Favorable long term effects of intensified immunosuppression combined with therapeutic plasma exchange in patients with early-onset progressive systemic sclerosis-related interstitial lung disease

J. Potjewijd a, *, R. Tobal a, D. Silvertand a, H.A. Gietema b, J.G.M.C. Damoiseaux c, P. van Paassen a

a Department of Internal Medicine, Division Nephrology and Clinical Immunology, Maastricht University Medical Center, Maastricht, the Netherlands
b Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, the Netherlands
c Diagnostic Laboratory, Maastricht University Medical Center, Maastricht, the Netherlands

A B S T R A C T

Objective: Systemic sclerosis (SSc) related mortality and morbidity remains high. Immunosuppressive therapy is considered most effective when immune activity and inflammation but not fibrosis still dominates the disease process. This study evaluated long-term intensified immunosuppression combined with therapeutic plasma exchange (TPE) in early-onset progressive SSc-related interstitial lung disease (ILD).

Methods: The study cohort consisted of 161 SSc patients, with a median follow-up time of 8.9 years. The standardized mortality rate (SMR) and overall survival was calculated in patients with and without cardiopulmonary involvement. We used a standardized, pragmatic, non-randomized approach to treat 24 consecutive early progressive SSc-ILD patients with intensified immunosuppressive therapy, including plasma exchange. Outcome measurements were event-free survival (EFS), pulmonary function and safety profile. The outcome was compared with the analyzed data from the other SSc-ILD patients, who did not fulfill the inclusion criteria, and instead were treated with estimated optimal care (EOc).

Results: The age-adjusted SMR of all 161 SSc patients was 3.0 (CI95%; 0.32–5.68). EFS at 10 years was 49.9% in the intensified treatment group and 43.3% in the EOc group (p = 0.019). Improvement of the percentage of predicted forced vital capacity (%pFVC) and percentage of predicted diffusing capacity for carbon monoxide (%pDLoC) in the intensified treatment group was +10.1% respectively +3.6%, compared to a decrease of respectively 10.8% and 7% in the EOc (p < 0.001 resp. p = 0.019), Safety analysis showed 1 death (female patient, over 75 years of age), due to pneumosepsis, in the intensified treatment group.

Conclusion: Intensified and long-lasting immunosuppression combined with TPE is safe in early severe systemic sclerosis and is associated with improved EFS and pulmonary function as compared to the outcome in the variable but EOc group. Our findings warrant larger studies for confirmation.

1. Introduction

Systemic sclerosis (SSc) is characterized by fibrosis of the skin and internal organs, small-vessel vasculopathy and immune dysregulation. Prevalence is low but SSc-related morbidity and mortality is high and a great burden to the patient and their relatives [1]. Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the main causes of death in SSc [2,3]. Treatment encompasses four major different domains: general conservative measures such as statins and vasodilators, the use of different classes of PAH medication, immunosuppression, including stem cell transplantation, and more recently, antifibrotic therapy.

At least three randomized controlled studies demonstrated superior efficacy of autologous hematopoietic stem cell transplantation (HSCT) in selected SSc patients [4–6]. Treatment in high-risk patients with rapidly progressive SSc improved survival and prevented major organ failure compared to one year cyclophosphamide pulse therapy, however at the cost of high treatment-related mortality up to 10% [7]. HSCT is only available in highly specialized centers and patient selection is vital. Moreover, the comparator immunosuppression may not have been optimized in previous studies. Thus, alternative treatment regimens particularly in early progressive and severe disease are needed in order to prevent the long-term fibrotic sequelae and reduce SSc-related morbidity and mortality. In 2004 we initiated a pragmatic,
fibrosis on high resolution computed tomography (HRCT) and/or evi-
SSc-ILD was diagnosed in the presence of ground glass opacification or
September 1, 2019, development of ILD and/or PAH was monitored.
met the 2013 ACR/EULAR criteria for SSc [7]. During follow-up until
hospital between January 1, 2004 and July 1, 2017, and retrospectively
was received.
Medical Research Ethics Committee of Maastricht University Medical
all data for efficacy and safety. Ethical approval was obtained from the
involvement. Patients were informed and consented that no standard
therapy was available at that time. Finally, we retrospectively evaluated
in the absence of significant ILD, meaning less than 10% lung
monary vascular resistance (PVR)
Eosinophilia cutaneous arteritis and gangrene (ECA-G)
vasculitis (WHO criteria).
In order to compare outcome measures of the intensified treatment
group we selected a control group by including all patients from the
complete SSc cohort, who fit the same definition of pulmonary
involvement as the intensified treatment group. However, these patients
were either not treatment naïve, suffered from earlier renal crisis,
refused to give informed consent for TPE, or had a disease duration >3
years. They were treated with what was considered estimated optimal
care (EOc) by their treating physician. Procedure of enrollment is shown
in Fig. 1. Patients were considered lost to follow-up if the vital status was
not confirmed. For these patients, vital status and date of last visit was
noted.

