Immunosuppressive Therapy After Autologous Hematopoietic Stem Cell Transplantation in Systemic Sclerosis Patients—High Efficacy of Rituximab

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Background: Systemic sclerosis (SSc) patients often need immunosuppressive medication (IS) for disease control. If SSc is progressive despite IS, autologous hematopoietic stem cell transplantation (aHSCT) is a treatment option for selected SSc patients. aHSCT is effective with good available evidence, but not all patients achieve a treatment-free remission after aHSCT. Thus far, data about the need of IS after aHSCT in SSc is not published. The aim of this study was to investigate the use of IS after aHSCT, its efficacy, and the occurrence of severe adverse events (SAEs).

Methods: Twenty-seven patients with SSc who had undergone aHSCT were included in this single-center retrospective cohort study. Clinical data, including IS, SAEs, and lung function data, were collected.

Results: Sixteen of 27 (59.3%) patients received IS after aHSCT. Methotrexate, rituximab, mycophenolate, cyclophosphamide, and hydroxychloroquine were most commonly used. The main reason for starting IS was SSc progress. Nine patients received rituximab after aHSCT and showed an improvement in modified Rodnan skin score and a stabilization of lung function 2 years after rituximab. SAEs in patients with IS after aHSCT (50.0%) were not more common than in patients without IS (54.6%). SAEs were mostly due to SSc progress, secondary autoimmune diseases, or infections. Two deaths after aHSCT were transplantation related and three during long-term follow-up due to pulmonary arterial hypertension.

Conclusion: Disease progression and secondary autoimmune diseases may necessitate IS after aHSCT in SSc. Rituximab seems to be an efficacious treatment option in this setting. Long-term data on the safety of aHSCT is reassuring.

Keywords: systemic sclerosis, scleroderma, autologous hematopoietic stem cell transplantation, immunosuppression, adverse events, rituximab
BACKGROUND

The pathogenesis of systemic sclerosis (SSc) comprises fibrosis, inflammation, and vasculopathy (1). These three components of SSc pathogenesis often need to be addressed with different treatment modalities. SSc patients with lung fibrosis can be treated with nintedanib (2). Inflammation can be treated with immunosuppressive medications (IS). The European League against Rheumatism (EULAR) recommendations (3) include methotrexate (MTX), which can improve skin sclerosis in early forms of SSc (4), and cyclophosphamide (CYC), which can stabilize SSc interstitial lung disease (5). Further IS, which showed some efficacy on disease manifestations, are mycophenolate (MMF) (6), rituximab (RTX) (7–9), and tocilizumab (10). Autologous hematopoietic stem cell transplantation (aHSCT) has the best evidence for effective treatment of SSc with the three randomized controlled trials ASSIST (11), ASTIS (12), and SCOT (13). These showed that aHSCT is superior to intravenous cyclophosphamide regarding skin and lung involvement, quality of life, and overall survival. However, not all SSc patients achieve a treatment-free remission of SSc after aHSCT. Progressive disease despite aHSCT was shown in 11.1%. A CD34+ selection of stem cells was done in 96.3%. All patients received anti-thymocyte globulin (ATG; Grafalon, Neovii Biotech, Gräfeling, Germany) were given. On day 6, at least 2.0 × 10⁶ CD34⁺ autologous hematopoietic stem cells/kg bw were reinfused.

Statistical Analysis

Calculations were done with SPSS Statistics v 26.0 (IBM, Armonk, NY). Shapiro–Wilk tests were used to test for normal distribution. When normal distribution was absent, medians with interquartile ranges (IQR) were calculated. For continuous variables, differences between unpaired groups were examined with Wilcoxon signed-rank tests and differences between unpaired groups with Mann–Whitney U-tests. For metrical variables, differences between unpaired groups were calculated with Fisher’s exact tests. Differences were considered significant when two tailed p-values were <0.05. Excel (Microsoft, Redmond, Washington) was used to collect the data and draw the graphs. Figures were grouped with Photoshop (Adobe, San Jose, CA).

