Effects of cyclophosphamide and rituximab in patients with connective tissue diseases with severe interstitial lung disease

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Abstract

Objective

We aimed to analyse the effects of real-life immunomodulatory therapy with cyclophosphamide and rituximab for interstitial lung disease (ILD) in patients with systemic sclerosis (SSc-ILD), anti-synthetase syndrome (ASS-ILD), or Sjögren's syndrome (SjS-ILD), in a single academic centre.

Methods

All inpatients with connective tissue diseases treated with intravenous bolus cyclophosphamide or rituximab were identified from the Medical Centre records. Information on patient characteristics, chest CT results, pulmonary function tests, therapies, and severe adverse events, were extracted from inpatient and outpatient records.

Results

Intravenous cyclophosphamide bolus therapy was used in 27 patients with SSc. Cyclophosphamide improved forced vital capacity (FVC) by more than 10% in 4 patients and stabilised it at -0.4% to +3.25% in 8. Rituximab constituted a rescue therapy in 14 SSc patients, and was used for treating 4 patients with ASS-ILD, 2 patients with SjS-ILD and one additional SSc-ILD patient. Rituximab led to FVC improvements of at least 5% in 8 patients and to stabilisation in another 6. 6 patients under cyclophosphamide and 8 patients under rituximab experienced severe adverse events. 8 of the 34 patients died, half of them from causes potentially related to therapy.

Conclusion

In this subset of severely sick patients with connective tissue diseases, cyclophosphamide and/or rituximab led to improvement in 12 patients, and stabilisation was seen in 14. Despite the new options with nintedanib, immunomodulation remains a relevant therapeutic modality for ILD associated with connective tissue disease.

Key words

scleroderma, polymyositis, interstitial lung disease, cyclophosphamide, rituximab

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Introduction

For patients with connective tissue diseases (CTDs), particularly those with systemic sclerosis (SSc) and anti-synthetase syndrome (ASS), fibrosing interstitial lung disease (ILD) constitutes the most common cause of death (1, 2). While nintedanib was recently approved for ILD in SSc-ILD (3) and other rheumatic diseases (4), immunomodulation will presumably retain a role in managing CTD-ILD.

For SSc-ILD, cyclophosphamide (CYC) was shown effective (5). Mycophenolate mofetil, otherwise non-inferior to cyclophosphamide (6), may not be effective if SSc-ILD failed to respond to CYC (7, 8). For refractory SSc-ILD, rituximab (RTX) is an alternative with somewhat variable efficacy data (9-12). For ASS-ILD, there is insufficient evidence overall (13), but some record of RTX (14, 15). Given this background, we analysed our single-centre experience with intravenous immunomodulatory drugs, *i.e.* CYC and RTX, in patients with CTD-ILD.

Methods

A chart review was performed on all patients who underwent i.v. treatment with either CYC or RTX for CTD-ILD 2008 to 2018. We identified 28 patients with SSc, 4 with ASS and 2 with Sjögren's syndrome (SjS) and followed them in a historical prospective way, to their last visit or the end of 2018. All decisions were made clinically, by the treating physician or the CTD board. Patients gave their informed written consent to the analysis of their routine clinical data. This approach was approved by the local Ethics committee.

ILD was diagnosed by high-resolution CT and pulmonary function tests (PFTs), including forced vital capacity (FVC), total lung capacity (TLC) and corrected diffusion capacity for carbon monoxide (DLCOc). PFTs two months prior to two months after the beginning of CYC or RTX were considered baseline values. PFT data were collected from one year before CYC or RTX until the end of the study. Mean changes in FVC% predicted, TLC% predicted and DLCOc% predicted at baseline were compared to values 2-12 months before (pre-CYC/pre-RTX) and after (post-CYC/post-RTX) the initial i.v. administration. Improvement was defined as ≥5%, stable PFTs as -1% to less than +5%. If RTX was started as (an additional) rescue therapy, the further course was attributed to RTX. Severe adverse events were documented within six months after the last RTX or CYC administration.

