Supplemental Online Content

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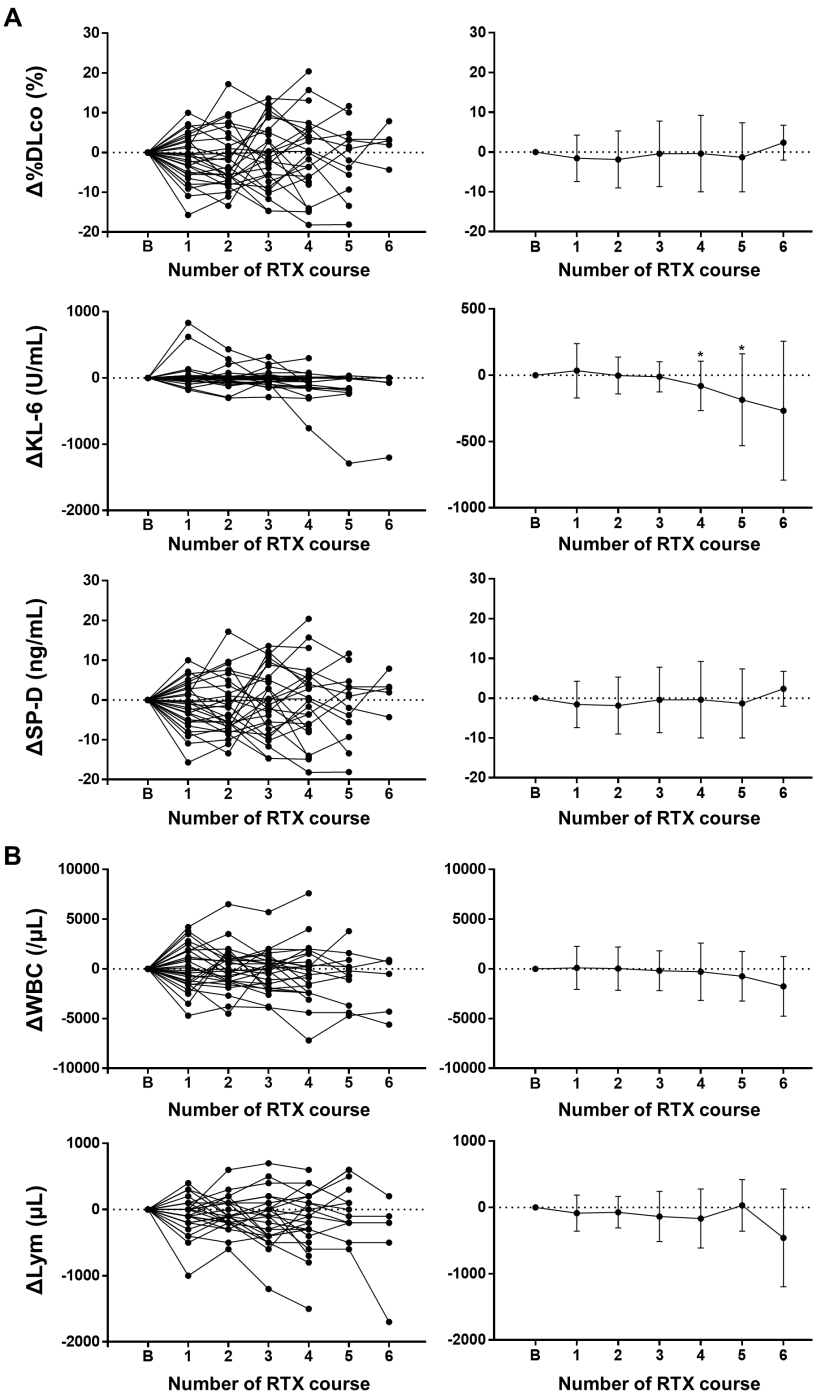
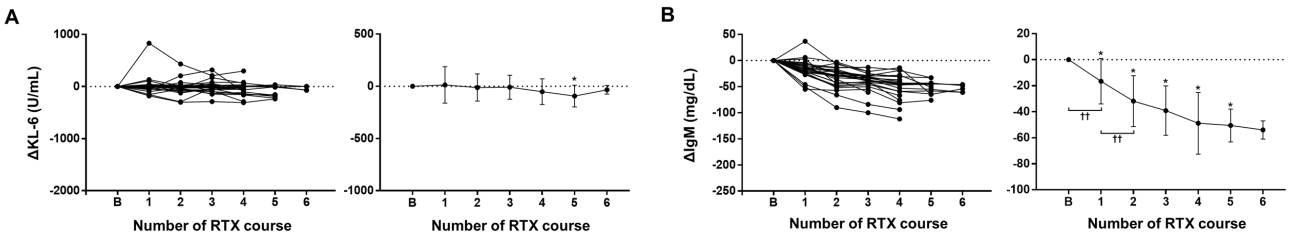
This supplemental material has been provided by the authors to give readers additional information about their work.



