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ORIGINAL ARTICLE

Systemic sclerosis: comparison of efficacy of oral cyclophosphamide and azathioprine on skin score and pulmonary involvement—a retrospective study

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Abstract The aim of this study was to evaluate efficacy of azathioprine (AZA) and cyclophosphamide (CYC) as a therapeutic regimen for interstitial lung disease associated with systemic sclerosis (SSc). Thirty-six selected patients included in this retrospective cohort and received one of the two drugs; the first group consists of 15 patients who were treated with AZA (1.5–2 mg/kg/day) and the second group with 21 patients received oral CYC (up to 2 mg/kg/day). Both groups received additional low dose of prednisolone ($\leq$10 mg) for 6 months. Forced vital capacity (FVC), diffusion lung capacity for carbon monoxide (DLCO) and skin score were assessed as outcome measures. Modified Rodnan skin score (mRSS), pulmonary function test and DLCO were evaluated at entry and at the end of study after 12 months. The mean (SD) FVC percentages obtained at baseline and post-treatment in AZA-treated patients were 62.8 $\pm$ 9.8 and 71.1 $\pm$ 20.9 with mean difference of FVC% +7.6 $\pm$ 13.1, $p = 0.05$, and in CYC-treated patients 59.5 $\pm$ 10.7, 63.1 $\pm$ 16.2 and +2.9 $\pm$ 11.5, respectively, $p = 0.19$. Baseline and post-treatment DLCO% in AZA-treated patients were 61.4 $\pm$ 25.8 and 76.7 $\pm$ 24.0 with mean difference of +15.0 $\pm$ 14.5, respectively, $p = 0.01$. In CYC-treated patients, those measures were 67.7 $\pm$ 27.5 and 60.0 $\pm$ 22.9 with mean difference of -8.0 ± 23.7 ($p = 0.12$). Following 12 months of treatment in AZA-treated patients, mean difference of changes in mRSS was -2.9 ± 3.7 and -1.4 ± 4.5 in CYC-treated patients. Our results indicated that AZA can be effective in ameliorating or stabilizing lung function in selected SSc patient groups.

Keywords Interstitial lung disease (ILD) · Systemic sclerosis (SSc) · Azathioprine · Cyclophosphamide

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Introduction

Systemic sclerosis (SSc) is a chronic connective tissue disease characterized by skin thickening with vascular and visceral involvements [1] such as interstitial lung disease (ILD).

To treat scleroderma-associated ILD, various therapeutic strategies have been proposed. Since 1993, when the first report on efficacy of cyclophosphamide (CYC) in treating SSc-related ILD [2] was published, CYC has been widely used [3–5].

Recently, the results of two randomized controlled trials on use of CYC in treatment of pulmonary manifestations of SSc are published [6, 7]. In one study, titled "fibrositis alveolitis in scleroderma trial (FAST)," Tashkin et al. [6] demonstrated that CYC could reduce the rate of decline in pulmonary function and improve dyspnea and skin thickness over 12 months of active treatment. In the second study, scleroderma lung study (SLS) [7], improvement in lung physiology parameters was shown in the CYC-treated group.

There are limited data on the use of azathioprine (AZA) as a medication to treat clinical manifestations of SSc. Favorable efficacy and tolerability of AZA in patients with idiopathic pulmonary fibrosis (IPF) [8, 9] prompted researchers to its use in SSc–ILD. In a retrospective study on eleven patients with SSc-associated ILD who were treated with AZA for 12 months, the results demonstrated stabilization (or no further decline) of lung function and improved symptoms [10]. Although AZA has also been used for maintenance therapy after treatment with pulse CYC, its efficacy on the outcome has not independently been assessed [7]. To our knowledge, there is only one published report on head-to-head comparison of the therapeutic use of CYC versus AZA in patients with SSc–ILD [11].

We conducted a retrospective cohort study on 36 SSc patients with pulmonary manifestation who were treated with CYC and AZA and evaluated the efficacy and safety of these two commonly used medicines on the study subjects and in daily practice.

