COMPARISON OF LONG-TERM CYCLOPHOSPHAMIDE (CYC) AND MYCOPHENOLATE MOFETIL (MMF) EFFICACY AND SAFETY IN PATIENTS WITH SYSTEMIC SCLEROSIS (SSc) AND INTERSTITIAL LUNG DISEASE (ILD)

O. Koneva, O. Ovsyannikova, O. Desiniva, L. Garzanova, L. Ananieva, M. Starovoytova

Nasonova Research Institute of Rheumatology, Moscow, Russian Federation

Background

CYC is considered to be the drug of choice for ILD therapy in patients with SSc. However, based on published evidence, only temporary and modest improvement of pulmonary fibrosis is usually achieved, therefore search for new more effective and safe agents is ongoing, with specific attention given to MMF.

Objectives

To compare CYC and MMF effects on SSc clinical manifestations and activity, and safety of both agents in an open prospective non-randomized study.

Methods

The study included patients with a documented SSc diagnosis and ILD signs based on HRCT data. All patients were treated with immunosuppressant's in combination with low and medium doses of glucocorticoids. 36 pts (mean age 47±12 years, m/f 1/11, SSc duration 5.0±4.8 years, diffuse/limited – 1/1,6) were administered parenteral CYC during 12±6 months, with a cumulative dose of 10.6±5 g. 45 pts (mean age 49±13 years, m/f – 1/10, SSc duration 7.6±6.3 years, diffuse/limited – 1/1,3) were administered MMF at 2 g/day during 13±2 months. The following parameters were monitored during the study: FVC%, DLCO%, modified skin score (mRSS), activity index (EScSG), gastrointestinal tract symptoms, left ventricle ejection fraction, presence of diastolic ventricle dysfunction, PASP (Echo-CG), heart rhythm and conduction disoders (ECG), count of digital ulcers and necrosis.

Table 1 Characteristics of groups

Characteristics	CYC (n=36)	MMF (n=45)	p
SSc duration since the first non-Raynaud syndrome, M± δ, years	5.0±4.8	7.6±6.3	>0.05
male/female ratio	1/11	1/10	>0.05
Age, M± δ, years	47±12	49±13	>0.05
diffused/limited disease ratio	1/1.6	1/1.3	>0.05
immunosuppressant's therapy	average cumulative dose of CYC M± δ, g 10.6±5	daily MMF dose, mg 2000	
the therapy duration, M± δ, months	12±6	13±2	>0.05
mRSS, points, M± δ,	11.2±9.8	7.5±6.9	>0.05
Baseline FVC %, M± δ	80.5±20.1	90.3 ±20.8	=0.05
Baseline DLCO %, M± δ	53.5 ±16.2	52.2 ±17.4	>0.05

Results

MMF therapy led to a significant reduction of the mRSS (7.5±6.9 and 4.8±3.9, p=0.0006), EScSG (1.9±1,5 and 1.22±0.9, p=0.005), number of patients with heart conduction disorders (13/29% and 5/11%, p=0.03. The FVC improvement by ≥10% was documented in 6 (13%) pts, and DLCO – in 3 (7%); while worsening was observed in 4 (9%), and 2 (4%) cases, respectively. Mean FVC (90.3 ±20.8 and 92.2±21, p=0.09), and DLCO (52.2±17.4 and 51.9±17, p=0.86) values did not change significantly. CYC therapy resulted in significant FVC increase (80.5±20.1 and 85.9±20.5; p=0.034), reduction of EScSG (2.8±2 and 1.4±1.2, p=0,0002) and mRSS (11.2±9.8 and 7.9±6.8, p=0,009). ≥10% FVC increase was observed in 11 (31%) pts, which was significantly more than in MMF group (p=0.043). FVC loss was noticed in 2 (5.6%) cases. The median FVC increase was 5.4% (25th%=-0.6, 75th%=12.3). ≥10% DLCO improvement and worsening was observed in 2 (6.7%) pts. The mean DLCO values (53.5±16.2 and 54.4±15.5) did not change significantly. The other parameters monitored did not show significant deviations during the observation period. Drug tolerability was better in MMF group: the rate of adverse drug reactions was significantly lower in MMF group (12/27%), compared to CYC group (19/53%), p=0.03.

Fig 1 Dynamics of FVC during CYC-therapy

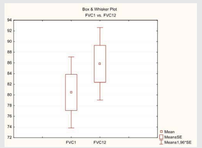


Fig 2 Dynamics of FVC during MMF-therapy

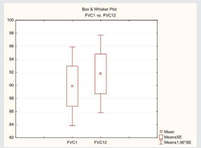
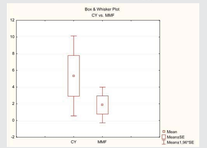
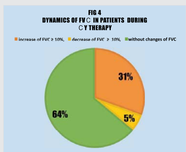


Fig 3 Delta of FVC during CY- and MMF-therapy





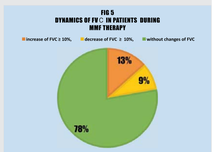


Table 2 Comparison of characteristics during CYC- and MMF-therapy

Characteristics	CYC-therapy (n=36)		p	MMF-therapy (n=45)		p
	Before CYC	After CYC		Before MMF	After MMF	
mRSS, points, M± δ	11.2±9.8	7.9±6.8	0,009	7.5±6.9	4.8±3.9	0.0006
number of patients with heart conduction disorders, n/%	10/28%	11/31%	0.8	13/29	5/11	0.03
FVC %, M± δ	80.5±20.1	85.9±20.5	0.034	90.3 ±20.8	92.2±21	0.09
DLCO %, M± δ	53.5±16.2	54.4±15.5	0.6	52.2±17.4	51.9±17	0.86
delta FVC %, Median	5.4 (25th% = -0.6, 75th%=12.3)		-	2.8 (25th% = -3.2, 75th%=6.0)		0.17
EScSG, points, M± δ	2.8±2	1.4±1.2	p=0.0002	1.9±1,5,	1.22±0.9	0.005
the rate of adverse drug reactions, n/%	19/53		-	12/27		0.03

Conclusions

Both drugs effectively reduced mRSS and EScSG in SSc patients. However, CYC more often led to a clinically significant increase in FVC, in contrast to MMF, mostly contributing to stabilization of FVC. The obtained results justify a differentiated approach to SSc pharmacotherapy depending on disease severity. A CYC induction therapy should be considered as appropriate practice in patients with more severe pulmonary disease. A MMF induction therapy should be considered in SSc patients with cardiomyopathy and mild pulmonary disease, with poor CYC tolerability. In other cases, MMF should be used for maintenance therapy after induction with CYC.