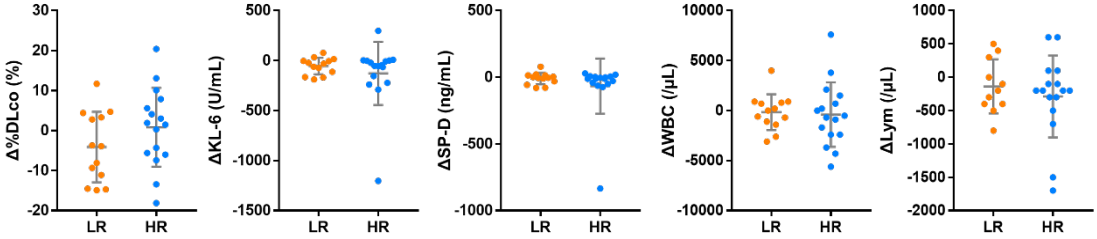
eFigure 1. Effect of rituximab on physiological and laboratory data in SSc.

A, Longitudinal changes in %DLco, serum KL-6 levels, and serum SP-D levels from baseline during follow-up. B, Longitudinal changes in WBC and Lym from baseline during follow-up. N = 29, 29, 29, 28, 25, 13, and 5 at baseline, and 1st, 2nd, 3rd, 4th, 5th, and 6th course of rituximab, respectively. Data are presented for each individual (left) or as mean ± SD (right). Error bars represent SD. *p<0.05 vs. baseline. B, baseline; RTX, rituximab; %DLco, percentage of predicted diffuse diffusing capacity of the lung for carbon monoxide, KL-6, Krebs von den Lungen; SP-D, surfactant protein-D; WBC, white blood cell count; Lym, lymphocyte count.



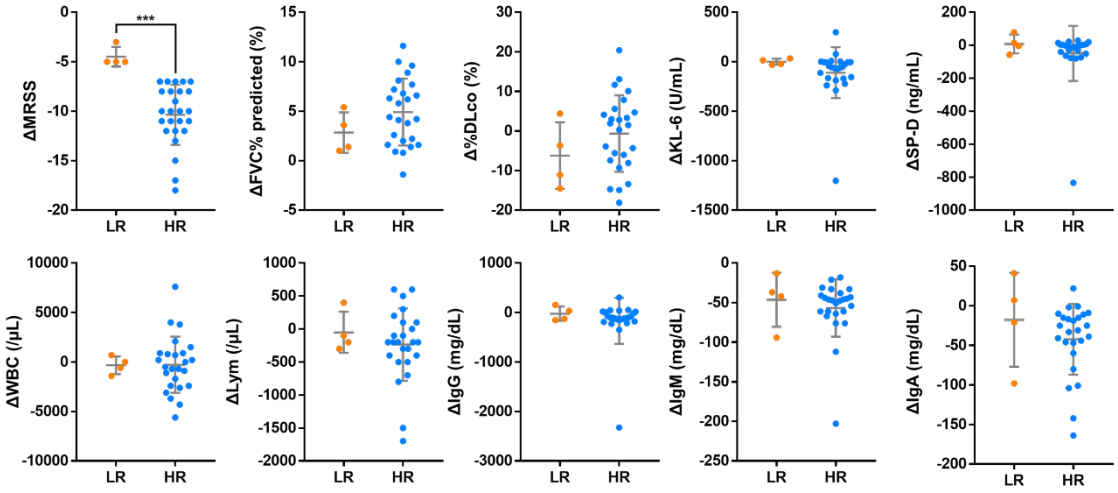
eFigure 2. Longitudinal changes in serum KL-6 and IgM levels after excluding the outliers.