Patients and methods

Patients and setting

We used a database of patients with SSc who were evaluated, diagnosed and registered at Firoozgar Hospital, a Tehran University affiliated academic center, between February 1, 1998, and January 1, 2012.

Inclusion criteria

All patients who fulfilled SSc diagnostic criteria proposed by American College of Rheumatology (ACR) were included in the study [12]. Subjects had a high-resolution computed tomography of chest (HRCT), pulmonary function test (PFT) and diffusion lung capacity for carbon monoxide (DLCO) at the time of start of treatment and at 12 months post-treatment. All patients received their prescribed medication as instructed and were regularly followed for 1 year. To be included in the study, patients also required to have a forced vital capacity (FVC) <70 % and HRCT which was compatible with scleroderma-related ILD [13]. Patients received immunosuppressive therapy if they had fibrotic alveolitis or evidence of recent progression of ILD.

Exclusion criteria

Patients who had pulmonary arterial hypertension (PAH) in association with ILD and/or severe left ventricular failure (ejection fraction <50 %) were excluded from the study. We also excluded patients with normal HRCT and FEV <70 % if the low volume was found to be a result of skin thickness.

Measurements

Pulmonary function testing was performed according to the ATS/ERS TASK FORCE guideline [14]. PFT included forced spirometry and lung transfer capacity studies (DLCO). Spirometry was performed using flow-volume loops using Ganshorn spirometer, Germany. Single-breath diffusion capacity for carbon monoxide (DLCO) was tested using a conventional carbon monoxide/helium gas mixture and was corrected for hemoglobin.

Chest HRCT (Siemens) was performed using a high-resolution protocol of 1.0–1.5 mm width at 15-mm interval from lung apex to the base in supine position at full inspiration. In HRCT, ILD is defined as ground glass opacity with or without fibrosis. The ground glass pattern refers to an increased density of lung parenchyma, and lung fibrosis included architectural distortion with honey combing and/or intra-lobular reticulation, traction bronchiectasis, distorted interlobular septal, reticulations or irregular linear opacities [15].

Reports of HRCT were independently reviewed by two specialists including one radiologist and one pulmonologist. In case of disagreement between the two, a consensus must be reached. As previously defined by Wells et al. [16], we classified HRCT into three groups: isolated ground glass opacity, isolated fibrotic pattern and mixed pattern (ground glass with fibrosis).

We obtained patients variables from our data bank: Clinical and Research Rheumatology Information Software (CRIS). That is locally designed software to record rheumatic disease patients' information and serves as a data bank for research purposes.

Type of information that is obtained from data bank included demographic data, patients age at first disease onset, age at diagnosis, as well as the age at the time ILD needs to treat, gender, tobacco use, skin score and extension, data of vascular, musculoskeletal, gastrointestinal involvement and autoantibody status (ACA, topoisomerase I (TOPO I, RNA Polymerase III (Pol3) U1, U3 RNP and

TH/To). Abs were determined based on our previous published definition [17].

Patients with skin manifestation of SSc had either limited (lcSSc) or diffuse (dcSSc) cutaneous systemic sclerosis which was defined based on Le Roy et al. [18] classification. The disease onset was marked as the date of the first symptom attributable to scleroderma such as Raynaud's phenomenon, swollen fingers and renal crisis. We measured variations in corrected diffusion capacity of carbon monoxide percentage (DLCO%) for hemoglobin and FVC% values before the therapy begins (at baseline) and 12 months later in both treatment groups. We have considered absolute changes in FVC% as well as absolute changes in DLCO% [10].

The response to therapy was defined as follows: (a) improved or stabilized, if decline in ΔFVC% <10 % and/or ΔDLCO% <15 % and (b) deteriorated or worsened, if there was a decline ≥10 % in ΔFVC%/or ΔDLCO% ≥15 % of the baseline [8, 19]. Skin scores were measured by modified Rodnan skin score (mRSS) [20] at baseline and after 12 months.

