Systemic sclerosis associated interstitial lung disease - individualized immunosuppressive therapy and course of lung function: results of the EUSTAR group

Sabine Adler1*, Dörte Huscher2,3, Elise Siegert3, Yannick Allanore4, László Czirják5, Francesco DelGaldo6, Christopher P. Denton7, Oliver Distler6, Marc Frerix9, Marco Matucci-Cerinic10, Ulf Mueller-Ladner9, Ingo-Helmut Tarner9, Gabriele Valentini11, Ulrich A. Walker12, Peter M. Villiger1, Gabriela Riemekasten13 and EUSTAR co-workers on behalf of the DeSScipher project research group within the EUSTAR network

Abstract

Background: Interstitial lung disease in systemic sclerosis (SSc-ILD) is a major cause of SSc-related death. Immunosuppressive treatment (IS) is used in patients with SSc for various organ manifestations mainly to ameliorate progression of SSc-ILD. Data on everyday IS prescription patterns and clinical courses of lung function during and after therapy are scarce.

Methods: We analysed patients fulfilling American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) 2013 criteria for SSc-ILD and at least one report of IS. Types of IS, pulmonary function tests (PFT) and PFT courses during IS treatment were evaluated.

Results: EUSTAR contains 3778/11,496 patients with SSc-ILD (33%), with IS in 2681/3,778 (71%). Glucocorticoid (GC) monotherapy was prescribed in 30.6% patients with GC combinations plus cyclophosphamide (CYC) (11.9%), azathioprine (AZA) (9.2%), methotrexate (MTX) (8.7%), or mycophenolate mofetil (MMF) (7.3%). Intensive IS (MMF + GC, CYC or CYC + GC) was started in patients with the worst PFTs and ground glass opacifications on imaging. Patients without IS showed slightly less worsening in forced vital capacity (FVC) when starting with FVC >75% or >75%. GC showed negative trends when starting with FVC <50%. Regarding diffusing capacity for carbon monoxide (DLCO), negative DLCO trends were found in patients with MMF.

Conclusions: IS is broadly prescribed in SSc-ILD. Clusters of clinical and functional characteristics guide individualised treatment. Data favour distinguished decision-making, pointing to either watchful waiting and close monitoring in the early stages or start of immunosuppressive treatment in moderately impaired lung function. Advantages of specific IS are difficult to depict due to confounding by indication. Data do not support liberal use of GC in SSc-ILD.

Keywords: Systemic sclerosis, Interstitial lung disease, Immunosuppressants, Follow up, Lung function

* Correspondence: sabine.adler@insel.ch
Sabine Adler and Dörte Huscher contributed equally to this work
Peter M. Villiger and Gabriela Riemekasten contributed equally to this work
1Department of Rheumatology, Immunology and Allergology, University Hospital and University of Bern, Freiburgstrasse 4, 3010 Bern, Switzerland
Full list of author information is available at the end of the article

© The Author(s). 2018 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Background

Interstitial lung disease (ILD) in systemic sclerosis (SSc-ILD) is caused by alveolitis-induced fibrosis of the intra-alveolar tissue, leading to progressive decline in lung function [1]. It is the most frequent cause of SSc-associated death [2]. Current treatment options aim at reducing pulmonary interstitial inflammation in order to prevent progression of fibrosis and consecutive deterioration of lung function.