A, Longitudinal changes in serum KL-6 levels from baseline during follow-up in patients after excluding 1 outlier with a marked decrease in KL-6. B, Longitudinal changes in serum IgM levels from baseline during follow-up in patients after excluding 1 outlier with a marked decrease in IgM. N = 28, 28, 28, 27, 24, 12, and 4 at baseline, and the 1st, 2nd, 3rd, 4th, 5th, and 6th course of rituximab, respectively. Data are presented for each individual (left) or as mean ± SEM (right). *p<0.05 vs. baseline. ††p<0.01 between two consecutive time points. B, baseline; RTX, rituximab; KL-6, Krebs von den Lungen.



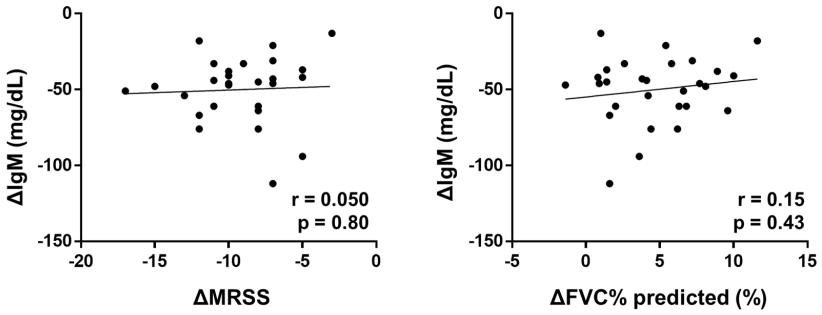
eFigure 3. Changes in clinical parameters and response to rituximab in SSc.

Changes in clinical parameters were compared between HR and LR during follow-up. P values = 0.23 (%DLco), 0.66 (KL-6), 0.52 (SP-D), 0.61 (WBC), 0.87 (Lym). N = 29. Data are presented as mean ± SD. Error bars represent SD. HR, high responders; LR, low responders; %DLco, percentage of predicted diffuse diffusing capacity of the lung for carbon monoxide; KL-6, Krebs von den Lungen; SP-D, surfactant protein-D; WBC, white blood cell count; Lym, lymphocyte count.