Treatment

Patients in CYC group received CYC up to 2 mg/kg/day (50–100 mg/day) for 12 months; in addition, they received 10–15 mg prednisolone daily for 2 months. Following this 2 months, prednisolone was tapered to 5 mg for the remaining 10 months. In AZA group, patients received daily dose of AZA 1.5–2 mg/kg/day (50–150 mg) in addition to 5 mg prednisolone once a day. Decision for prescribing one of the two above therapies was based on both physician's judgment and patient's preferences as in routine clinical practice. Influencing elements in selection of therapy included: patient's plan to become pregnant, use of less or more aggressive agent, affordability for more expensive therapy, ability to do more frequent laboratory test in those who use CYC drug and patient's living distance from a medical center. Out of 16 patients in CYC group with age under 45 years old, for 12 females who were concerned about loss of fertility, gonadotropin-releasing hormone agonist (GnRH-A) and oocyte cryopreservation for 4 and 8 women were used, respectively.

Monitoring of side effects

Laboratory assessments to monitor toxicity effects included complete blood count, urine analysis, liver function test and serum creatinine as were recorded in the data bank. For patients treated with CYC, a routine laboratory test and clinical evaluation were conducted on a monthly basis. In AZA-treated patients, however, these routine evaluations were performed every 2 months.

Statistical analysis

A Chi-square test was used to compare differences in nominal baseline and demographic data. When necessary, we used Fisher's exact test. Student's t test was used to compare continuous variables in the two treatment groups. Mann–Whitney U test was applied when the normal distribution was absent. During the treatment period to calculate changes in the continuous values, we used paired t test and Chi-square test (for nominal values). Probability values of <0.05 were considered as statistically significant. All statistical analyses were performed by SPSS software version 17.

Results

Data of 225 patients with diagnosis of SSc which had been recorded throughout 13 years in our center were reviewed. We used interim time and out of a total of 70 (31.1 %) patients with the diagnosis of SSc–ILD which existed in the data base, we extracted the data related to 36 patients who met the inclusion criteria. Patients had taken CYC or AZA regularly for 1 year. The spirometry and DLCO were available at baseline and throughout follow-up period. A 12-month follow-up FVC and DLCO was performed in 21 and 15 of patients in CYC and AZA groups, respectively.

Baseline and demographic data

Table 1 shows detailed baseline demographic and clinical information on two treatment groups. Median age at time of diagnosis of SSc (IQR interquarter range) in AZA group was 35.0 (IQR 30.1–45.0) and in CYC group 33.0 (IQR 29.0–40.5). Median age (IQR) at the time that diagnosed ILD patients needed a treatment in AZA group was 42. 0 (IQR 35–54) compared to 34.0 (IQR 29.6–48.5) in CYC group. Median age (IQR) at the time of first symptoms emergence of pulmonary interstitial involvement to that of diagnosing of interstitial pulmonary involvement was 86.0 (IQR 36–132) and 37.0 (IQR 14–126) months in the AZA- and CYC-treated patients, respectively.

In both treatment groups, female gender was preponderant (more than 80 %) and lower proportion of patients had diffuse cutaneous (dcSSc) subtype of the disease; 1 (6.7 %) in AZA compared to CYC group 8 (38.1 %), $p = 0.05$. In AZA-treated patients, the median (IQR) mRSS was 10 (7.0–19.0) and in CYC treated 15.0 (11.0–21.0).

There was only one smoker (a female) with dcSSc type in CYC-treated group. There was no smoker patient in AZA group. Baseline data demonstrated a pure ground glass appearance on HRCT in 6 (40.0 %) patients in the AZA group and 4 (19.0 %) patients in the CYC group. A

Table 1 Demographic and baseline data in both AZA- and CYC-treated study groups (patients with SSc-related ILD)