D'Agostino-Pearson omnibus test was used to test for normality. Normally distributed group results are expressed as mean (SD), not normally distributed as median [IQR]. Respectively, paired t-tests and Wilcoxon matched pairs signed rank test were used for comparisons. p-values <0.05 were considered significant.

Results

Patients

Age at CTD-ILD diagnosis ranged from 27 to 75 years (mean 53.7 (SD 13.5) years). 47% of the patients were female (Table I). At the last follow-up, 4.4 (3.1) years after the initial treatment was started, 24 (19 SSc, 3 ASS, 2 SjS) patients were stable. Two dcSSc patients were lost to follow-up. One dcSSc patient was stable three years after successful double lung transplantation following CYC and RTX. Eight patients had died (see below).

Cyclophosphamide treatment

27/28 SSc patients received a mean of 7.6 (3.4) i.v. CYC infusions, usually 750 mg/m^2 BSA every four weeks. The mean cumulative CYC dose was 11.0 (6.0) g. Patients SSc_09, SSc_16 and SSc_18 received two CYC cycles, all other patients one cycle, *i.e.* 2-12 consecutive i.v. administrations. Patients SSc_03 and SSc_17 had received oral CYC until 3.3 and 1.6 years before i.v. CYC, respectively. Patient SSc_03 had also received three cycles of RTX before the initial i.v. CYC administration.

Rituximab therapy

Six SSc patients and patient ASS_01 received rescue RTX before the CYC cycle was completed, eight additional patients following CYC treatment. Patient SSc_08 received RTX, but no CYC, due to previous CYC intolerance.

Table I. Individual patient characteristics and indications for cyclophosphamide and rituximab.