RESULTS

Patients’ Characteristics Before aHSCT and Transplantation Parameters

Twenty-seven SSc patients, who are in our care after aHSCT, were included in the study. Of the patients, 48.1% were female, with a median age of 47.2 years and a median disease duration of 25.0 months before aHSCT; 93.3% were positive for anti-nuclear antibodies (ANA), and 74.1% were positive for Scl-70 antibodies; 88.9% had a diffuse cutaneous form (dcSSc) with a mean modified Rodnan skin score (mRSS) of 23.0; and 37.0% had ever smoked (active smokers during aHSCT were 7.4%). Pulmonary fibrosis on thoracic computed tomography was present in 77.8% of the patients. Cardiac involvement (i.e., high-sensitive troponin above the upper limit of normal + myocardial late enhancement in cardiac MRI or myocarditis in myocardial biopsy) was present in 44.4%; 25.9% had a history of myocardial biopsy (Table 1).

Need of Immunosuppression After aHSCT in SSc

The immunosuppressive medications (IS; except glucocorticoids), which were started after aHSCT, were recorded. Eleven patients...
TABLE 1 | Characteristics of the study population and therapy.

| Characteristics | Values |
|----------------|--------|
| Patients’ characteristics before aHSCT |        |
| Female, n (%) | 13/27 (48.1) |
| Age at aHSCT, mean (range), years | 47.2 (23–64) |
| Disease duration before aHSCT, median (range), months | 25.0 (5–156) |
| Diffuse cutaneous form, n (%) | 24/27 (88.9) |
| mRSS, mean (range), points | 23.0 (5–44) |
| Anti-nuclear antibody positivity, n (%) | 26/27 (96.3) |
| Anti-Scl-70 antibody positivity, n (%) | 20/27 (74.1) |
| Anti-Centromere antibody positivity, n (%) | 0/0 (0.0) |
| Smoking history: | During aHSCT, n (%) | 2/27 (7.4) |
| | Ever, n (%) | 10/27 (37.0) |
| Pulmonary fibrosis on thoracic computed tomography, n (%) | 21/27 (77.8) |
| Cardiac involvement§, n (%) | 12/27 (44.4) |
| Pulmonary arterial hypertension, n (%) | 7/27 (25.9) |
| Transplantation parameters |         |
| Indication for aHSCT: |         |
| | Skin, n (%) | 9/27 (33.3) |
| | Lung, n (%) | 15/27 (55.6) |
| | Skin and lung, n (%) | 3/27 (11.1) |
| CD34+ selection for stem cell autograft, n (%) | 26/27 (96.3) |
| ATG use for conditioning regimen, n (%) | 27/27 (100.0) |
| Immunosuppression (glucocorticoids not regarded) after aHSCT |         |
| Patients without IS after aHSCT, n (%) | 11/27 (40.7) |
| Follow-up time after aHSCT, median (IQR), months | 29.0 (10.0–122.0) |
| Patients with IS after aHSCT, n (%) | 16/27 (59.3) |
| Follow-up time after aHSCT, median (IQR), months | 67.0 (39.0–124.5) |
| Cumulative IS-free time after aHSCT, median (IQR), months | 29.5 (9.5–49.3) |
| Proportion of cumulative IS-free time/follow-up time, median (IQR), % | 60.3 (18.8–74.0) |
| IS used: |         |
| | MTX, n (%) | 9/27 (33.3) |
| | Rituximab, n (%) | 9/27 (33.3) |
| | Hydroxychloroquine, n (%) | 3/27 (11.1) |
| | MMF, n (%) | 3/27 (11.1) |
| | Cyclophosphamide, n (%) | 3/27 (11.1) |
| | Colchicine, n (%) | 2/27 (7.4) |
| | Cyclosporine A, n (%) | 1/27 (3.7) |
| | Azathioprine, n (%) | 1/27 (3.7) |
| | Tocilizumab, n (%) | 1/27 (3.7) |
| | Anakinra, n (%) | 1/27 (3.7) |

aHSCT, autologous hematopoietic stem cell transplantation; ATG, anti-thymocyte globulin; IS, immunosuppression; IQR, interquartile range; MMF, mycophenolate; mRSS, modified Rodnan skin score; MTX, methotrexate.

§That is, high-sensitive troponin above upper limit of normal or myocardial late enhancement in cardiac MRI or myocarditis in myocardial biopsy.

(40.7%) did not need any IS after aHSCT within the median follow-up time of 29.0 (IQR, 10.0–122.0) months. Sixteen of the 27 SSc patients (59.3%) needed IS after aHSCT within the median follow-up time of 67.0 (39.0–124.5) months (comparison between median follow-up time between no IS and IS: p = 0.148). The 16 patients receiving IS had a median cumulative immunosuppression-free time to the overall follow-up time resulted in a median of 60.3 (18.8–74.0) %.