	Azathioprine *N* (%)[a]	Cyclophosphamide *N* (%)	*p* value
Number of patients	15	21	–
Age at disease diagnosis median (IQR)[b]	35.0 (30.1–45.0)	33.0 (29.0–40.5)	0.51
Age at time ILD need to treatment/months median (IQR)	42.0 (35.0–54.0)	34.0 (29.6–48.5)	0.35
Duration from first symptom to develop ILD/month median (IQR)	86.0 (36–132)	37 (14.0–80.5)	0.12
Female no (%)	12 (80.0)	18 (85.7)	0.67
Diffuse no (%)	1 (6.7)	8 (38.1)	0.05
mRSS at first visit median (IQR)[c]	10.0 (7.0–19.0)	15.0 (11.0–21.0)	0.04
HRCT pattern at entry no (%)			
Pure ground glass	6 (40.0)	4 (19.0)	0.13
Isolated fibrosis	7 (46.7)	8 (38.0)	
Mixed	2 (13.3)	9 (42.9)	
FVC% at entry mean (SD)	62.7 (9.8)	59.6 (10.7)	0.351
DLCO% at entry mean (SD)	62.8 (25.8)	67.7 (9.8)	0.496
Raynauds	12 (80.0)	16 (76)	0.30
Telangiectasia	13 (86.7)	17 (81.0)	0.32
Dig ulcer/gangrene	8 (53.3)	11 (52.4)	0.26
Esophageal reflux	13 (86.7)	18 (85.7)	0.37
Arthritis	6 (40.0)	14 (66.7)	0.08
Myositis	2 (13.3)	5 (23.8)	0.25
Renal (non-SRC[d] presentation)	4 (26.7)	6 (28.6)	0.29
ESR mean (SD)	30.5 (20.7)	22.8 (13.9)	0.19
ANA available no (%)	10 (66.6)	14 (66.6)	
ANA+	10 (100)	12 (85)	0.50
Anti-TOPO+ no (%)	7 (70)	11 (91.6)	0.66
Anti-u1 RNP	1 (10)	0	

[a] Number (percentage), [b] *IQR* interquartile range, [c] *mRSS* modified Rodnan skin score [d] *SRC* scleroderma renal crisis presentation

reticular pattern was found in 7 (46.7 %) and in 8 (38.0 %) patients, and a mixed pattern was observed in 2 (13.3 %) and in 9 (42.9 %) patients in the AZA and CYC groups, respectively.

The mean (SD) FVC percentage at entry in AZA- and CYC-treated patients was 62.8 (9.8) and 59.5 (10.7), $p = 0.35$. The DLCO percentage was 61.4 (28.3 %) and 67.3 (29.6 %) in AZA- and CYC-treated groups, respectively, $p = 0.49$.

Clinical findings such as Raynauds phenomenon, telangiectasia, Dig ulcer/gangrene, myositis and esophageal reflux occurrence were similar with no statistical difference between the two groups. Arthritis occurred more prevalently in CYC group; however, the difference between the two groups was not significant. It was observed in 6 (40.0 %) patients in AZA group and in 14 (66.7 %) in CYC groups, $p = 0.08$. Scleroderma renal crisis (SRC) did not happen before or during the study in the study subjects, but non-SRC renal involvement such as Proteinuria > +1/hematuria/RBC cast was observed in both AZA 4 (26.7 %) and CYC group 6 (28.6 %), $p = 0.29$.

Erythrocyte sedimentation rate (ESR) mean and standard deviation (SD) in AZA-treated patients were 30.5 ± 20.7 and 22.8 ± 13.9 in CYC group.

ANA: ANA Abs results were available in 24 (66.6 %) patients; positive ANA in 22 (91.6 %), TOPO I in 17 (71.0 %) and U1 RNP in 1 (4 %) were detected. Details for each finding are shown in Table 1.

Outcome measures in each treatment group

Azathioprine group

Table 2 summarizes demographic data, serologic features and outcome measures at baseline and at 12 months in 15 patients in AZA treatment group.

The FVC% mean (SD) at baseline and post-treatment in the AZA-treated patients were 62.7 ± 9.8 and 71.1 ± 20.9 with mean difference of FVC +7.6 ± 13.1, $p = 0.05$.