2.2. Data collection

Data were retrospectively retrieved from medical records. Sclero-
derma renal crisis was defined as new onset malignant hypertension and
oligo-/anuric renal failure. Gastrointestinal tract involvement included
reflux, dysmotility, diarrhea, or signs of malabsorption. Cardiovascular
disease was defined as ischemic heart failure or cerebral infarction.
Antinuclear antibody (ANA) was tested by indirect immunofluorescence
assay (IFA) on Hep-2 cells, followed by specific extractable nuclear
antigens (ENA) test and SSc blot of Euroimmun.
HRCs were scored by an experienced radiologist, according to the
Goh criteria [9], which divide patients into those with extensive disease
(>20% disease extent at HRCT, or indeterminate disease extent and %
P/FVC<70%), or limited disease (<20% disease extent at HRCT, or
indeterminate disease extent and %pFVC<70%). Only scans following a
HRCT protocol and reconstructed at 1 mm slices were read.

2.3. Outcome measures

The primary endpoint was EFS, defined as time in days from devel-
operation of ILD until death due to any cause, or the development of
consistent major organ failure (heart, lung, kidney), defined as left
ventricular ejection fraction less than 30% by echocardiography, resting
arterial oxygen tension less than 8 kPa (60 mmHg) and/or resting
carbon dioxide tension greater than 6.7 kPa (50 mmHg) without
supply oxygen, or the need for renal replacement therapy. Secondary
endpoints were the change in pulmonary function compared to baseline
as a measurement of morbidity, and safety profile defined as treatment-
related mortality and number of hospital admissions. Outcome measures
of the intensified treatment group were compared with the residual SSc-
ILD group treated with what was considered estimated optimal care
(EOc) by their treating physician.

2.4. Intensified immunosuppressive treatment procedure

The intensified treatment protocol consisted of 7–10 sessions of TPE
in a period of 2–3 weeks, 6 months oral cyclophosphamide (2–3 mg/kg,
adjusted in case of low leucocyte number) followed by long-term
mycophenolate mofetil (MMF). In case of intolerance to mainte-
nance treatment, patients switched to rituximab. In addition prednisone
(maximum 30 mg a day, tapering to 5 mg in three to four months) was
given. TPE procedures were carried out with Haemonetics MCS+©. At
each session approximately 50% plasma volume was exchanged, using a
10% albumin solution as replacement fluid.

2.5. Statistical analysis

Statistical analysis was performed by using IBM SPSS Statistics for
Windows, version 25.0. Descriptive statistics were calculated for de-
ographic and clinical characteristics. Continuous variables are pre-
duced as mean (± standard deviation) in case of a normal distribution or
median (interquartile range (IQR)) in case of non-normal distribution.
Categorical variables are presented as numbers (percentage). Charac-
teristics of each cohort were compared with control group using t-test or
Mann-Whitney U test (whichever appropriate based on variable distri-
bution) for continuous variables and Pearson chi-2 or Fisher exact test
for categorical variables.

To calculate SMR, mortality rates of the general population adjusted
for age were obtained from the Central Statistical Office of the
Netherlands. SMR was defined as the ratio of observed deaths in the SSc cohort to the number of expected deaths of the Dutch age-matched population in 2011–2016. The expected number of deaths is the product of the number of people in each age group of the SSc cohort multiplied by the age-matched mortality rate of the general population. The observed number of deaths was divided by the person time under observation. Cumulative survival rates at 1, 3, 5 and 10 years were computed by the Kaplan-Meier method and significance was tested with the log-rank test. To evaluate whether there was a significant change over time in %pFVC and %pDLco between the two SSc-ILD treatment groups, a linear mixed-effects model with a fixed effect for time (continuous, in years) was used. Figures were made using GraphPad Prism version 5.03 for Windows.