Different immunosuppressive drugs were used in the 16 SSc patients, who needed IS after aHSCT: methotrexate (MTX) in nine patients, rituximab (RTX) in nine, hydroxychloroquine (HQC) in three, mycophenolate (MMF) in three, cyclophosphamide (Cyc) in three, colchicine in two, and cyclosporine A (CSA), azathioprine (AZA), tocilizumab, and anakinra in one patient each (for summary, see Table 1; for details, see Table 2). The median time after aHSCT when IS was started was 9.5 (5.3–19.5) months. The most common indication for starting an IS was cutaneous or pulmonary SSc progress in 12 patients. Indications for the start of rituximab were cutaneous progress of SSc (n = 4), pulmonary progress (n = 2), and secondary autoimmune diseases like microscopic polyangiitis (MPA; n = 1), immune thrombocytopenia (n = 1), and myositis (n = 1) (Table 2).

Prevalence of Severe Adverse Events Does Not Differ Between Patients Taking IS and Patients Without IS

Of the 16 patients who took IS after aHSCT, eight (50.0%) developed a severe adverse event (SAE), which caused hospitalization. The median time after aHSCT, when the first SAE occurred, was 17.0 (9.8–26.8) months. Of the 11 SSc patients not taking IS after aHSCT, six (54.6%) had an SAE at a median of 10.0 (3.3–36.8) months after aHSCT. Neither the prevalence of SAEs was significantly different between the groups (p = 1.000) nor the time of occurrence after aHSCT (p = 0.414). Relevant reasons for SAEs were SSc progress, autoimmune diseases, infections, and malignancy (Table 2). Five autoimmune diseases were recorded: MPA, immune thrombocytopenia,
| Patient | IS before aHSCT | IS after aHSCT, drug, dose, begin (months after aHSCT), intake duration (months after aHSCT), indication | Time without IS after aHSCT, months | Follow-up after aHSCT, months | SAE# Begin after aHSCT (months), treatment | Death time after aHSCT (months) |
|---------|----------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------|---------------------------------|-----------------------------------------------|-------------------------------|
| 1       | CYC, Imatinib  | MTX, 15 mg s.c./p.o., 35 mo, 55 mo, cutaneous progress, RTX, 2× 1 g, 44 mo, na, microscopic polyangiitis          | 86                                 | 141                             | Esophageal stenosis, 15 mo, endoscopic dilatation | na                           |
|         |                |                                                                                                                 |                                    |                                 | Microscopic polyangiitis, 44 mo, RTX           |                               |
| 2       | MTX, CSA, MMF, CYC | MTX, 15 mg s.c., 15 mo, 2 mo, cutaneous progress, MMF, 1–3 g, 17 mo, 38 mo, cutaneous progress, RTX, 2× 1g, 23 + 30 + 48 mo, na, cutaneous progress, CYC, 1× 750 mg/m², 48 mo, na, pulmonary progress | 32                                 | 72                             | Esophageal stenosis, 29 mo, endoscopic dilatation | na                           |
|         |                |                                                                                                                 |                                    |                                 | Pneumonia, 53 mo, piperacillin/tazo bacterium   |                               |
| 3       | CYC            | RTX, 2× 1 g, 21 + 27 mo, na, pulmonary progress                                                                  | 41                                 | 47                             | None                                          | na                           |
| 4       | MTX, HCQ, CSA  | RTX, 4× 375 mg/m², 18 mo, na, immune thrombocytopenia, CSA, 150 mg, 20 mo, 50 mo, immune thrombocytopenia          | 84                                 | 141                             | Immune thrombocytopenia, 16mo, RTX + CSA       | na                           |
|         |                |                                                                                                                 |                                    |                                 | Primary hyperthyroidism, 18 mo, thiamazole      |                               |
| 5       | CYC, AZA       | MTX, 15 mg s.c., 5 mo, 2 mo, cutaneous progress, Tocilizumab, 162 mg s.c., 6 mo, 1 mo, cutaneous progress, RTX, 2× 1 g, 6 mo + 14 mo, na, cutaneous progress | 29                                 | 39                             | Pneumocystis pneumonia, 18 mo, cotrimoxazole   | na                           |