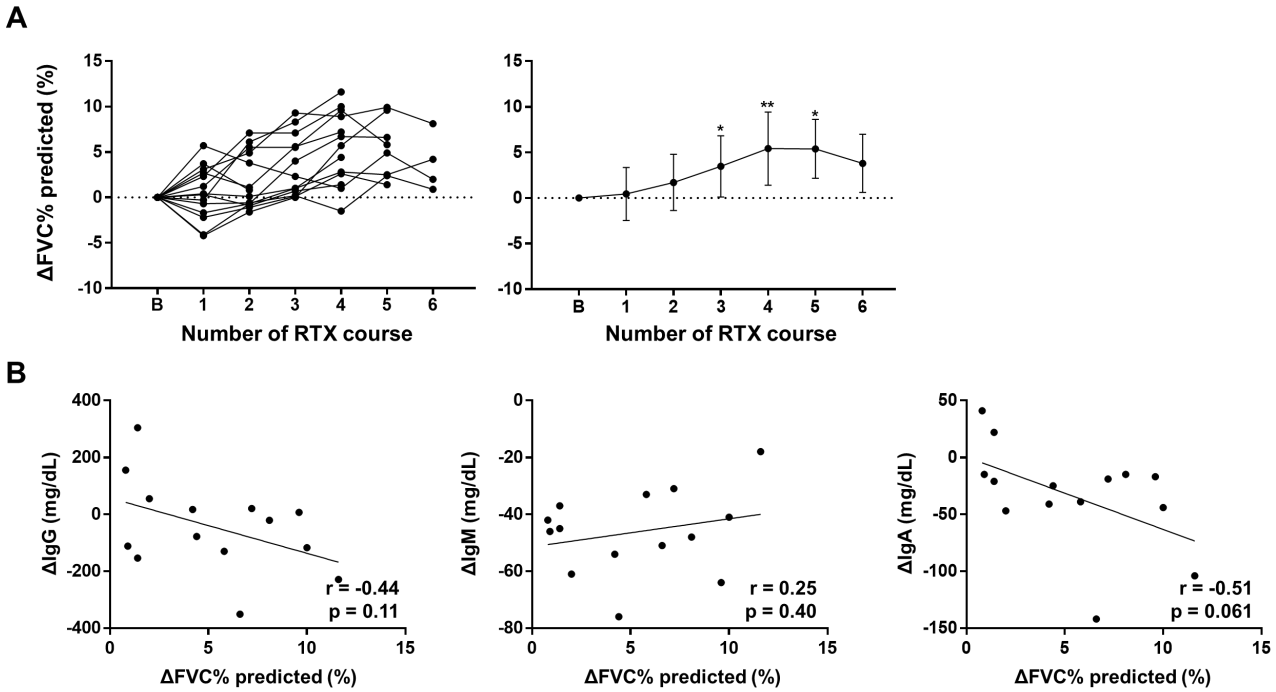


eFigure 4. Changes in clinical parameters in patients with MRSS improvement of > 5 and ≥ 25% and those with MRSS improvement of ≤ 5 or < 25%.

Changes in clinical parameters were compared between HR (MRSS improvement of > 5 and ≥ 25%) and LR (MRSS improvement of ≤ 5 or < 25%) during follow-up. P values = 0.000084 (MRSS), 0.18 (FVC% predicted), 0.41 (%DLco), 0.096 (KL-6), 0.38 (SP-D), 0.99 (WBC), 0.57 (Lym), 0.52 (IgG), 0.37 (IgM), 0.27 (IgA). N = 29. Data are presented as mean ± SD. Error bars represent SD. ***p<0.001. HR, high responders; LR, low responders; MRSS, modified Rodnan skin score; FVC, forced vital capacity; %DLco, percentage of predicted diffuse diffusing capacity of the lung for carbon monoxide; KL-6, Krebs von den Lungen; SP-D, surfactant protein-D; WBC, white blood cell count; Lym, lymphocyte count.