Patient	Age		CTD	Autoantibodies	CYC Indication		RTX Indication	
					Parameter		Parameter	
SSc_01	41	F	dcSSc	Scl-70, RF	CT, PFT	New	CT, PFT	Worse
SSc_02	38	M	dcSSc	Scl-70	CT, PFT, NYHA lll	Worse	FVC, DLCO	Worse
SSc_03	46	F	dcSSc	Scl-70, RF, CCP	CT, DLCO	Worse	CT, PFT	Worse
SSc_04	47	M	dcSSc	Scl-70	CT, PFT	New	CT, PFT	Worse
SSc_05	59	F	dcSSc	Scl-70	CT, TLC, DLCO	New	-	-
SSc_06	38	M	dcSSc	Scl-70	CT, DLCO, NYHA ll	New	CT, DLCO, NYHA lll	Worse
SSc_07	61	M	dcSSc	Scl-70, RF	CT, PFT, NYHA ll	Worse	CT, PFT, NYHA ll	Worse
SSc_08	49	F	dcSSc	Scl-70, RF, CCP	-	-	FVC, TLC, RA	Worse
SSc_09	70	F	dcSSc	Scl-70, RF, CCP	CT, PFT	New	-	-
SSc_10	27	M	dcSSc	Scl-70, RF	CT, DLCO	New	-	-
SSc_11	54	F	dcSSc	Scl-70, RF	CT, DLCO, NYHA ll	New	-	-
SSc_12	62	M	dcSSc	Scl-70	CT, PFT, NYHA ll	Worse	CT, NYHA lll	Worse
SSc_13	40	M	dcSSc	Scl-70	CT, PFT, NYHA lll	Worse	-	-
SSc_14	41	M	dcSSc	Scl-70, pANCA	CT, PFT, NYHA lll	New	-	-
SSc_15	66	M	dcSSc	Scl-70	CT, PFT, NYHA lV	New	-	-
SSc_16	54	M	dcSSc	Scl-70, NOR-90	CT, NYHA ll	New	PFT, NYHA lll	Worse
SSc_17	52	M	dcSSc	Scl-70, RNAPol3	CT, PFT, NYHA lll	Worse	CT, PFT, NYHA lll	Worse
SSc_18	68	M	dcSSc	RNAPol3, RF, CCP	CT, DLCO, NYHA ll	New	CT, DLCO, NYHA lll	Worse
SSc_19	73	F	dcSSc	RNAPol3	CT, FVC, TLC, NYHA lll	Worse		-
SSc_20	42	F	dcSSc	RF, CCP	PFT, NYHA lll	Worse	RA	Worse
SSc_21	65	M	dcSSc	Ro	CT, PFT, NYHA lll	New	CT, PFT (FVC, TLC)	Worse
SSc_22	44	M	lcSSc	No specific	CT, PFT, NYHA lll	New	DLCO, NYHA lll	Not improved
SSc_23	70	F	lcSSc	CENP-B, PM-Scl	CT, TLC, NYHA IV	New	-	-
SSc_24	31	F	lcSSc	CENP-B, RF	CT, DLCO, NYHA ll	Worse	-	-
SSc_25	75	F	lcSSc	CENP-B	CT, TLC, NYHA lll	Worse	CT, PFT, NYHA lV	Worse
SSc_26	63	F	lcSSc	Ro	CT, PFT, NYHA lll	Worse	-	-
SSc_27	52	M	lcSSc	Ro, Th/To	CT, DLCO	New	-	-
SSc_28	58	M	lcSSc	No specific	CT, NYHA lll	New	-	-
SjS_01	40	F	SjS	Ro, La, RF	-	-	CT, PFT	Worse
SjS_02	69	F	SjS	Ro, La, RF	-	-	CT, PFT, NYHA lll	Worse
ASS_01	60	M	ASS	Jo1, RF	CT, PFT, NYHA ll	New	CT, PFT, NYHA lll	Worse
ASS_02	59	F	ASS	Jo1	-	-	CT, PFT, NYHA lV	New
ASS_03	75	F	ASS	Jo1, RF	-	-	CT, DLCO, NYHA lll	Worse
ASS_04	35	M	ASS	Jo1	-	-	CT, NYHA ll	Worse

SSc: systemic sclerosis; SjS: Sjögren's syndrome; ASS: anti-synthetase syndrome; F: female, M: male; CTD: connective tissue disease; dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; Scl-70: anti-topoisomerase; RF: rheumatoid factor; CCP: antibodies to cyclic citrullinated peptides; pANCA: perinuclear anti-neutrophil cyctoplasma antibodies; RNAPol3: anti-RNA-polymerase 3; CENPB: anti-centromere protein B; CYC: cyclophosphamide; CT high resolution computed tomography of the lungs; PFT: pulmonary function tests (if all abnormal in the same direction). RTX: rituximab; FVC: forced vital capacity; TLC: total lung capacity; DLCO: diffusing capacity of the lungs for carbon monoxide; NYHA: dyspnoea.

Three ASS and 2 SjS patients were treated with RTX without CYC (Table II). Most patients received one cycle (median 1 [IQR 1–3]) of 2x1 g with a two-week interval, usually in combinations (Table II), and with anti-histamine and paracetamol premedication. Since 2015, SSc patients received no prednisolone (100 mg) to not provoke SSc renal crisis. After the first cycle, patient SSc_06 was switched to 2 x 0.69 g, patients SSc_20 and ASS_03 to 1 x 1 g.

Safety

Patient SSc_15 succumbed to an acute myocardial infarction after emergency surgery for lower intestinal perforation one month after the first CYC infusion. Patient SSc_17 died of acute pulmonary embolism six months after i.v. CYC plus RTX. Two more RTX treated patients developed pulmonary embolism one month each after their last RTX infusions. While Patient SjS_02 suffered mild embolism without lasting limitations, patient SSc_16, who was treated palliatively for colon carcinoma, died four months after the event. Patient SSc_21 died from pneumonia 11 days after the first RTX and 30 days after the last CYC infusion. Patient SSc_10 had rapidly progressive ILD despite CYC and died 30 months after autologous hematopoietic stem cell transplantation. Three patients died from malignancies, namely patients SSc_27 and SSc_08 of non-small cell lung cancer (NSCLC), 28 and 29 months after their last *i.v.* CYC or RTX, respectively, and patient ASS_02 of cancer of unknown primary seven months after her last RTX.