Cyclophosphamide (CYC) is widely used in the treatment of SSc-ILD, especially in induction therapy as reflected by the European League Against Rheumatism (EULAR) recommendations for SSc-ILD treatment [3]. Unfortunately, the toxicity of CYC makes it unsuitable for long-term use. Furthermore, within the first scleroderma lung study, the effect of CYC waned a few months after cessation [4]. Mycophenolate mofetil (MMF) has been suggested as an alternative for induction and maintenance IS [5] and has been shown to stabilise lung function in two studies [6, 7]. There are recent data from the scleroderma lung study II on the risks and benefits of a 2-year course of MMF versus a 1-year course of oral CYC. Herein, MMF displayed a better safety profile and a 1-year course of CYC improved skin and lung function to a comparable extent [8]. Azathioprine (AZA) reflects the common practice of introducing a steroid-sparing anti-rheumatic agent in patients with idiopathic pulmonary fibrosis yet might be rather harmful [9]. In SSc-ILD, the evidence for AZA is inconclusive [10–12]. Methotrexate (MTX) is recommended for treatment of skin manifestations in early diffuse cutaneous SSc (dcSSc) [13]. Its use in SSc-ILD remains controversial as lung fibrosis is a rare but potentially severe side effect [14] and evidence for anti-fibrotic efficacy in the lungs is lacking. As skin and lung involvement may appear simultaneously, MTX is sometimes prescribed in SSc-ILD. Rituximab (RTX) is among the most frequently used biological agents in SSc with a recent case-control study and an observational study suggesting beneficial effects on lung function [15]. As elevated interleukin-6 (IL-6) in SSc-patients has been associated with higher incidence of progressive pulmonary decline, tocilizumab (TCZ) was recently introduced as a therapeutic strategy within the faSSCinate study [16, 17]. This randomised controlled trial demonstrated a benefit from TCZ, with a significantly smaller decline in forced vital capacity (FVC); unfortunately, this effect waned at 48 weeks. Low-dose glucocorticoids (GCs) used to be the standard treatment for SSc-ILD. This is remarkable as GCs have never been shown to improve ILD outcomes and are suspected to dose-dependently increase the risk of SSC renal crisis [18]. GCs are variously prescribed at least initially in combination therapy in severe and progressive ILD [13, 19]. Overall, current evidence does not allow convincing recommendations on the use of IS in ILD. The updated EULAR/European League against Rheumatism Scleroderma Trial and Research (EUSTAR) guidelines will be in line with this conclusion [20].

The EUSTAR database offers a unique opportunity to analyse IS therapy in SSc-ILD. The aims of this study were (1) to analyse current use of IS drugs, (2) to test correlation between drug use and lung function tests and (3) to define specific treatments for defined disease characteristics.

Methods

We included patients aged ≥18 years fulfilling the American College of Rheumatology (ACR) 1980 or ACR/EULAR 2013 classification criteria for SSc [21] with signs of ILD on pulmonary high resolution computed tomography (HRCT) and/or chest x-ray and at least one report on IS.

Data analysis comprised first EUSTAR documentation from 2004 until 6 May 2014. The entire observation period of each patient since initial diagnosis of ILD was considered. In order to receive comprehensive overviews of IS in SSc-ILD we referred to all documented visits at which IS was used. Missing IS information was counted as “never IS” if at least one item from the list of immunosuppressive therapies was answered. Patients with IS therapy (“ever IS”) at any time were compared to patients who had never received IS (“never IS”). For our analysis of “never IS” versus “ever IS” patients were included at the visit when IS was documented for the first time or time of first ILD documentation for “never IS”. For comparison of the features of patients receiving different IS we selected patients with at least one follow up since the documentation of ILD. We then grouped patients according to forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) at the initiation of therapy, mimicking the classification by Steen [22] in order to generate three groups with different SSc-ILD severity: “mild” for DLCO >60% and FVC >85%, “moderate” for DLCO 51–60% and FVC 80–85% and “severe” for DLCO <51% and FVC <80%.

Standard EUSTAR documentation comprises current history, past medical history, medications, physical examination including modified Rodnan skin score (mRSS), laboratory results, lung and heart function tests, radiological imaging and capillaroscopy [23]. Disease duration is calculated from the time since first non-Raynaud’s symptom. Yearly follow-up documentation is recommended. As a EUSTAR rule, each participating centre must obtain an ethics vote from their respective ethics committee. Afterwards, participating patients need to sign an individual consent form prior to inclusion into EUSTAR analysis.
Statistics
Continuous parameters were compared by the Mann-Whitney test, frequencies by the chi² or Fisher exact test; p values <0.05 were considered significant. No adjustment for multiple testing was done. Course of lung function under treatment was evaluated by linear regression analysis of change in DLCO and FVC from treatment start to at least one follow-up measurement. Patients were grouped by ranges of starting values (<50%, 50–75% and >75% predicted). Due to small numbers of cases for many treatment combinations, no individual combinations could be considered. Instead, additive and multiplicative effects of single drugs on the overall group trend were tested within each stratum: with additive effects indicating patients were taking that drug over the same overall time trend, but at a higher or lower level, meaning better or worse initial lung function, but afterwards the same course of DLCO or FVC; and with multiplicative effects signalling a steeper slope of the trend for patients using that drug, meaning either a better or worse course than the overall trend. We adjusted for the potential confounders of sex, age, extent of skin involvement, disease duration and initial DLCO or FVC values, respectively. Statistical analyses were performed using IBM SPSS Statistics, version 19.