Baseline and post-treatment DLCO% in the AZA-treated patients were 62.8 ± 25.8 and 76.7 ± 24.0 with

Table 2 Demographic, serologic features and outcome measures at baseline and at 12 months post-treatment in AZA-treated group

Patients number, name	Gender	Subtype	ESR	ANA	Specific Abs	Age at diagnosis of ssC	Age at the time ILD need to treatment	Dx of ILD from symptom/months	mRSS0	mRSS12	FVC% 0	FVC% 12	DLCO% 0	DLCO% 12
1SD	M	lcSSc	10	NA	NA	39	40	54	10	5	68.7	73.0	57.0	90.0
2 GB	F	lcSSc	33	+	TOPO I+	38	35	115	6	5	69.2	88.0	26.1	50.0
3HA	M	lcSSc	55	+	–	26	27	36	7	7	69.6	66.0	65.1	70.0
4RAM	F	lcSSc	15	+	TOPO I+	22	22	132	19	20	53.0	58.0	75.2	105.0
5NAD	F	lcSSc	27	+	TOPO I+	33	34	86	5	6	69.0	102.0	95.0	65.0
6ABR	F	lcSSc	32	+	TOPO I+	36	36	65	8	6	69.0	91.0	97.4	104.0
7NJ	F	lcSSc	23	NA	NA	66	66	26	7	5	67.0	73.0	29.6	44.0
8MP	F	lcSSc	26	+	U1RNP	35	36	75	5	4	70.0	104.0	108.0	110.0
9MAE	F	lcSSc	35	+	TOPO I+	35	59	552	11	4	36.0	32.0	35.6	41.0
10JAL	F	lcSSc	34	+	–	34	43	120	12	6	68.9	66.0	56.6	70.0
11AZ	F	lcSSc	15	NA	NA	46	52	218	21	16	58.0	81.0	74.0	102.0
12ZAL	F	lcSSc	27	NA	NA	42	42	96	20	16	59.0	42.0	62.1	87.0
13HO	M	lcSSc	93	+	TOPO I+	73	75	30	14	7	64.0	71.0	62.0	80.0
14HOS	F	lcSSc	11	NA	NA	45	43	3	9	13	69.1	75.0	77.3	89.0
15AB	F	dcSSc	21	+	TOPO I+	28	54	192	21	11	51	45.0	21.8	44.0