Two pneumonias occurred under CYC (Table II). Patient SSc_07 developed neutropenic fever at her calculated CYC dosage, but tolerated CYC after dose adjustment. Fever after the first RTX infusion occurred in patient SSc_12 and minor respiratory infections in patients SjS_01 and ASS_03. No infusion reactions were observed.

Effects on PFT

CYC baseline PFTs are available for 25 of the 27 i.v. CYC treated SSc pa-

Table II. Cyclophosphamide, rituximab, other therapies and SAEs.

Patient	i.v. CYC		RTX	Other therapies			SAE
	infusions	g total	g total	after CYC	with RTX	after RTX	
SSc_01	8	11.1	2.0	RTX	None		-
SSc_02	9	12.6	2.0	AZA	CYC	AZA	-
SSc_03	3	3.7	6.0	poCYC, LuTx	MTX	CYC, MMF	pneumonia
SSc_04	12	27.2	4.0	AZA	CYC	AZA	-
SSc_05	6	7.9	-	AZA	-	-	-
SSc_06	8	8.4	6.1	RTX, MTX	MTX	MTX	-
SSc_07	12	13.5	2.0	AZA, MTX	CYC	AZA, MTX	neutropenic fever
SSc_08	-	-	2.0	-	MTX	MTX	†(follow-up) cancer
SSc_09	6 (+6)	18.6	-	MMF, AZA	-	-	-
SSc_10	3	3.9	-	IAT, ASCT	-	-	†(follow-up) septicaemia
SSc_11	10	14.1	-	AZA	-	-	-
SSc_12	12	17.0	4.0	AZA	CYC	AZA	fever
SSc_13	6	11.1	-	NA	-	-	NA
SSc_14	12	17.4	-	MTX	-	-	NA
SSc_15	3	4.3	-	NA	-	-	† sigma perforation
SSc_16	8 (+6)	22.0	6.0	IAT, RTX, AZA	CYC/AZA	AZA	† pulmonary embolism
SSc_17	2	2.0	2.0	NA	CYC	None	† pulmonary embolism
SSc_18	5 (+6)	17.1	2.0	RTX, AZA	CYC	None	pneumonia
SSc_19	6	8.0	-	AZA	-	-	-
SSc_20	6	7.8	4.0	RTX, MTX, TCZ	MTX	None	-
SSc_21	3	4.6	1.0	RTX	None	None	† pneumonia
SSc_22	9	12.7	2.0	AZA	CYC	AZA	-
SSc_23	6	8.6	-	AZA	-	-	-
SSc_24	9	10.6	-	AZA	-	-	-
SSc_25	6	9.3	2.0	RTX, AZA	AZA	AZA	-
SSc_26	6	5.1	-	AZA	-	-	-
SSc_27	6	8.0	-	AZA	-	-	†(follow-up) cancer
SSc_28	6	9.5	-	MTX	-	-	-
SjS_01	-	-	2.0	-	HCQ, GC	HCQ, GC	respiratory infection
SjS_02	-	-	2.0	-	HCQ, GC	HCQ, GC	pulmonary embolism
ASS_01	6	9.3	2.0	AZA, MMF, RTX	CYC, GC	AZA, MMF, GC	-
ASS_02	-	-	12.0	-	GC	GC	† cancer
ASS_03	-	-	7.0	-	MTX, GC	NA	respiratory infection
ASS_04	-	-	2.0	-	AZA, GC	AZA, GC	-