Results
Patients on IS have more severe and active ILD compared to those without IS
Epidemiological data are shown in Table 1. Overall, IS was used in 2681/3778 (71%) patients with SSc-ILD, but only in 39.8% of patients with SSc without ILD (p < 0.05, data not shown).

IS is used in a wide variety of monotherapy or combination therapy
Frequencies of immunosuppressants ever used and highest therapy combinations ever used per patient are shown in Fig. 1. Of the patients taking GC therapy, the average prednisone dosage was >10 mg/day in 17%, and >20 mg/day in 5.3% of patients.

Individual treatment regimens are shown in Fig. 2, with more than 3 immunosuppressive drugs being exceptions (n = 17 patients, not shown).

Intensive IS is reserved for patients with severe and active ILD
Patient characteristics at the start of the most frequent monotherapy and combination therapy are described in Table 2.

Compared to patients in the never IS group, patients receiving GC monotherapy had significantly higher prevalence of SSc-related organ complications except for pulmonary hypertension and renal crisis. Within the “ever IS” group, patients receiving GC monotherapy were the oldest and had the longest disease duration. Patients who took MTX were only slightly different from patients in the never IS group. Patients who took MTX/GC had significantly worse DLCO, forced expiratory volume in one second (FEV-1) and modified Rodnan skin score (mRSS), indicating more severe disease and possibly also concomitant obstructive pulmonary disease. Patients who took AZA had significant impairment in FVC and DLCO, but no differences in New York Heart Association (NYHA) class. Interestingly, they had lower mRSS values than the never IS group. AZA/GC was used in patients with a more prominent reduction in DLCO and FVC values and with more patients in NYHA III and IV than in AZA monotherapy. Patients who took MMF had severe impairment of FVC and DLCO, which was even more pronounced when GC was added to MMF. Values for DLCO and FVC were lower and severe NYHA classification more frequent than in MMF monotherapy. Patients who took CYC had the most severely impaired lung function and highest rate of restrictive lung disease. Patients receiving MTX monotherapy had the best values for DLCO, FVC (p < 0.001) and total lung capacity (TLC), lowest prevalence of pulmonary hypertension (p < 0.05) and shortest disease duration. In contrast, patients who took CYC monotherapy had worst impairment in lung function and the highest rates of ground glass opacifications on imaging, plus the most severe skin fibrosis and highest mRSS values.

A cluster of lung function parameters is associated with specific choices of IS
Sorting different therapy arms by average impairment in FVC and DLCO revealed clusters of ranges of lung function. Consequently, we grouped patients based on mean FVC and DLCO according to the classification of Steen [22]. Group I (mild impairment) had FVC of 86.9% and DLCO of 60.8%; group II (moderate impairment) had FVC of 83.4% and DLCO of 56.7%; and group III (severe impairment) had FVC of 76.6% and DLCO of 49.6%. Next we assessed whether other parameters were associated with specific choices of IS (Fig. 3).

Patients in group III had the worst FVC and DLCO, highest mRSS values, worst NYHA class and the highest rates of ground glass opacifications and restrictive defects. Compared to patients in the never IS group, patients in all three groups had significantly worse FVC, DLCO and TLC and more frequent ground glass opacifications. Patients in groups II and III had more severe NYHA class (both p < 0.001).