|         |                |                                                                                                                 |                                    |                                 | Candida esophagitis, 19 mo, fluconazole         |                               |
| 6       | MMF            | RTX, 2× 1 g, 11 mo, na, cutaneous progress, MTX, 15 mg s.c., 12mo, 3mo, cutaneous progress                  | 14                                 | 17                             | None                                          | na                           |
| 7       | MTX, AZA, CYC  | RTX, 2× 1g, 2 + 8 + 16 + 23+29mo, pulmonary progress                                                          | 8                                  | 39                             | None                                          | na                           |
| 8       | HCQ, AZA, CYC, RTX | MMF, 2 g, 22 mo, 83 mo, myositis, RTX, 2× 1 g, 24 + 20 + 99 mo, na, myositis and pulm. Progress           | 22                                 | 120                            | Infected finger ulcer, 26 mo, amoxicillin/clavulanic acid, Intestinal bleeding, 90 mo, endoscopy | Yes, 120 mo                 |
|         |                |                                                                                                                 |                                    |                                 | Worsening of PAH, 118 mo, uk                   |                               |
| 9       | MTX, CSA, MMF  | HCQ, 400 mg, 6 mo, 30 mo, cutaneous progress, MTX, 15 mg p.o., 10 mo, 2 mo, cutaneous progress, RTX, 2× 1 g, 12 mo, na, cutaneous progress, CYC, 1× 750 mg/m², 12 mo, na, cutaneous progress | 44                                 | 72                             | None                                          | na                           |
| 10      | CYC, MMF       | MTX, 15 mgs.c./p.o., 6 mo, 35 mo, inflammatory bursitis                                                          | 0                                  | 41                             | None                                          | na                           |
| 11      | MTX, CYC       | MTX, 15 mg p.o., 8 mo, 6 mo, cutaneous progress                                                               | 57                                 | 64                             | Desmoid tumor 3rd left rib, 27 mo, excision    | na                           |
| 12      | MTX, HCQ, CYC  | MTX, 10 mg s.c., 2 mo, 5 mo, cutaneous progress                                                              | 26                                 | 36                             | None                                          | na                           |
| 13      | MTX, AZA, CSA, RTX, infunonide, MMF, CYC, tocilizumab | HCQ, 400 mg, 3 mo, 2 mo, arthritis, Colchicine, 0.5 mg, 4 mo, 27 mo, CPPD disease, Anakinra, 100 mg, 6 mo, 2 mo, arthritis, CYC, 1× 750 mg/m², 18 + 19 + 20 + 21 mo, na, pulmonary progress, MMF, 1–3 g, 23 mo, 108 mo, pulmonary progress, Colchicin, 0.5 mg, 99mo, 6mo, arthritis urica | 2                                  | 31                             | Pneumonia, 8 mo, moxifloxacin Worsening of PAH, 23 mo, selexipag + iloprost | Yes, 41 mo                 |
| 14      | CYC, RTX       | CYC, 1× 750 mg/m², 18 + 19 + 20 + 21 mo, na, pulmonary progress, MMF, 1–3 g, 23 mo, 108 mo, pulmonary progress, Colchicin, 0.5 mg, 99mo, 6mo, arthritis urica | 30                                 | 150                            | None                                          | na                           |
primary hyperthyroidism (two times), and Sjögren’s syndrome. Seven severe infections (six pneumonias and one infected finger ulcer) led to hospitalization. One patient developed malignancy (lung adenocarcinoma) 116 months after aHSCT. Death occurred in five of our patients, of which two were aHSCT-associated (one in the first month after aHSCT due to respiratory insufficiency assumedly because of progressive lung disease and another 10 months after aHSCT due to pneumonia with lactate acidosis), and three were due to respiratory insufficiency because of progressive PAH (29, 41, and 120 months after aHSCT, respectively).

**IS Improves Skin and Stabilizes Lung Function in SSc Patients After aHSCT**

The 16 patients, who received IS after aHSCT, were analyzed according to their course of mRSS (n = 15), forced vital capacity (FVC; in percentages of predicted), and diffusion capacity for carbon monoxide (DLCO; in percentage of predicted) (n = 14). Baseline mRSS values were collected at the time when the respective IS was initiated (0.0 months [IQR 0.0–0.0]), and the follow-up value was collected 24.0 (22.0–26.0) months later. Median mRSS was 19.0 (8.0–29.0) at baseline and 8.0 (2.0–14.0) 2 years after initiation of IS ($p = 0.001$) (Figure 1A).