SSc: systemic sclerosis; ASS: anti-synthetase syndrome; CYC: cyclophosphamide; RTX: rituximab; AZA: azathioprine; poCYC: oral cyclophosphamide; LuTX: lung transplantation; MTX: methotrexate; MMF: mycophenolate mofetil; IAT: immunoadsorption therapy; ASCT: autologous stem cell transplantation; TCZ: tocilizumab; GC: glucocorticoids; HCQ: hydroxychloroquine; SAE: severe adverse event.
Numbers in brackets in the infusions column refer to a previous *i.v.* CYC series.

tients and patient ASS_01. These 26 patients received CYC at a mean FVC of 76.7% (SD 21.1%), TLC of 75.0% (SD 17.1%) and DLCOc of 41.2% (SD 15.2%). Improvements in FVC were seen in four SSc patients (Table III). Eight patients stabilised (ΔFVC -0.4% to +3.25%). Thirteen patients further deteriorated and/or received rescue RTX. Of 21 RTX treated patients, 8 (4 SSc, 3 ASS, 1 SjS) patients had FVC improvement and 6 patients (4 SSc, 1 ASS, 1 SjS) stabilised between -0.1% and +3.5% (Table III). Four SSc patients worsened (median -5.6, range -2.2 to -7.9%).

In 12 patients with PFTs available for the year before CYC, FVC decreased 5.1% (SD 12.3%) before and 0.6% [IQR -4.2–8.2%] under CYC, TLC decreased 7.5% (SD 9.4%) before and increased 4.3% [IQR -0.6–13.5%] under CYC ($p<0.05$) (Fig. 1), and DLCOc decreased 7.6% (SD 10.8%) before and 0.85% (SD 9.4%) under CYC therapy. Under RTX, statistically significant improvement was seen for FVC (-6.4 (SD 11.8)% before, +5.2 (SD 9.0)% after RTX, $p<0.01$) and TLC (-3.2 (SD 8.5)% pre-RTX to +2.6 (SD 8.1)% post-RTX , $p<0.05$), but not for DLCOc (-2.8 [IQR -12.2–0.8]%, pre-RTX, -1.8% [IQR -3.3–11.1%] post-RTX).

Discussion

This analysis from a single academic centre shows that i.v. CYC, combined with or followed by RTX in case of insufficient CYC response, stabilised SSc-ILD in most patients. In ASS-ILD and SjS-ILD, RTX, used first line in all but one patient, was successful.

CYC showed efficacy when comparing FVC before and after therapy and led to SSc-ILD improvement in 4 of 27 patients. Another 7/27 patients stabilised at an acceptable level, for a success rate of approximately one half. RTX rescue therapy was initiated in 14 SSc-ILD patients. Four of these patients improved under RTX, another 4 stabilised, resulting in a total 70% of SSc-ILD patients controlled with the combined approach. RTX without previous *i.v.* CYC improved FVC in 3 ASS patients and one SJS and SSc patient each. Thus, patients with ILD

Table III. FVC and TLC under cyclophosphamide and rituximab.