NA not available

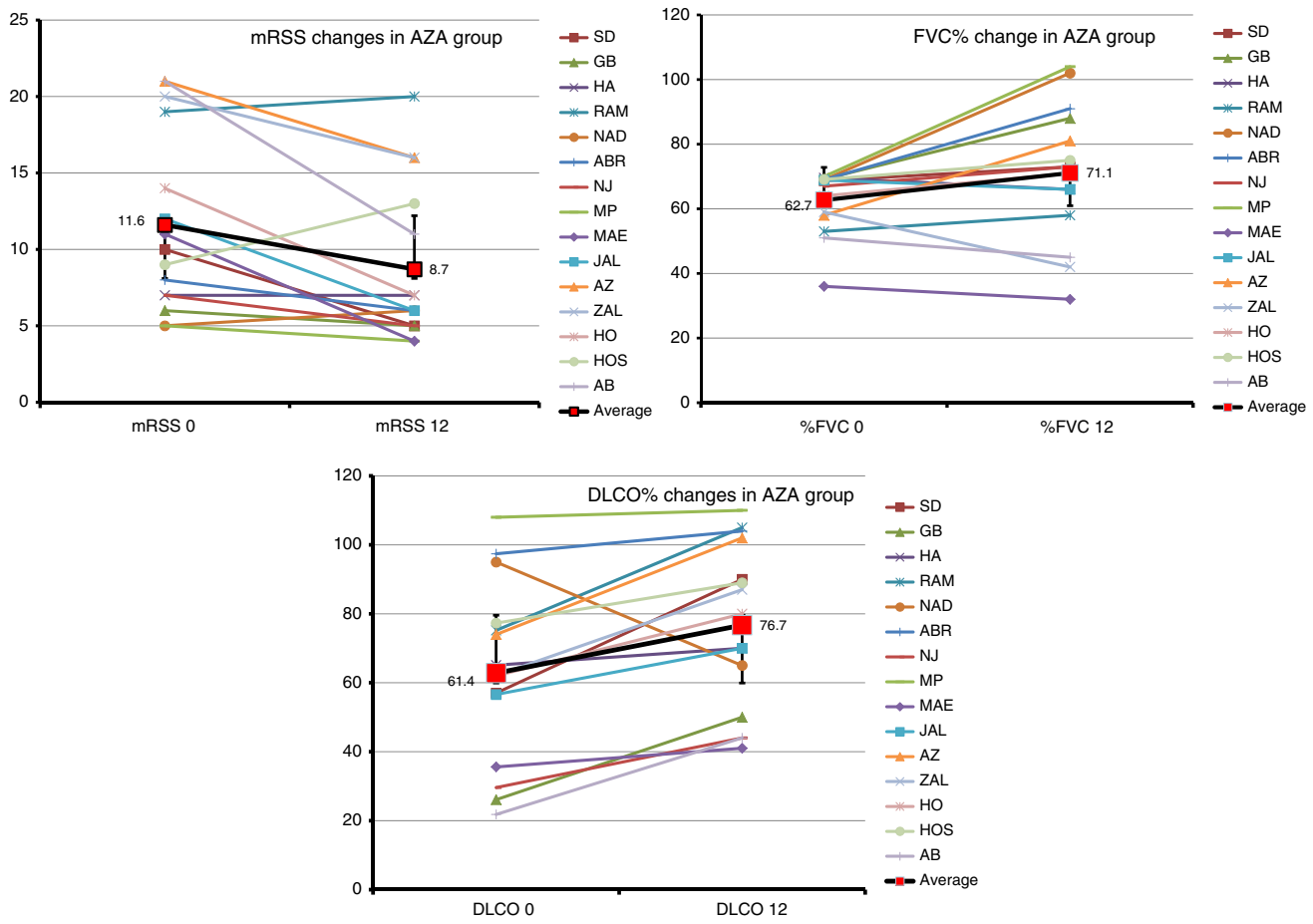

Fig. 1 Changes in modified skin score, FVC% and DLCO% at baseline and post-treatment in azathioprine group. *Bold line* shows the average in each series. Mean and standard deviation (SD) values are shown in figure

mean difference of $+15.0 \pm 14.5$, respectively, $p = 0.01$. Following 12 months of treatment in AZA-treated patients, mean difference (SD) of change in mRSS was -2.9 ± 3.7 (from 11.6 ± 5.9 to 8.7 ± 5.1, $p = 0.09$). Changes in outcome measures during 1 year of treatment with AZA are shown in Fig. 1.

Individually, 7 out of 15 patients show improvement in PFT, and 6 patients were stable after 12 months of treatment. Likewise, 8 patients showed improvement, and 6 had stable DLCO during treatment period.

Cyclophosphamide group

The FVC% mean (SD) at baseline and post-treatment in CYC-treated patients were 59.5 ± 10.7 and 63.1 ± 16.2, mean difference of FVC (SD) $+2.9 \pm 11.5$, ($p = 0.19$).

Baseline and post-treatment DLCO% were 67.7 ± 27.5 and 60.0 ± 22.9, respectively, with mean difference (SD) of -8.0 ± 23.7, $p = 0.12$. Following 12 months of treatment, skin score was -1.4 ± 4.5 [from 16.4 ± 7.5 to 15.1 ± 7.7 ($p = 0.16$)] (Fig. 2).

At 12 months, 5 out of 21 patients showed improvement and 14 patients were stable on FVC%. Only one patient showed DLCO improvement, and 14 had stabilized DLCO.

Safety

Following 1 year of treatment, in AZA-treated group, no side effect was reported. However, in CYC-treated group, two patients presented leucopenia that required temporary dose reduction.

Discussion

We investigated the response of ILD to different treatment options in SSc patients. At study completion, AZA group showed significant improvement in FVC% and DLCO% compared to baseline, whereas in CYC group, those measurements did not show any statistically significant changes. Skin score did not show significant improvement in neither of the two groups.