3. Results

3.1. Survival and standardized mortality rate of the total SSc cohort

The entire cohort consisted of 161 SSc patients, including 57 SSc-ILD (35.4%) and 17 SSc-PAH (10.6%) patients. Demographics and clinical characteristics of the cohort are shown in Table 1. During the median 8.9 years (IQR 8.6) follow-up there were 48 deaths recorded in the whole cohort of 161 patients, corresponding with an age-adjusted SMR of 3.0 (CI 95% 1.39–5.55). The mean age at death was 71.5 years (±7.6) with a median disease duration of 7.7 years (IQR 8.0). There were 9 deaths (52.9%) reported in the SSc-PAH group, compared to 27 (47.4%) in the SSc-ILD group, corresponding with a collective age-adjusted SMR of 4.1 (CI 95% 1.93–8.60). The age-adjusted SMR in patients without ILD and/or PAH is 1.58 (CI 95% 0.84–4.98). Of 41 patients, the cause of death was identified (Table 2). The number of malignancies of any kind did not differ between patients with (15.6%) or without (6.5%) immnosuppression (p = 0.694). Overall survival rates from disease onset in the total SSc cohort, SSc-ILD and SSc-PAH patients are shown in Fig. 2.

3.2. Demographics and baseline clinical characteristics in the SSc-ILD cohort

The 57 patients in the SSc-ILD cohort consisted of 32 (56.1%) females and the mean age of ILD onset was 60.5 (±11.9) years. Four patients were lost to follow-up and five patients were excluded from analysis, because of incomplete clinical details. Of the remaining 48 SSc-ILD patients, 24 patients fulfilled the inclusion criteria for the early-onset intensified treatment including TPE. Clinical outcomes were compared with the 24 SSc-ILD patients in the EOc group. Patients in the EOc group were excluded for the early-onset intensified treatment because they were not treatment-naïve (n = 10 earlier immunosuppressive treatment, n = 1 antifibrotic treatment), had a disease duration >3 years (n = 6), suffered from a renal crisis (n = 2), or declined informed consent for TPE (n = 4). Of note, even in the EOc cohort 7/24 patients received TPE, a clinical decision based on inflammatory features such as elevated sIL2r or signs of active alveolitis on the DTPA scan. Demographics and clinical characteristics of the two groups are shown in Table 3. Treatment within the EOc group was heterogeneous, less patients received either cyclophosphamide (50% vs 95.8%; p = 0.001), TPE (29.2% vs 100%; p < 0.001), or maintenance MMF (37.5% vs 83.3%; p = 0.003) (see Table 3).

Of the 24 included patients in the intensified treatment arm, 21 patients had a disease duration of <1 year. They all received 6 months of oral cyclophosphamide combined with a minimum of 10 cycles of TPE, then followed by maintenance treatment with MMF in 20 patients with a median duration of 60 months (IQR 65). Three patients received...
Table 1
Demographic and clinical characteristics of the single center Maastricht cohort.

| Clinical features | All patients (n = 161) | Without CPI (n = 87) | SSc-ILD (n = 57) | SSc-PAH (n = 17) |
|-------------------|------------------------|----------------------|------------------|------------------|
| Age at disease onseta, mean ± SD, y | 56.5 ± 14.0 | 55.1 ± 13.8 | 56.3 ± 14.0 | 64.5 ± 12.6 |
| Female sex | 118 (73.3) | 69 (79.3) | 32 (56.1) | 17 (100) |
| Duration of follow-up, median, IQR, y | 8.9 (8.8) | 8.4 (9.1) | 9.6 (6.6) | 5.0 (12.4) |
| Skin involvement, n (%) | 160 (99.4) | 87 (100) | 56 (98.2) | 15 (100) |
| Antibody | | | | |
| Limited | 114 (70.8) | 70 (80.5) | 32 (56.1) | 12 (70.6) |
| Diffuse | 22 (13.7) | 3 (3.4) | 18 (31.6) | 5 (5.9) |
| Sine sclerosis | 24 (14.9) | 14 (16.1) | 6 (10.5) | 4 (23.5) |
| Disease manifestations | | | | |
| ILD | 59 (36.6) | 0 (0.0) | 57 (100) | 2 (11.8) |
| PAH | 33 (20.5) | 0 (0.0) | 16 (28.0) | 17 (100) |
| Renal crisis | 4 (2.5) | 0 (0.0) | 3 (5.3) | 1 (5.9) |
| GI involvement | 101 (62.7) | 40 (46.0) | 48 (84.2) | 13 (76.5) |
| Digital ulcers | 85 (52.8) | 44 (50.8) | 31 (54.4) | 10 (58.8) |
| Comorbidities | | | | |
| CVD | 51 (31.7) | 24 (27.6) | 19 (33.3) | 8 (47.1) |
| Malignancy | 36 (22.4) | 17 (19.5) | 14 (24.6) | 5 (29.4) |
| Treatment | | | | |
| PAH medication | 65 (40.4) | 23 (26.4) | 26 (45.6) | 16 (94.1) |
| Immunosuppression | 104 (64.6) | 46 (52.9) | 50 (87.7) | 8 (47.1) |