Patient	FVC (% expected)					
	CYC			RTX		
	Δpre	BL	Δpost	Δpre	BL	Δpost
SSc_01	NA	80.1	-11.6	-18.6	60.3+26.2	
SSc_02	0	64.3	NC	-5.7	53.0	+5.7
SSc_03	0	62.8	-3.0	-5.1	66.5	-2.2
SSc_04	NA	72.4	NC	-15.6	52.8	-0.1
SSc_05	NA	83.0	+11.4	-	-	-
SSc_06	+8.5	122.8	-0.8	-1.3	120.7	+3.3
SSc_07	NA	NA	NA	-37.4	55.9	-6.3
SSc_08	-	-	-	-2.0	74.0	+8.6
SSc_09	NA	75.0	+3.3	-	-	-
SSc_10*	-9.4	86.1	-43.1	-	-	-
SSc_11	NA	104.5	+0.2	-	-	-
SSc_12	-10.0	73.0	NC	0.7	81.0	+1.5
SSc_13	-19.3	60.8	-0.4	-	-	-
SSc_14	-30.8	65.4	+10.3	-	-	-
SSc_15†	NA	41.6	NC	-	-	-
SSc_16	NA	NA	NA	-6.6	53.4	0
SSc_17†	NA	77.2	NC	NA	77.2	NA
SSc_18	+8.9	84.4	-4.2	+7.3	82.9	-7.9
SSc_19	-6.8	54.9	+26.1	-	-	-
SSc_20	0.0	70.9	-6.3	+3.8	67.9	-4.9
SSc_21†	NA	62.1	NC	NA	41.7	NA
SSc_22	-26.6	56.7	NC	+7.3	64.0	+15.7
SSc_23	NA	109.0	+0.4	-	-	-
SSc_24	+12.1	117.6	+2.2	-	-	-
SSc_25	-4.7	81.6	-4.2	0	77.3	+5.6
SSc_26	-12.3	56.7	+23.8	-	-	-
SSc_27	+1.0	110.5	+1.3	-	-	-
SSc_28	NA	65,6	+1.4	-	-	-
SjS_01	-	-	-	-14.1	62.4	+12.3
SjS_02	-	-	-	-20.3	52.5	+3.5
ASS_01	NA	55.3	NC	-8.3	47.0	+16.3
ASS_02†	-	-	-	+2	37.0	+1.2
ASS_03	-	-	-	-11.3	84.3	+14.3
ASS_04	-	-	-	+8.6	74.0	+9.0

SSc: systemic sclerosis; SjS: Sjögren's syndrome; ASS: anti-synthetase syndrome; FVC: forced vital capacity; CYC: cyclophosphamide; RTX: rituximab; TLC total lung capacity; NA: data not available; NC: not calculated because of addition of RTX.
Δpre change (% expected) in the year before CYC/RTX; Δpost change (% expected) in the year following the first CYC/RTX infusion.

associated with SjS or ASS had a still higher rate of success with RTX. The death of one ASS patient was attributed to a malignancy and pulmonary embolism rather than to ILD progression.

Still, the data underline the severity of CTD-ILD, and with 7/28 patients having died by the last follow-up, of SSc-ILD, in particular. Causes of death were mixed, with 3 cancer associated deaths, 2 cases of fatal pulmonary embolism (one with cancer), 2 fatal infections, of which one was temporally associated with cyclophosphamide and rituximab and one case of lower abdominal perforation complicated by myocardial infarction. One other patient successfully underwent lung transplantation as her ultimate chance to control deteriorating ILD. These data drastically shows that SSc-ILD is a commonly fatal disease manifestation.

This study has the typical limitations of a real-life cohort study. These include individual physician decisions related to factors outside the scope of the study and incomplete pulmonary function test data on some patients and on those treated outside this centre before CYC or RTX therapy. However, the real-life data shown here are complete and represent all CTD-ILD patients treated with CYC and/or RTX in our centre in the ten-year time period.

In conclusion, these single-centre real-life data suggest that an immunomodulatory approach, with intravenous cyclophosphamide followed by rituximab in case of insufficient response, was able to stabile disease in three out of four SSc patients. Likewise, monotherapy with rituximab looked highly effective in small groups of patients with ILD associated with anti-synthetase or Sjögren's syndrome. Despite the severity of the condition and the necessity for additional options, including nintedanib, immunomodulation constitutes an important therapeutic approach.