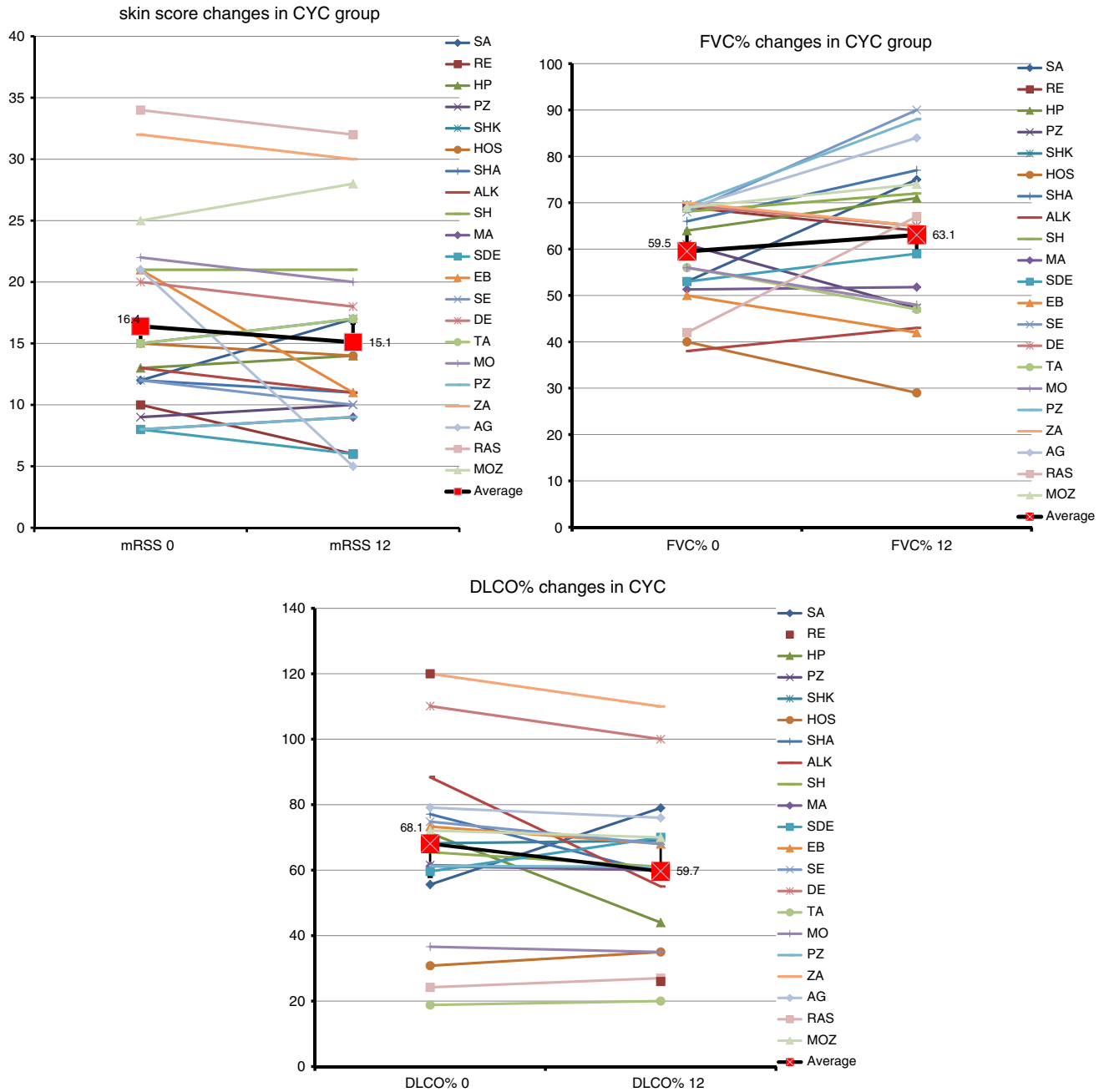

Fig. 2 Changes in modified skin score, FVC% and DlCO% at the baseline and post-treatment in cyclophosphamide group. Mean and standard deviation (SD) values are shown in figure

At entry, FVC% and DlCO% did not have any significant differences between the two groups; however, it seems patients who received more aggressive therapy (cyclophosphamide) were younger at time of diagnosis of ILD. They also had more diffuse subtype, shorter duration of disease and less ground glass pattern on HRCT.