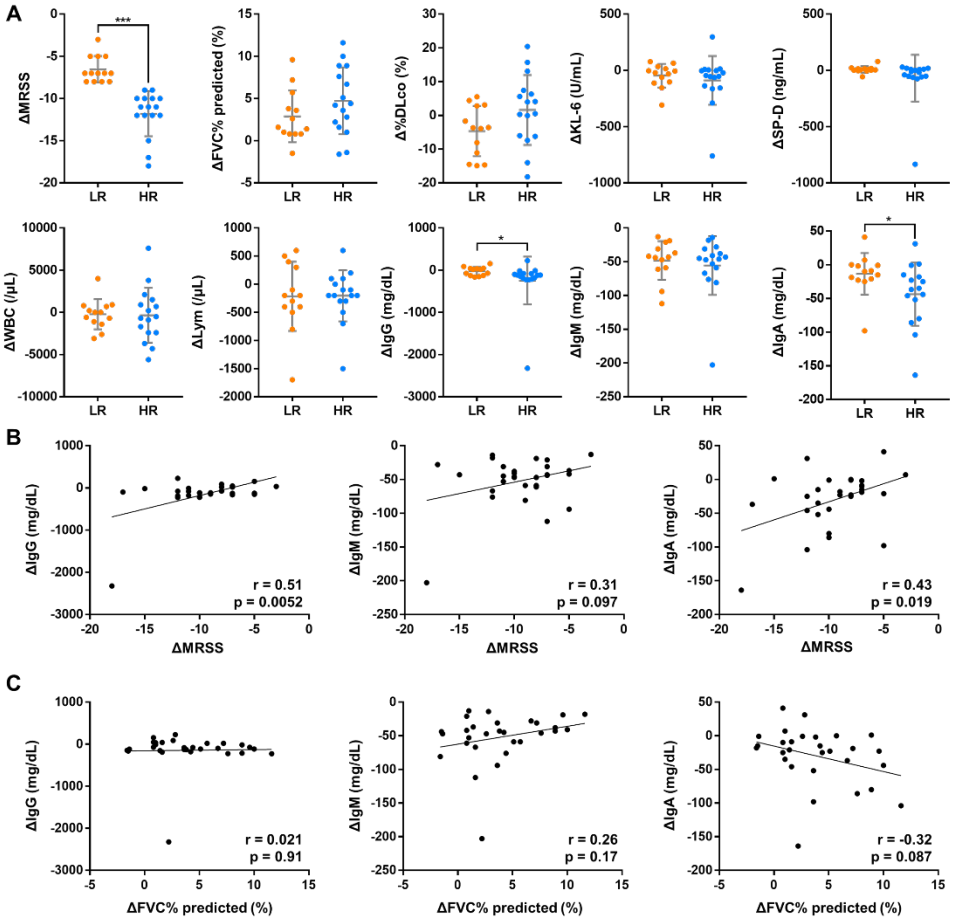


eFigure 5. Correlation between changes in clinical parameters and serum IgM levels after excluding the outlier.
Correlation between changes in MRSS or FVC% predicted and serum IgM levels after excluding 1 outlier with a marked decrease in serum IgM. The solid lines show the regression lines. N = 28. MRSS, modified Rodnan skin score; FVC, forced vital capacity.



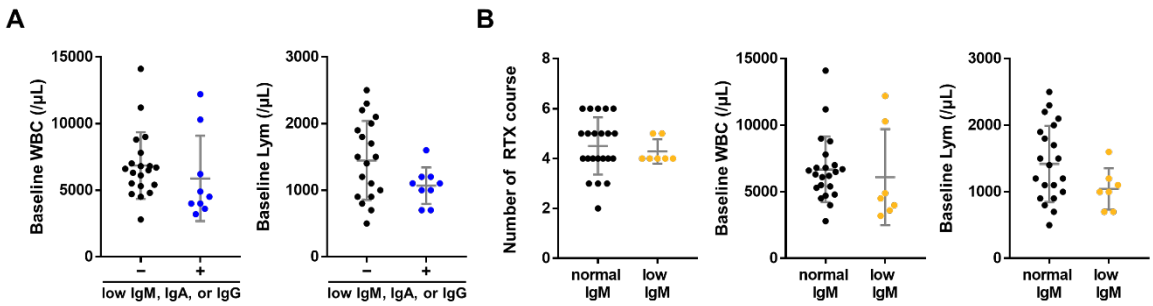
eFigure 6. Changes in FVC% predicted and their correlation with serum immunoglobulin levels in patients with FVC% predicted < 80% at baseline.

A, Longitudinal changes in serum FVC% predicted from baseline during follow-up in patients with FVC% predicted < 80% at baseline. N = 14, 14, 14, 13, 13, 8, and 4 at baseline, and the 1st, 2nd, 3rd, 4th, 5th, and 6th course of rituximab, respectively. Data are presented for each individual (left) or as mean ± SEM (right). *p<0.05 and **p<0.01 vs. baseline. B, Correlation between changes in FVC% predicted and serum immunoglobulin levels. The solid lines show the regression lines. N = 14. Data are presented as mean ± SD. B, baseline; RTX, rituximab; FVC, forced vital capacity.



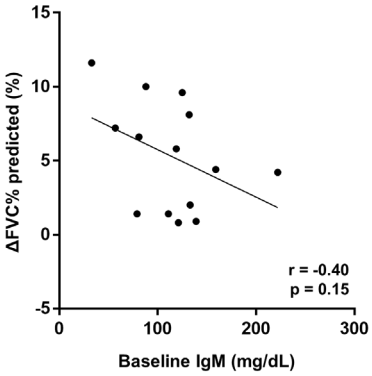
eFigure 7. Serum immunoglobulin levels and clinical response during the first 4 courses of rituximab.