Compared to patients in the never IS group, the rate of ground glass opacification rates (24.4%) was twice that in groups I and II (43.9% and 40.2%, respectively), and even more often in group III (54.3%, all treatment
### Table 1 Characteristics of patients with SSc-ILD never or ever using immunosuppressive therapy

|                                | Total          | Never used IS therapy | Ever used IS therapy | P value |
|--------------------------------|----------------|-----------------------|----------------------|---------|
| **Number of patients**         | 3778           | 1097 (29%)            | 2681 (71%)           |         |
| **Age (mean, SD)**             | 55.5 ± 13.4    | 59.0 ± 13.6           | 54.0 ± 13.0          | <0.001  |
| **Female**                     | 83.6%          | 86.5%                 | 82.4%                | 0.002   |
| **BMI (mean, SD) (n = 1901)**  | 24.6 ± 4.7     | 24.5 ± 5.1            | 24.7 ± 4.6           | n.s.    |
| **Duration of SSc, years (mean, SD)** | 8.5 ± 7.9     | 10.8 ± 9.2            | 7.6 ± 7.1            | <0.001  |
| **mRSS (n = 3515)**            | 6.2 (2.8; 11.9) | 8.4 (4.3; 15.0)       | 5.4 (2.4; 10.8)      |         |
| **Extent of skin involvement (n = 3713)** |              |                       |                      |         |
| diffuse                        | 44.4%          | 29.4%                 | 50.3%                |         |
| limited                        | 46.9%          | 60.9%                 | 41.3%                | <0.001  |
| sclerodactyly only             | 7.5%           | 7.4%                  | 7.6%                 |         |
| none                           | 1.2%           | 2.4%                  | 0.8%                 |         |
| **Present scleroderma pattern (n = 1081)** |              |                       |                      |         |
| active                         | 92.6%          | 92.3%                 | 92.7%                | n.s.    |
| early                          | 40.7%          | 41.5%                 | 40.4%                |         |
| late                           | 21.1%          | 25.3%                 | 19.4%                | 0.076   |
| **SSc activity index ≥3 (n = 3557)** | 20.0%          | 12.8%                 | 22.9%                | <0.001  |
| **DLCO, % predicted (mean, SD) (n = 2909)** | 62.0 ± 20.2    | 67.4 ± 19.8           | 59.9 ± 20.0          | <0.001  |
| **FVC, % predicted (mean, SD) (n = 2239)** | 87.5 ± 21.8    | 94.9 ± 20.9           | 84.4 ± 21.5          | <0.001  |
| **FVC/DLCO ratio (n = 2072)**  | 1.5 ± 0.5      | 1.5 ± 0.5             | 1.5 ± 0.5            | n.s.    |
| **FEV-1, % predicted (mean, SD) (n = 2239)** | 86.2 ± 19.9    | 90.7 ± 19.0           | 84.2 ± 20.0          | <0.001  |
| **TLC, % predicted (mean, SD) (n = 2239)** | 85.0 ± 20.5    | 90.6 ± 20.1           | 82.6 ± 20.2          | <0.001  |
| **History (n = 3755)**         |                |                       |                      |         |
| worsening of skin              | 18.2%          | 12.5%                 | 20.6%                | <0.001  |
| worsening of fingers           | 22.7%          | 20.7%                 | 23.6%                | n.s.    |
| esophageal symptoms            | 66.2%          | 65.0%                 | 66.6%                | n.s.    |
| stomach symptoms               | 25.9%          | 22.1%                 | 27.5%                | <0.001  |
| intestinal symptoms            | 24.9%          | 24.2%                 | 25.2%                | n.s.    |
| arterial hypertension          | 23.2%          | 23.7%                 | 23.0%                | n.s.    |
| renal crisis                   | 2.0%           | 1.7%                  | 2.1%                 | n.s.    |
| dyspnoea                       | 17.3%          | 12.2%                 | 19.4%                | <0.001  |
| worsening of cardiopulmonary manifestations | 19.1%          | 14.8%                 | 20.9%                | <0.001  |
| palpitations                   | 27.9%          | 23.8%                 | 29.5%                | <0.001  |
| Raynaud’s present              | 96.7%          | 96.1%                 | 97.0%                | n.s.    |
| **NYHA class (n = 2426)**      |                |                       |                      |         |
| I                              | 44.0%          | 49.9%                 | 41.6%                |         |
| II                             | 38.7%          | 37.8%                 | 39.0%                | <0.001  |
| III                            | 15.2%          | 10.1%                 | 17.3%                |         |
| IV                             | 2.1%           | 2.1%                  | 2.1%                 |         |
| **Laboratory measures (n = 1346 –648)** |                |                       |                      |         |
| ANA+                           | 94.9%          | 95.6%                 | 94.6%                | n.s.    |
| ACA+                           | 21.9%          | 38.6%                 | 15.1%                | <0.001  |
The same trend was seen in the frequency of restrictive defects with the lowest rates in patients in the never IS group (36%) and an increasing frequency of 46.3% in group II and 61.0% in group III (both \( p < 0.001 \)). Specific types of IS display minimal influence on the course of lung function

