cough Visual analogue Score

Following treatment there was a definite improvement in the clinical aspects of the patient which was assessed by dyspnoea Borg score & cough visual analogue score. These observations were also statistically significant (p-value-0.0001). Tashkin et al has proven clinical benefits like improvement in dyspnoea and cough in patients with CTD-ILD after cyclophosphamide treatment (12)
PFT: Following treatment there was a definite improvement in PFT (FVC, FEV1) which was also statistically significant (p-value-0.0001). Improved pulmonary function after treatment with cyclophosphamide in CTD-ILD has been proven in various studies .The Scleroderma Lung Study has also proven beneficial effects in PFT after treatment with cyclophosphamide (12).
6– Minute Walk Test: Following treatment there was a definite improvement in 6-minute walk test assessed by the distance covered in metres in 6 minutes which was also statistically significant (p-value-0.0001).
HRCT –Type: According to our study we had 2 main patterns of ILD- NSIP (62%) & UIP (38%). Most of the RA patients (27 out of 37 i.e.72 % of RA patients) had a pattern of UIP proving that UIP is the most common pattern in RA patients. Studies proving the same have been Rest of our patients have a majority of NSIP pattern (62%) According to our graphs of results and statistics, NSIP had a better response to treatment than UIP (p-value-0.0001). This aspect has been proved in previous studies by Flavia V Castellano and John Varga (108). There is more of ground-glassing and less of fibrosis in NSIP which is sensitive to treatment. (13)
Study Limitation: This is only a small study of sample size 74. There was no control group to assess response with a placebo or a different drug. Most of our patients were clinically stable and not in respiratory failure. Those ILD's who have gone into respiratory failure will have to be assessed separately for treatment response.

Conclusion

We included connective tissue diseases like RA, MCTD, IPA (undifferentiated CTD), Sjogren, and Scleroderma and concluded that, statistically, the type of connective tissue disease did not have any effect on treatment outcome. The most common connective tissue disease was rheumatoid arthritis, constituting 50% of the cases, followed by MCTD, which constituted about 32.4 percent of the cases.

The duration of each disease before starting the treatment was studied, and our graphs prove that earlier institution of treatment gives a favorable treatment outcome. The average time from the onset of CTD to the development of ILD was 5.91 years. Those with associated PAH had a negative treatment outcome when compared to those without PAH. Hence, PAH should be considered as a negative determinant for treatment outcome in ILD. (p-value 0.021) 23% of the total patients had PAH. 25% of MCTD, 16% of RA, and 71% of scleroderma patients had associated PAH. While assessing treatment response to HRCT type, NSIP seems to be better responsive than UIP. 62% of the cases had NSIP. All the CTDs showed more of an NSIP pattern while RA had more of an UIP pattern. Because NSIP was associated with more ground glassing and thus reversibility, treatment outcome was improved.(P-value: 0.0001). In short, our study proves that there is definite improvement in CTD-ILD patients after giving treatment with cyclophosphamide. Improvement is seen both clinically and investigation wise. (P-value: 0.0001). Poor treatment response should be expected in patients with a longer duration of disease, UIP type in HRCT, and associated PAH.

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