Data are presented as number (%) unless otherwise indicated. IQR: interquartile range; CPI: cardiopulmonary involvement (ILD or PAH); ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; ANA: anti-nuclear antibodies; GI: gastro-intestinal; CVD: cardiovascular disease (myocardial or cerebral infarction); ¥ Defined as the date of the first non-Raynaud’s phenomenon symptom.

Table 2
Cause of death in total SSc cohort.

| Cause of death | n = 48 (29.8%) |
|----------------|---------------|
| SSc related n=17 (41.5%) | PAH | Pulmonary fibrosis | Heart disease (arrhythmia, heart failure) | GI failure (aspiration, ileus) |
| No-SSc related n=24 (58.5%) | Malignancy | Septis | Ischemic heart or cerebral disease | Other | Unknown |

There were 48 deaths recorded during the median 8.9 years (IQR 8.6) follow-up in the whole cohort of 161 patients. Of 41 patients, the cause of death was identified. Data are presented as numbers. PAH: pulmonary arterial hypertension. GI: gastrointestinal.

Fig. 2. Overall survival SSc cohort from age at disease onset, SSc without ILD and PAH, SSc-ILD and SSc-PAH. Overall survival rates at 1, 3, 5, and 10 years from disease onset in the total SSc cohort were 98.7%, 94.1%, 91.3%, 73.0% and 62.4% (not shown). Overall survival rates at 1, 3, 5, and 10 years from disease onset in the SSc patients without ILD and PAH were 100%, 98.7%, and 84.7%. Overall survival rates at 1, 3, 5, and 10 years from disease onset in the SSc-ILD patients were 100%, 91.0%, and 89.2% and 63.7%. Overall survival rates at 1, 3, 5, and 10 years from disease onset in the SSc-PAH patients were 88.2%, 75.6%, and 61.9% and 54.1%. Patients without ILD or PAH had significantly better survival rates compared to SSc-ILD (p = 0.005) and SSc-PAH (p < 0.001).

3.3. EFS and cause of death in SSc-ILD cohort

During follow-up from onset ILD 7 deaths (29.2%) were reported in the intensified treatment group and 12 deaths (50.0%) in the EOc group. EFS rates at 1, 5, and 10 years from onset ILD in the intensified treatment group were 100%, 86.7% and 49.9%. EFS rates at 1, 5, and 10 years were 83.3%, 53.6% and 43.3% in the EOc group (log rank p = 0.106; Fig. 3). A SSc-related cause of death occurred in 2 out of 7 patients in the intensified treatment group and in 7 out of 12 patients in the EOc group (not statistically compared due to limited data) (Table 3).

3.4. Response of interstitial lung disease to treatment

The change of %pFVC during 5 years in the intensified treatment group showed greater improvement compared to the EOc group (p < 0.001; Fig. 4a). The difference between groups in %pFVC was greatest at 4 years (Δ 20.5%; 95% CI 9.97–31.01). The intensified treatment induced a 10.1% increase of %pFVC as compared to the 10.8% decrease in %pFVC in the EOc arm, over 5 years follow-up. The difference between groups in %pDLco during 5 years showed a Δ of 10.6% (95% CI 1.75–19.57; p = 0.0019; Fig. 4b) in favor of the intensified treatment group, which improved by +3.6%, compared to the 7% decrease in %pDLco of the EOc group, over 5 years follow-up.