Follow-up documentation ranging from 1 month to 13 years was available in 73.6% of patients with SSc-ILD. Change in lung function over time was analysed in the respective subgroups of patients with <50%, 50–75% and >75% of FVC or DLCO predicted at treatment initiation and are shown in Fig. 4.

The group starting with < 50% of predicted FVC had the steepest decline in FVC (Fig. 4a). Here, GCs had negative multiplicative effects (Fig. 4c), thus there was even worse deterioration. In comparison, the group starting between 50 and 75% of predicted FVC had a less steep decline (Fig. 4a), with a positive additive effect in ACA-positive patients (Fig. 4b), but at the same time a negative multiplicative effect, meaning they started at higher FVC levels but had a steeper decline. Here, in patients in the never IS group a positive multiplicative effect was seen, indicating a less steep decline. The group starting with > 75% of predicted FVC had only a slight decline in FVC (Fig. 4a, b) with a negative additive effect in Scl70-positive patients but at the same time a positive multiplicative effect.

Table 1 Characteristics of patients with SSc-ILD never or ever using immunosuppressive therapy (Continued)

|                      | Total      | Never used IS therapy | Ever used IS therapy | \( P \) value |
|----------------------|------------|------------------------|----------------------|--------------|
| SCL70+               | 48.8%      | 36.4%                  | 53.8%                | <0.001       |
| U1 RNP+              | 6.4%       | 2.9%                   | 7.9%                 | <0.001       |
| RNA+                 | 4.5%       | 4.1%                   | 4.7%                 | n.s.         |
| PM-Scl+              | 4.5%       | 3.7%                   | 4.9%                 | n.s.         |
| CRP elevation        | 27.5%      | 18.5%                  | 31.3%                | <0.001       |
| CK elevation         | 9.3%       | 5.8%                   | 10.7%                | <0.001       |
| Proteinuria          | 6.4%       | 5.7%                   | 6.7%                 | n.s.         |
| Hypocomplementemia   | 6.0%       | 4.9%                   | 6.4%                 | n.s.         |
| ESR mm/h (mean, SD)  | 25.8 ± 20.7| 23.7 ± 17.6            | 26.7 ± 21.7          | 0.048        |
| Conduction blocks (n = 3451) | 14.1%       | 12.8%                  | 14.6%                | n.s.         |
| Pulmonary hypertension (n = 3451) | 23.2%      | 22.7%                  | 23.3%                | n.s.         |
| Diastolic function abnormal (n = 3363) | 24.3%     | 21.1%                  | 25.5%                | 0.008        |
| Pericardial effusion (n = 2227) | 12.6%      | 13.2%                  | 12.4%                | n.s.         |
| Ground glass opacification (n = 2014) | 41.1%      | 30.3%                  | 45.5%                | <0.001       |
| PFT restrictive defect (n = 3457) | 45.9%      | 35.6%                  | 49.9%                | <0.001       |
| Echo                 |            |                        |                      |              |
| LVEF (%) (n = 2095)   | 61.4 ± 6.2 | 62 ± 6.6               | 61.8 ± 6.5           | 0.005        |
| PAPsys (mmHg) (n = 1835) | 33 ± 14.9    | 32.4 ± 12.7            | 32.6 ± 13.4          |              |
| Right heart catheter  |            |                        |                      |              |
| RVSP (mmHg) (n = 96)  | 46.8 ± 21.9| 40.5 ± 17.9            | 42.5 ± 19.3          | n.s.         |
| PAPmean (mmHg) (n = 146) | 36.2 ± 15.4    | 28.5 ± 12.0            | 30.8 ± 13.5          | 0.003        |
| PVR (dyn · sec · cm-5) (n = 94) | 541.5 ± 498 | 213.5 ± 258.1        | 328.6 ± 391.2        | 0.001        |
| PWP (mmHg) (n = 113)  | 12.1 ± 7.0  | 12.2 ± 6.4             | 12.2 ± 9.0           | n.s.         |
| CI (l/min/m2) (n = 100) | 2.8 ± 0.6    | 3.3 ± 1.1              | 3.1 ± 1.0            | 0.021        |
| 6 MWD                 |            |                        |                      |              |
| 6 MWD (m) (n = 551)   | 444.9 ± 129.6| 421.3 ± 123.8         | 428.1 ± 125.9        | 0.021        |
| O2 saturation at rest (n = 457) | 96 ± 6.3    | 95.9 ± 4.3             | 96.0 ± 5.0           | n.s.         |
| O2 saturation at exercise (n = 389) | 92.9 ± 8.0   | 92.2 ± 8.0             | 92.4 ± 8.0           | n.s.         |