Baseline FVC and DLCO were collected at the time of IS initiation (0.0 [−2.0–0.0] months) and 23.0 (22.0–28.0) months after starting IS. Median baseline FVC was 79.0 (53.1–100.3) % and 2 years later 79.0 (58.0–101.7) % ($p = 0.694$) (Figure 1B). Baseline DLCO was 43.5 (31.1–65.2) % and 2 years later, 44.5 (40.1–66.4) % ($p = 0.675$) (Figure 1C).

**Figures 1A, C, E** show medians with IQRs of the patients, who received IS after aHSCT, and **Figures 1B, D, F**, the values for each patient.

In contrast, SSc patients who did not receive IS after aHSCT (n = 7) exhibited no improvement of mRSS (12.0 [12.0–40.0] months after aHSCT the mRSS was 6.0 [4.0–17.0]; 28.0 [23.0–119.0] months after aHSCT the mRSS was 7.0 [4.0–14.0], $p = 0.450$). For details see, **Supplementary Figure S1**.
SSc Patients Receiving Rituximab After aHSCT Show Improved Skin and Stabilized Lung Function

Nine (of the 16 patients receiving any IS) received rituximab after aHSCT and underwent subgroup analysis according to their course of mRSS, FVC, and DLCO. The median time after aHSCT, when RTX was given for the first time, was 18.0 (8.5–23.5) months.

mRSS values were collected before RTX application (~5.0 [−1.5 to −11.0] months), at the time of RTX application (baseline; 0.0 [−0.5 to 0.5] months), and after RTX (24.0 [18.5–
Use of Rituximab After aHSCT in SSc Patients for Non-skin and Non-lung Indications Is Effective

One SSc patient received rituximab because of the development of a microscopic polyangiitis (MPA) starting 44 months after aHSCT with positivity for myeloperoxidase anti-neutrophil cytoplasmic antibodies (MPO-ANCA) and with renal involvement proven by renal biopsy [for details, see the formerly published case report (17)]. At the time of rituximab application, hematuria and proteinuria were present and improved 26 months after rituximab (erythrocytes/µl urine, 39 vs. 10 [reference, <25]; total protein mg/g creatinine in urine, 524 vs. 102 [reference, <70]; albumin mg/g creatinine in urine, 471 vs. 50 [reference, <30]). A decline was observed in the MPO-ANCA titer (IU/ml, 43 vs. 9 [reference, <3.5]) (Supplementary Figure S2A). Another patient received rituximab because of the development of an immune thrombocytopenia 18 months after aHSCT. The thrombocytopenia were 28,000/µl (reference, 150,000–450,000/µl) at the time of rituximab application and increased to 142,000/µl 24 months after rituximab (Supplementary Figure S2B). A third patient received rituximab because of the development of myositis (the diagnosis based on creatine kinase (CK) elevation, proximal muscle weakness, and pathological electromyography) 22 months after aHSCT. The CK value was 467 U/L [reference, <190] at the time of rituximab application and 198 U/L 34 months after rituximab (Supplementary Figure S2C).

DISCUSSION

This study is the first description of the use and efficacy of immunosuppressive medication after aHSCT in SSc patients. We found a high prevalence of 59.3% among our SSc patients, who needed IS after aHSCT, mostly due to SSc progress. An increase in SAEs compared to SSc patients without use of IS could not be found. The IS receivers had improved skin and stabilized lung parameters 2 years after initiation of IS. As most of the patients received more than one IS in the course of time, attributing these effects to one specific IS difficult. However, subgroup analysis of the rituximab receivers (nine of our 16 patients) also showed improved skin and stabilized lung parameters 2 years after rituximab application.

Although the indications for RTX treatment were diverse and were not only due to progressive skin involvement, all of the RTX receivers showed an improvement of mRSS. It cannot be excluded that this improvement was promoted by a positive long-term effect of aHSCT but before RTX application the mRSS was stable (or progressively worsened due to progressive skin involvement).

The prevalence of IS use after aHSCT in our SSc cohort might have been underestimated, as the follow-up time in the group that received IS was considerably longer (67 months) than in the IS-free group (27 months), although this finding was statistically not significant. The IS-free patients might need IS in a longer follow-up period. Our data described that aHSCT cannot achieve a treatment-free remission in all SSc patients.