A, Changes in clinical parameters were compared between HR and LR during the first 4 courses of rituximab. P values = 0.000000015 (MRSS), 0.13 (FVC% predicted), 0.075 (%DLco), 0.48 (KL-6), 0.10 (SP-D), 0.84 (WBC), 0.80 (Lym), 0.019 (IgG), 0.67 (IgM), 0.027 (IgA). Data are presented as mean ± SD. Error bars represent SD. B, C, Correlation between changes in MRSS (B) or FVC% predicted (C) and serum immunoglobulin levels. The solid lines show the regression lines. *p<0.05 and ***p<0.001. HR, high responders; LR, low responders; MRSS, modified Rodnan skin score; FVC, forced vital capacity; %DLco, percentage of predicted diffuse diffusing capacity of the lung for carbon monoxide; KL-6, Krebs von den Lungen; SP-D, surfactant protein-D; WBC, white blood cell count; Lym, lymphocyte count.



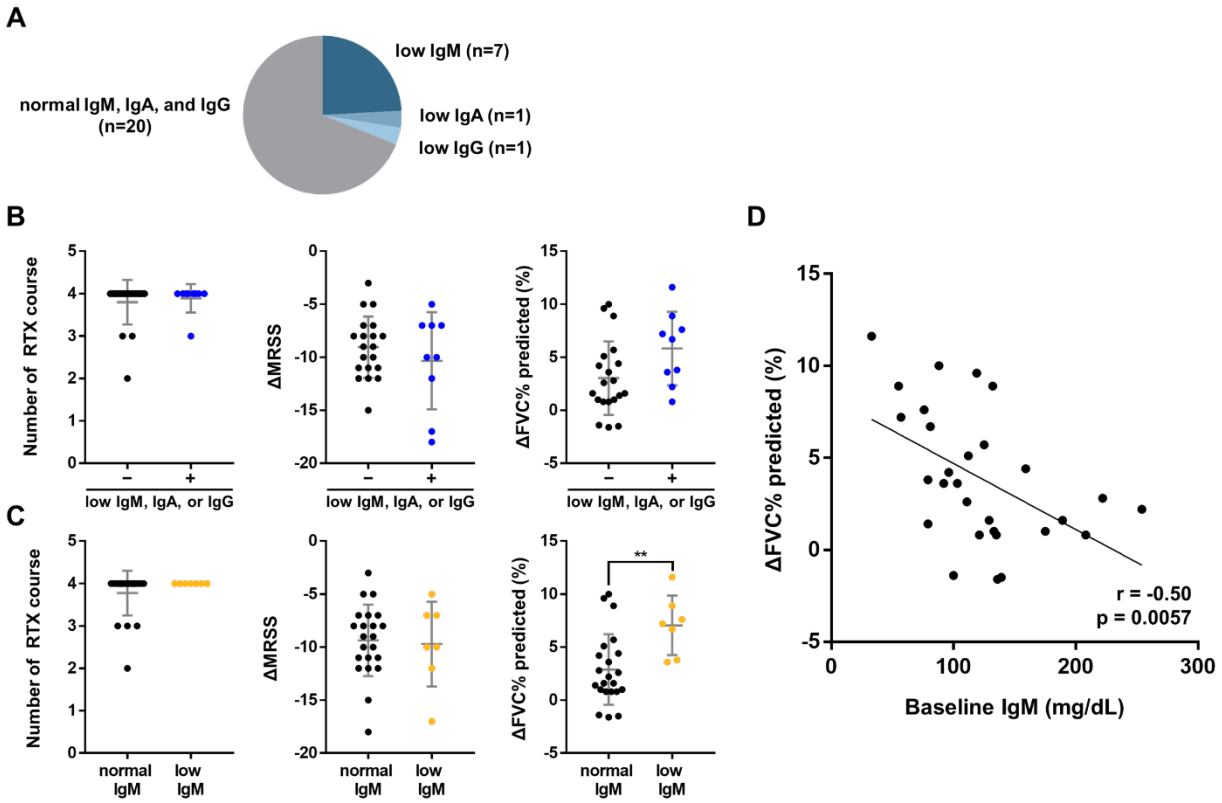
eFigure 8. Baseline laboratory data and low serum immunoglobulin levels following rituximab therapy in SSc.