BMI body mass index, mRSS modified Rodnan skin score, DLCO diffusing capacity of the lung for carbon monoxide, FVC forced vital capacity, FEV-1 forced expiratory volume in one second, TLC total lung capacity, NYHA New York Heart Association, ANA anti-nuclear antibodies, ACA anti-centromere antibodies, SCL70 anti-topoisomerase I antibody, U1 RNP U1-small nuclear ribonucleoprotein particle, RNA ribonucleic acid antibody, PM SCL polymyositis scleroderma antibody, CRP C-reactive protein, CK creatin kinase, ESR erythrocyte sedimentation rate, PFT pulmonary function test, LVEF left ventricular ejection fraction, PAPsys systolic pulmonary arterial pressure, RVSP right ventricular systolic pressure, PAPmean mean pulmonary arterial pressure, PVR pulmonary vascular resistance, PWP pulmonary wedge pressure, CI cardiac index, 6 MWD 6 minute walk distance, n.s. not significant
(Fig. 4c), meaning they started at lower FVC levels but had a flatter rate of decline. Here again, there were positive multiplicative effects in patients in the never IS group or in those receiving GCs, indicating less or no decline or even slight improvement.

Within the group starting with < 50% of predicted DLCO the overall course was represented by a slightly improving slope (Fig. 4b). Compared to that general trend, CYC and MMF had negative additive effects, meaning their course was following the same slope, but on a lower level, while ACA positivity had a positive additive effect, hence the course was on a higher level (Fig. 4d). In patients starting with DLCO values between 50 and 75% of predicted the overall trend was of slight
Table 2: Characteristics of patients with dSSc or lSSc at the start of specific therapy

|                | Never used IS | AZA | CYC | MMF | MTX | GC | AZA + GC | CYC + GC | MMF + GC | MTX + GC |
|----------------|--------------|-----|-----|-----|-----|----|---------|---------|---------|---------|
|                | n            | %   | n   | %   | n   | %   | n       | %       | n       | %       |
| Sex            |              |     |     |     |     |    |         |         |         |         |
| male           | 103          | 14.4| 14   |    | 10.6| 24.0| 22      | 18.4    | 18      | 17.8    |
|                |              |     |     |     |     |    |         |         |         |         |
| female         | 612          | 85.6| 118  | 18.4| 57  | 76.0| 86      | 79.6    | 83      | 82.2    |
|                |              |     |     |     |     |    |         |         |         |         |
| total          | 715          | 100.0| 132 | 100.0| 75  | 100.0| 108     | 100.0   | 101     | 100.0   |
| Extent of skin involvement |             |     |     |     |     |    |         |         |         |         |
| diffuse        | 278          | 38.9| 74   | 56.1| 46  | 61.3| 79      | 73.1    | 71      | 70.3    |
| limited        | 437          | 61.1| 188  | 43.9| 29  | 38.7| 129     | 26.9    | 30      | 29.7    |
| total          | 715          | 100.0| 132 | 100.0| 75  | 100.0| 108     | 100.0   | 101     | 100.0   |
| NYHA           |              |     |     |     |     |    |         |         |         |         |
| I              | 200          | 53.2| 63   | 50.0| 21  | 30.9| 43      | 45.3    | 47      | 52.2    |
|                |              |     |     |     |     |    |         |         |         |         |
| II             | 128          | 34.0| 50   | 39.7| 26  | 38.2| 34      | 35.8    | 34      | 37.8    |
|                |              |     |     |     |     |    |         |         |         |         |
| III            | 40           | 10.6| 10   | 7.9 | 19  | 27.9| 17      | 17.9    | 9       | 10.0    |
|                |              |     |     |     |     |    |         |         |         |         |
| IV             | 8            | 2.1 | 3    | 2.4 | 2   | 2.9 | 1.1     | 1.1     | 0.0     | 28      |
|                |              |     |     |     |     |    |         |         |         |         |
| total          | 376          | 100.0| 126 | 100.0| 68  | 100.0| 95      | 100.0   | 90      | 100.0   |