In 20 out of 22 of the patients in the intensified treatment group,
Table 3
Baseline characteristics of the SSc-ILD cohort.

| Clinical features                  | Intensified Treatment (n = 24) | EoC treatment (n = 24) | p     |
|------------------------------------|-------------------------------|-----------------------|-------|
| Age at disease onset, mean ± SD, y | 57.7 ± 11.7                  | 56.2 ± 14.9           | 0.247 |
| Male sex                           | 58.9 ± 11.9                  | 61.9 ± 12.1           | 0.639 |
| Disease duration, median, IQR, y   | 11 (45.4)                    | 13 (54.2)             | 0.564 |
| Duration total follow-up           | 8.8 (5.1)                    | 10.2 (10.6)           | <0.001|
| Duration from first non-RP symptom to ILD diagnosis | 0.8 (1.0) | 3.3 (9.0) | 0.003 |
| Duration follow-up from onset ILD  | 7.7 (6.4)                    | 5.5 (8.7)             | 0.048 |
| Smoking                            | 10 (41.7)                    | 8 (33.3)              | 0.627 |
| BMI median, IQR, kg/m²             | 25.0 (5.8)                   | 23.6 (3.9)            | 0.061 |
| Skin involvement                  | n = 24 (100)                 | n = 23 (95.8)         |       |
| Limited                            | 10 (41.7)                    | 15 (62.5)             | 0.106 |
| Diffuse                            | 12 (50.0)                    | 5 (20.8)              | 0.044 |
| Sine sclerosis                    | 2 (8.3)                      | 3 (12.5)              | 0.666 |
| Antibody                           |                              |                       |       |
| Centromere                        | 1 (4.2)                      | 7 (29.2)              | 0.048 |
| Topoisomerase I                    | 17 (70.8)                    | 9 (37.5)              | 0.020 |
| RNA polymerase III                | 1 (4.2)                      | 1 (4.2)               | 1.000 |
| Other                              | 0                            | 1 (4.2)               | 1.000 |
| ANA only                           | 4 (16.7)                     | 6 (25.0)              | 0.477 |
| None                               | 1 (4.2)                      | 1 (4.2)               | 1.000 |
| Raynaud                            | 21 (87.5)                    | 24 (100)              | 0.234 |
| Pulmonary function tests, mean ± SD |                     |                       |       |
| TLC % predicted                    | 81.2 ± 17.8                  | 79.0 ± 18.6           | 0.921 |
| FVC % predicted                   | 84.8 ± 21.5                  | 92.0 ± 25.9           | 0.449 |
| DLCO/VA % predicted               | 68.8 ± 16.0                  | 67.1 ± 19.9           | 0.396 |
| Right heart catheterization       | 22 (91.7)                    | 22 (91.7)             |       |
| Extensive disease (Goh stage)      | 11 (45.8)                    | 9 (37.5)              | 0.537 |
| DTPA scan                          | 22 (91.6)                    | 8 (33.3)              |       |
| Positive                           | 20 (90.9)                    | 5 (62.5)              | 0.102 |
| 6MWD                               | 12 (50.0)                    | 14 (58.3)             |       |
| Median, IQR, m                     | 491 (128)                    | 397 (206)             | 0.548 |
| Distance % predicted               | 76 (65-94)                   | 63 (28–101)           | 0.031 |
| Pulmonary hypertension             | 3 (12.5)                     | 4 (16.7)              | 0.699 |
| Right heart catheterization mPAP, median, IQR, mmHg | 6 (25.0)          | 5 (20.8)              |       |
| WMP, median, IQR, mmHg             | 26 (11.5)                    | 35 (21)               | 0.126 |
| PVR, median, IQR, dyn.sec.cm⁻²-5   | 7 (8.8)                      | 10 (7.5)              | 0.329 |
| Creatinine, median, IQR, umol/L    | 77 (19)                      | 83 (30)               | 0.267 |
| CRP median, IQR, mg/L              | 8.0 (19)                     | 3.0 (11)              | 0.158 |
| sIL2r, median, IQR, ng/mL          | 722 (511)                    | 333 (482)             | 0.658 |
| Earlier treatment                  | 2 (8.3)                      | 10 (41.7)             |       |
| Hydroxychloroquine                 | 0                            | 1 (4.2)               | 1.000 |
| Methotrexate                       | 0                            | 5 (20.8)              | 0.050 |
| Prednisone                         | 2 (8.3)                      | 8 (33.3)              | 0.033 |
| Immunosuppressive treatment first year |               |                       |       |
| Plasma exchange                     | 24 (100)                     | 7 (29.2)              | <0.001|
| Cyclophosphamide                   | 23 (95.8)                    | 12 (50.0)             | 0.001 |
| Ciclosporin + azathioprine         | 1 (4.2)                      | 1 (4.2)               | 1.000 |
| Methotrexate                       | 0                            | 3 (12.5)              | 0.234 |
| Ciclosporin + Rituximab            | 0                            | 1 (4.2)               | 1.000 |
| Mycophenolate mofetil              | 0                            | 1 (4.2)               | 1.000 |
| No immunosuppression               | 0                            | 6 (25.0)              | 0.009 |