The aHSCT aims to achieve a reset of the immune system (18) and thereby promote its positive effects on SSc disease manifestations. The reset has been described within the B-cell compartment, as aHSCT induces a decrease in memory B cells and an increase in naive B cells (15). These changes were present for at least 1 year after aHSCT. The reset of the immune system seems not to last in all patients in the long term. A recurrence or persistence of autoreactive lymphocytes has to be assumed (19). This could be an explanation why SSc patients exhibit disease progress after aHSCT and need immunosuppression. To date, no data are available on which treatment option is the best after aHSCT; often treatment strategies are used that are recommend for not-transplanted SSc patients. We found that rituximab had positive effects on skin and lung manifestations of SSc. Rituximab causes similar changes in B-cell subsets as aHSCT with a reduction in memory B cells and increased naive B cells (20, 21). Therefore, rituximab application after aHSCT is a reasonable treatment option for progressive disease, and it is not surprising that our patients benefited from rituximab application.

Long-term follow-up after aHSCT in SSc is described, and event-free survival was described in 64% of the patients after 5 years (22). SSc progress or relapses were described in 28% of the initial responders within 2.7 years, and corticosteroids, mycophenolate, and cyclophosphamide were used for treatment. In the SCOT trial, the initiation of disease-modifying anti-rheumatic drugs was reported in 9% of SSc patients 2 years after aHSCT (13). In other autoimmune diseases, also scarce data are available for the need and use of IS after aHSCT. In multiple sclerosis in a study of 10 patients, two needed IS after aHSCT within the follow-up time of 10 years (23).
FIGURE 2 | Course of skin and lung parameters of the nine SSc patients receiving rituximab (RTX) after aHSCT. Values before RTX (before RTX, gray boxes) are shown, and baseline values (gray boxes) were taken when RTX was initiated and follow-up values (after RTX, white boxes) 2 years later. (A) Median modified Rodnan skin score (mRSS) and (B) mRSS values of each of the nine RTX receivers. (C) Median forced vital capacity (FVC) in percentages of predicted and (D) individual FVC values of each patient. (E) Median diffusion capacity for carbon monoxide (DLCO) in percentage of predicted and (F) individual DLCO values of each patient. Box plots show medians with interquartile range, whiskers indicate minimums and maximums; *Significant (p < 0.05) difference compared to baseline in a Wilcoxon signed-rank test.
Our study is limited due to the small sample size and the prospective and the single-center study design.

CONCLUSION

aHSCT seems to cause a long-lasting disease control in a subgroup of SSc patients. Another subgroup needs temporary immunosuppressive treatment despite aHSCT. Close and long-lasting follow-up for SSc patients seems to be necessary to detect progressive disease early and to treat it appropriately. Further studies evaluating the efficacy of rituximab after aHSCT should be performed.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

MG had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: MG and MS. Acquisition of data: MG, MS, and MF. Analysis and interpretation of data: MG, MS, H-PT, and ES. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.817893/full#supplementary-material

Supplementary Figure 1 | Course of skin and lung parameters of 7 SSc patients, who did not receive immunosuppression after aHSCT. The mRSS did not change after aHSCT (12.0 [12.0–20.0] months after aHSCT) and the median mRSS was 6.0 [4.0–17.0] months after aHSCT the mRSS was 7.0 [4.0–14.0], P = 0.450. The median FVC and DLCO (each in percentage of predicted) did not show significant differences 14.0 [12.0–40.0] months after aHSCT compared to 29.0 [23.0–119.0] months after aHSCT (FVC: 65.0 [52.0–87.0] % vs 76.0 [66.0–87.0] %, P = 0.674; DLCO: 30.0 [27.0–51.0] % vs 34.0 [23.0–48.0] %, P = 0.865). The individual data is shown for (A) mRSS, (B) FVC, and (C) DLCO. The cohort of SSc patients after aHSCT, who did not receive IS, comprised 11 patients, but retrospective data was not available from 4 patients due to short follow up or because of fatal complications in the course of disease.

Supplementary Figure 2 | Improvements of non-skin and non-lung parameters in SSc patients with former aHSCT after rituximab (RTX) application. (A) Course of urine parameters and of MPO-ANCA of one SSc patient, who had developed a microscopic polyangiitis after aHSCT and therefore received RTX. (B) Course of thrombocytes of one SSc patient, who developed immune thrombocytopenia and therefore received RTX. (C) Course of creatine kinase (CK) of a SSc patient, who developed myositis after aHSCT and therefore received RTX; mo, months; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic antibodies.
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