A, Changes in baseline WBC and Lym were compared between patients with and without low IgM, IgA, or IgG at the last follow-up. B, The number of rituximab courses, baseline WBC, and baseline Lym were compared between patients with low and normal IgM at the last follow-up. N = 29. Data are presented as mean ± SD. Error bars represent SD. RTX, rituximab; WBC, white blood cell count; Lym, lymphocyte count.



eFigure 9. Correlation between baseline IgM levels and FVC% predicted in patients with FVC% predicted < 80% at baseline.

Correlation between baseline IgM levels and changes in FVC% predicted during follow-up. The solid line shows the regression line. N = 14. Data are presented as mean ± SD. *p<0.05 and ***p<0.001. FVC, forced vital capacity.



eFigure 10. Low IgM, IgA, or IgG after the first 4 courses of rituximab.

A, Frequencies of low serum IgM, IgA, or IgG levels in 29 SSc patients after the first 4 courses of rituximab. B, The number of rituximab courses and changes in MRSS and FVC% predicted were compared between patients with and without low IgM, IgA, or IgG after the first 4 courses of rituximab. C, The number of rituximab courses and changes in MRSS and FVC% predicted were compared between patients with low and normal IgM after the first 4 courses of rituximab. D, Correlation between baseline IgM levels and changes in FVC% predicted during the first 4 courses of rituximab. The solid line shows the regression line. N = 29. Data are presented as mean ± SD. Error bars represent SD. **p<0.01. RTX, rituximab; MRSS, modified Rodnan skin score; FVC, forced vital capacity.

eTable 1. Baseline characteristics of the patients with MRSS improvement of > 5 and ≥ 25% and those with MRSS improvement of ≤ 5 or < 25%.

	LR (n = 4)	HR (n = 25)	P values
Age (years)	53 [39.3–54.8]	47 [35–53]	0.416
Sex (No., women/men)	4/0	23/2	>0.999
Disease duration (months)	94.5 [28.3–157.8]	52 [30–135.5]	0.842
Disease type (No., dcSSc/lcSSc)	2/2	23/2	>0.999
Number of rituximab courses	3.5 [2.3–4.0]	5.0 [4.0–5.0]	0.026*
Follow-up period (weeks)	84 [54–96]	120 [96–120]	0.026*
Clinical features			
MRSS	9.5 [7.5–13.8]	14 [11.5–16.5]	0.031*
Pitting scars/digital ulcers	4 (100)	21 (84)	>0.999
Raynaud's phenomenon	4 (100)	24 (96)	>0.999
Nail fold bleeding	1 (25)	16 (64)	0.279
Telangiectasia	3 (75)	6 (24)	0.076
Calcinosis	0 (0)	1 (4)	>0.999
Lungs			
Pulmonary fibrosis	3 (75)	21 (84)	0.553
FVC% predicted (%)	82.5 [70.6–94.0]	80.1 [73.5–97.3]	>0.999
%DLco (%)	83.4 [68.4–98.7]	79.7 [69.7–97.3]	0.981
Laboratory findings			
KL-6 (U/mL)	337 [200–574]	421 [216–624]	0.692
SP-D (ng/mL)	141 [71–193]	154 [79–214]	0.927
White blood cell count (/μL)	6100 [4725–8300]	6200 [4600–7400]	0.867
Lymphocyte count (/μL)	1300 [1125–1475]	1100 [900–1850]	0.697
$CD19^+$ cell number (/μL)	141 [55–330]	179 [121–278]	0.562
$CD20^+$ cell number (/μL)	137 [47–328]	181 [115–258]	0.516
IgG (mg/dL)	1510 [1074–1573]	1257 [1150–1454]	0.516
IgM (mg/dL)	112 [85–162]	119 [85–138]	0.933
IgA (mg/dL)	397 [170–474]	219 [181–271]	0.109
Anti-topoisomerase I antibody	2 (50)	16 (64)	0.622
Anticentromere antibody	1 (25)	3 (12)	0.467
Anti-RNA polymerase III antibody	0 (0)	1 (4)	>0.999
Concurrent medication			
Oral prednisolone	2 (50)	13 (52)	>0.999
Dose (mg/day)	3 [0–9]	4 [0–7.3]	0.826