Data are presented as number (%) unless otherwise indicated. IQR: interquartile range; BMI: Body Mass Index; TLC: total lung capacity; FVC: forced vital capacity; DLCO/VA: diffusing capacity for carbon monoxide; 6MWD: 6-min walking distance; ANA: antinuclear antibodies; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; PWP: pulmonary arterial wedge pressure; RP: Raynaud phenomenon; ¥ Defined as the date of the first non-Raynaud’s phenomenon symptom.

Table 4
Cause of death in SSc-ILD patients.

| Cause of death                  | Intensified treatment n = 7 (29.2%) | EoC n = 12 (50%) |
|---------------------------------|-------------------------------------|------------------|
| SSc related                     | PAH                                 | 0                |
|                                | Pulmonary fibrosis                   | 1                |
|                                | Heart disease (arthritis, heart failure) | 1                |
|                                | GI failure (aspiration, ileus)       | 0                |
| Non-SSc related                 | Lung cancer                          | 3                |
|                                | Respiratory tract infection           | 2                |
| Unknown                         |                                     | 0                |

Data are presented in numbers. PAH: pulmonary arterial hypertension. GI: gastrointestinal.

DTPA scanning showed active alveolitis. During follow-up 18 out of the 20 positive DTPA scans improved with normalization in 16 cases, 1 patient deteriorated and 1 case remained unchanged. During follow-up no patient in the intensified treatment and 1 patient in the EoC group developed PAH, the latter classified as group 3 PH [8].

3.5. Safety of intensified immunosuppressive treatment

Safety of intensified immunosuppression was estimated by evaluating the number of treatment related hospitalizations. In both treatment groups, there were 8 infection-related admissions noted. Other indications were cardiovascular disease (1 vs 2), digital ulcers (11 vs 3) or other (8 vs 10). Treatment-related mortality was low. Only one death during treatment was recorded, in a patient older than 75 years, who died of infection. During follow-up 4 patients in the intensified treatment group developed malignancy and 8 patients in the EoC group (p = 0.182).

4. Discussion

In this single-center study investigating a large SSc cohort, we found an age-adjusted SMR of 3.0 which corresponds to reported outcomes in previous studies [10,11]. The age-adjusted SMR of 4.1 in the SSc patients with ILD and/or PAH is even higher, reflecting the high mortality related to cardiopulmonary involvement in these patients. Our treatment study was set up in an exploratory pragmatic way as we felt the urge to treat patients as early as possible with intensified
immunosuppression during remission-induction, followed by prolonged maintenance therapy. The rationale for this approach was fueled by the assumption that in the early phase of progressive severe systemic sclerosis immune dysregulation and inflammation is the dominant disease driving factor. At the time we started our study no standardized and well evaluated treatment modalities were available, and in many cases a more restrained approach was usual. To date, HSCT is available, but still only in tertiary centers and selection of patients is still a critical issue.

The 5 years EFS rates in the ASTIS (79.7%) and SCOT (79%) trials (4, 5) is comparable to the 5 years EFS of 86.7% in the intensified and long-term immunosuppressive therapy in our high-risk SSc-ILD patients, but the safety profile in our study appeared to be more favorable, although the direct comparison needs to be interpreted with caution.