These findings may represent an inevitable misclassification in an open study and in a routine clinical practice. This also could be influenced on the response to treatment. It appears that the two groups are not similar at their baseline presentation that makes it hard to compare.

We emphasize that there were no major or irreversible adverse reactions in AZA-treated patients, but long-term complication of cyclophosphamide, including bladder cancer and other malignancies [21], may be significant and not detected in a short-term study with small sample size such as ours.

In our cohort, anti-TOPO I Abs were detected in 71 % of patients whose Abs were assayed. Our results seem similar to study by Bérezné et al. [22] that included 27 patients with SSc-related ILD and reported anti-TOPO I Abs in 23 (85 %) of patients.

A widely use of CYC in treating t ILD in SSc patients suggests its beneficial effects [2–5]; however, there are few reports in the literature that also suggest the use of AZA in such patients. A retrospective study of 11 patients with SSc-associated ILD who were treated with AZA reported that 8 patients completed 1 year of treatment successfully. Results of this study suggested that AZA may play a role in stabilizing or improvement of lung function and pulmonary symptoms in their group of SSc-associated ILD patients [10]. In a randomized, unblinded study which compared the use of CYC versus AZA in treatment of the SSc-associated ILD, thirty patients with early diffuse SSc included in each treatment arm for duration of 18 months. Patients in CYC group did not show changes in FVC% and DLCO% at the end of treatment period, but those in AZA group deteriorated significantly [11].

Nadashkovich study showed lack of efficacy in SSc-associated ILD patients; however, other studies reported efficacy of AZA in treatment of other fibrotic lung disease such as idiopathic pulmonary fibrosis (IPF) [8, 9].

Raghu et al. in a double-blind, randomized, placebo-controlled clinical study on IPF compared 13 patients who were treated with prednisolone and placebo with 14 patients treated with prednisolone and AZA. The authors found a marginally significant mortality benefit with AZA [8].

In other randomized controlled trial in which 20 patients with diffuse interstitial pulmonary disease (diagnosed by open lung biopsy) received combined prednisone and azathioprine therapy, 12 patients demonstrated improvement with therapy [9].

In the present study, although the subjects had different duration of disease at entry, skin thickening has improved to some extend in both treatment groups with no differences.

As shown in analysis of three large multicenter trials by Amjadi et al. [23], there was a general tendency for skin to soften over time with no difference among patients with different disease duration at baseline.

In the study of Nodashkevich et al. [11], mRSS in the CYC group had improved significantly ($p < 0.001$), but in the AZA group, no trend for improvement or worsening in mRSS was found. In one case report in a diffuse cutaneous systemic sclerosis, the beneficial effect of AZA was shown, although skin thickening relapsed after discontinuation or decrease dose of AZA therapy. The authors suggested a clinical controlled trial with AZA in SSc patients to be conducted [24].

Major limitations of our study were small size population and retrospective nature, which inevitably make the study unblinded with selection biases. Other limitations include lack of a comparative control group and a short follow-up period.

One value for the current research is that all patients completed 1 year of treatment. We also presented all out comes, clinical and serological variables in detail which will provide enough data for future comparative studies.

In conclusion, our findings may not provide unequivocal evidence for AZA treatment as an ideal treatment regimen for SSc-associated ILD patients. However, we could show that AZA had beneficial effects in some SSc patients with ILD. Given all findings in addition to acceptable safety profile of AZA, it would be worthwhile to conduct a prospective, randomized, controlled clinical trial for a head-to-head comparison of the efficacy of AZA and CYC treatment on SSc patients with ILD.

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Conflict of interest None.

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