Data are presented as No. (%) or median [IQR], unless otherwise noted. *p<0.05 and ***p<0.001 between HR (MRSS improvement of > 5 and ≥ 25%) and LR (MRSS improvement of ≤ 5 or < 25%). HR, high responders; LR, low responders; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; MRSS, modified Rodnan skin score; FVC, forced vital capacity; %DLco, percentage of predicted diffuse diffusing capacity of the lung for carbon monoxide; KL-6, Krebs von den Lungen; SP-D, surfactant protein-D.

eTable 2. Baseline characteristics of high responders and low responders after 4 courses of rituximab.

	LR (n = 13)	HR (n = 16)	p-value
Age (years)	50 [35–54.5]	46.5 [35.5–53.5]	0.657
Sex (No., women/men)	13/0	14/2	0.488
Disease duration (months)	77 [23–156]	51.5 [38.5–130]	0.706
Disease type (No., dcSSc/lcSSc)	10/3	15/1	0.299
Number of rituximab courses	4.0 [3.0–4.0]	4.0 [4.0–4.0]*	0.030*
Follow-up period (weeks)	96 [72–96]	96 [96–96]*	0.030*
Clinical features			
MRSS	11 [10–13.5]	15.5 [14–18.8]	0.00085***
Pitting scars/digital ulcers	14 (88)	11 (85)	>0.9999
Raynaud's phenomenon	13 (100)	15 (94)	>0.999
Nail fold bleeding	7 (54)	10 (63)	0.716
Telangiectasia	4 (31)	5 (31)	>0.999
Calcinosis	0 (0)	1 (6)	>0.999
Lungs			
Pulmonary fibrosis	10 (77)	14 (88)	0.6322
FVC% predicted (%)	79.1 [71.1–97.7]	82.9 [73.4–94.4]	0.619
%DLco (%)	79.7 [69.3–93.4]	81.2 [70.2–99.0]	0.567
Laboratory findings			
KL-6 (U/mL)	428 [172–659]	378 [251–570]	0.746
SP-D (ng/mL)	156 [91–185]	127 [69–237]	0.914
White blood cell count (/μL)	6500 [4700–6900]	5800 [4550–8700]	0.738
Lymphocyte count (/μL)	1200 [1000–1700]	1050 [750–1850]	0.537
$CD19^+$ cell number (/μL)	190 [84–367]	175 [124–234]	0.983
$CD20^+$ cell number (/μL)	190 [79–360]	173 [119–226]	0.940
IgG (mg/dL)	1327 [1217–1510]	1233 [1126–1604]	0.4824
IgM (mg/dL)	121 [91–157]	106 [83–135]	0.5518
IgA (mg/dL)	211 [168–328]	225 [184–277]	0.7461
Anti-topoisomerase I antibody	8 (62)	10 (63)	>0.999
Anticentromere antibody	2 (15)	2 (13)	>0.999
Anti-RNA polymerase III antibod			>0.999
y	0 (0)	1 (6)	
Concurrent medication			
Oral prednisolone	6 (46)	9 (56)	0.715
Dose (mg/day)	0 [0–7.5]	4 [0–7.4]	0.720

Data are presented as No. (%) or median [IQR], unless otherwise noted. *p<0.05 and ***p<0.001 between HR and LR. HR, high responders; LR, low responders; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; MRSS, modified Rodnan skin score; FVC, forced vital capacity; %DLco, percentage of predicted diffuse diffusing capacity of the lung for carbon monoxide; KL-6, Krebs von den Lungen; SP-D, surfactant protein-D.

eTable 3. Adverse events

	No. of patients
Any adverse event	27
Upper respiratory infection	18
Dermatitis	5
Skin ulceration	4
Stomatitis	3
Gastroesophageal reflux disease	3
Enterocolitis	3
Diarrhea	3
Any serious adverse event	1

Some patients had more than one adverse event. Common adverse events that occurred in more than 10% of the cohort are shown.