Differences in survival can possibly be explained by higher treatment-related mortality, which for instance in the ASTIS trial was 13.9% in the first year of follow up. Treatment-related mortality thus is a scope of interest, and for instance careful screening before selection of patients reduces treatment-related mortality in HSCT [12]. Age at inclusion appeared to matter, as the intensified treatment showed no treatment-related mortality during more than 5 years follow-up in SSc-ILD patients younger than 75 years. Treatment with oral cyclophosphamide during the first 6 months did not lead to more hospitalizations, probably due to clinical experience and close monitoring of leucocyte counts.

Moreover, pulmonary function in response to intensified treatment improved as compared to the change of pulmonary function in the EOC group. Recovery of pulmonary function, or its residual level after treatment, has great impact on the quality of life. Our study is one of few intervention studies in SSc-ILD that shows both survival and pulmonary function data, reflecting both mortality and morbidity. Randomized controlled trials (RCTs) that compare intensified immune suppression to HSCT in early onset inflammatory progressive SSc are needed. One may also argue whether immunosuppression in the control arm of these well-designed trials has been optimal.

The strength of our study is the inclusion of patients who were at high-risk for disease related mortality and progressive ILD as illustrated by their characteristics: high percentage male sex, anti-topoisomerase antibodies and diffuse skin disease [3,11,13–15]. 12.5% of our patients already had pulmonary hypertension at the start of intensified treatment and 41.7% were current smokers, both associated with worse outcome. We predominantly included patients with early onset SSc-ILD with a median disease duration of 0.8 years from first non-RP symptom, representing the early, immune-inflammatory phase of the disease. The presence of intrapulmonary inflammation was strongly supported by results of initial DTPA scanning, followed by normalization in response to treatment in the majority of cases. The reported outcomes also emphasize the importance of early and aggressive intervention in high-risk patients, even when pulmonary function is still in the normal range to prevent irreversible, fibrotic organ damage [16].

Our study is the first in combining TPE with long-term immunosuppression as treatment for SSc-ILD. Numerous RCTs and clinical studies showed that TPE is a safe and low cost option as additional treatment for SSc, but these studies use different outcome measures and did not use strict regimens of immunosuppression [17]. The mechanism of action remains largely unclear. Persistent injury to endothelial cells, activation of innate and adaptive immunity and downstream effects on smooth muscle cells and fibroblasts results in extracellular matrix production and vascular remodeling [18]. Different auto-antibodies like anti-endothelial cell antibodies (AECAs) may play an important role in fibroblast activation [16,19]. Related to this important role of pathogenic autoantibodies and cytokines in SSc-ILD, TPE seems an effective, steroid-sparing, additional therapy for the induction of clinical remission and subsequent prevention of disease progression [17]. The therapeutic efficacy of the intensified treatment supports the notion that SSC is driven by an aberrant immune response and that the disease process can be reversed [20,21].

The study is limited by its observational design. Another limitation is the small number in both groups, it is however striking that %pFVC and %pDLCO significantly improved in the intensified treatment group. EPS rates in the intensified treatment arm of our study did however not differ from those in the EOC arm, possibly due to the small numbers. The comparison is also hampered by the complexity of the heterogeneous EOC group. One third of these patients were also treated intensively including TPE. Our findings warrant confirmation in larger randomized controlled studies.

In conclusion, SMR in SSc patients with pulmonary involvement is still high. However, early recognition and upfront treatment have great impact on improvement of outcome and prevention of further damage [22]. The DTPA scan can be used as a new and early screening method for the detection of active alveolitis in SSc. Alternative intensified immunosuppressive treatments, with balanced toxicity profiles, are needed [23]. A treatment with TPE and long-term immunosuppressive therapy is safe, has low toxicity, and good overall survival and pulmonary outcome.

Credit author statement

J. Potjewijd: Formal analysis, Investigation, Resources, Writing – original draft, Visualization. R. Tobai: Formal analysis, Investigation, Visualization, Writing – review & editing. D. Silvertand: Investigation. H.A. Gietema: Investigation, Writing – review & editing. J.G.M.C. Damoiseaux: Writing – review & editing, Supervision. P. van Paassen: Conceptualization, Methodology, Resources, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
Data availability

Data will be made available on request.

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