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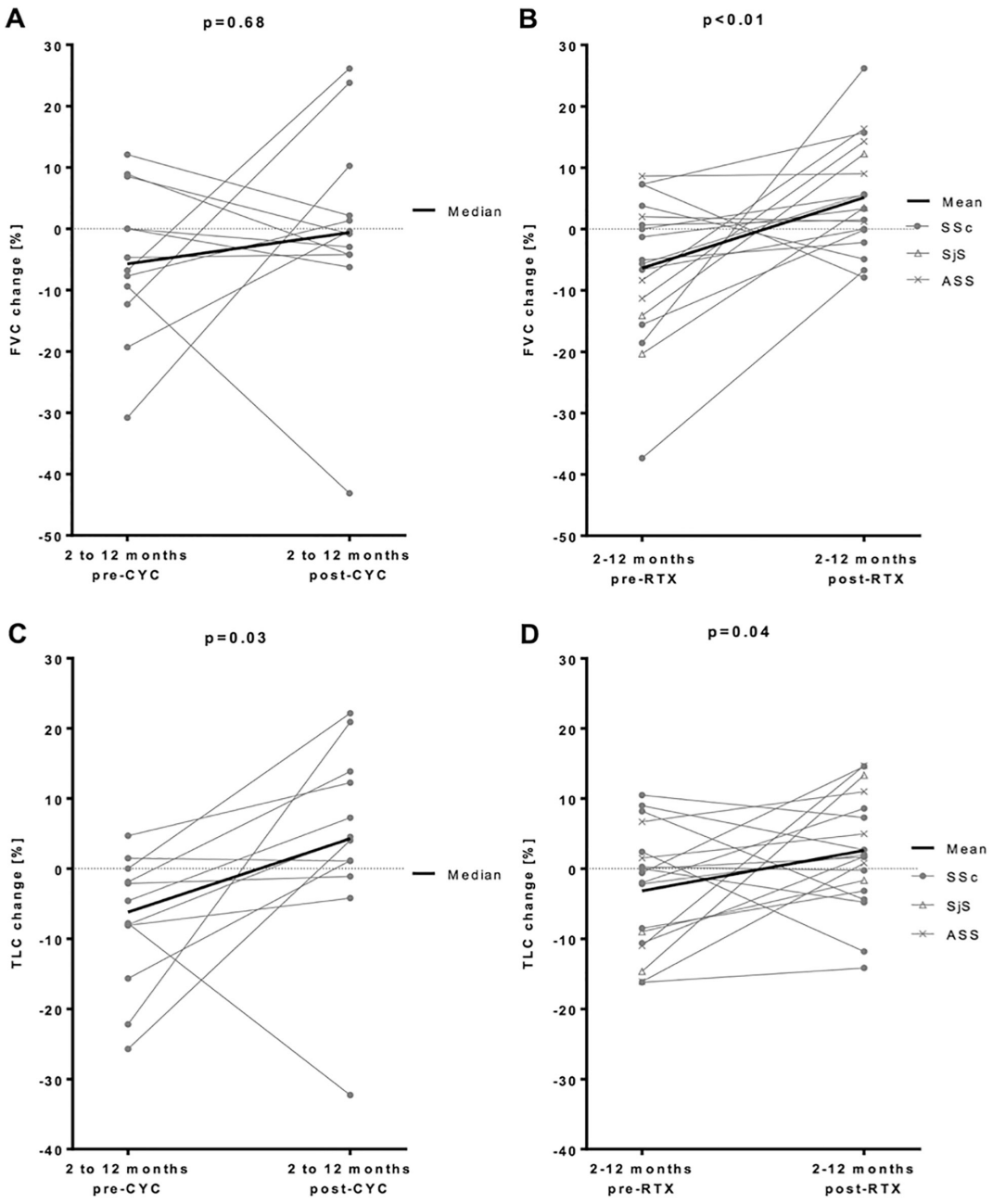

Fig. 1. Paired changes in forced vital capacity (FVC; **A**, **B**) and total lung capacity (TLC; **C**, **D**) before and under i.v. cyclophosphamide (CYC; **A**, **C**) or rituximab (RTX; **B**, **D**) therapy.

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