Only therapy regimens with frequencies of at least 5% are displayed (for patients on immunosuppressive therapy, only therapy episodes started during follow up were included to exclude possibly long-lasting therapy episodes documented at baseline). dSSc diffuse cutaneous systemic sclerosis, lSSc limited systemic sclerosis, IS immunosuppression, AZA azathioprine, CYC cyclophosphamide, MMF mycophenolate mofetil, MTX methotrexate, GC glucocorticoid, NYHA New York Heart Association, ACA anti-centromere antibodies, SCL70 anti-topoisomerase I antibody, PFT pulmonary function test, mRSS modified Rodnan skin score, DLCO diffusing capacity of the lung for carbon monoxide, FVC forced vital capacity, FEV-1 forced expiratory volume in one second, TLC total lung capacity, pred. predicted, N number of patients within this specific group of medication.
deterioration (Fig. 4b), with a negative additive effect of TNF inhibitors, again meaning it already started at a lower level but had the same gradient of deterioration. Here, ACA had a slightly negative multiplicative effect, meaning DLCO courses had a steeper decrease than the general trend, while in patients in the never IS group a positive multiplicative effect was seen, meaning a flatter decrease (Fig. 4b, d), with a positive additive effect of Scl70 positivity and a negative additive effect of GCs. There was a negative multiplicative effect of MMF, meaning an even steeper decrease than the general trend, while there was a positive multiplicative effect in patients in the never IS group (Fig. 4d), meaning less decline or even slight improvement compared to the overall trend.

Adjusted for potential confounders and initial FVC or DLCO value no other medications than GCs, MMF, or “never IS” showed multiplicative effects on the course of lung function divergent from the general trend of the entire patient population. CYC and TNF inhibitors had only additive effects, pointing toward lower initial DLCO or FVC values in these

**Fig. 3** Patients grouped according to severity of lung function combined with the respective immunosuppression (IS) and clinical parameters. *never IS* patients who had never taken immunosuppressant drugs, FVC forced vital capacity, DLCO diffusing capacity of the lung for carbon monoxide, SB single breath, MTX methotrexate, GC glucocorticoid, AZA azathioprine, MMF mycophenolate mofetil, CYC cyclophosphamide, PFT pulmonary function test, NYHA New York Heart Association, ACA anti-centromere antibodies, SCL70 anti-topoisomerase I antibody, CRP C-reactive protein.
patients, but no differing time trends compared to patients on other treatments.

**Discussion**

Our analysis of observational data describes current IS strategies in patients with SSc-ILD from the EUSTAR cohort. It shows clusters of clinical characteristics correlated with IS choices and identifies factors that might influence future IS decisions.

A large proportion of patients with SSc-ILD did not receive IS despite having dcSSc (34% of patients), active scleroderma pattern on nail fold capillaroscopy (40% of patients) and Valentini disease activity index (VDAI) ≥3 (12% of patients). On average these patients have longer disease duration and show fewer signs of alveolitis on HRCT. These characteristics may suggest that the greatest decline in lung function has already happened and stabilisation of lung function in the absence of active inflammation is expected without any further IS medication [22], or they might represent patients with overall benign disease courses. In our analysis, positive trends in lung function over time - especially in patients starting with 50–75% of predicted FVC - support this notion. It contrasts with a scleroderma lung study showing a mild 12-month decline in FVC of 4.2%, and in DLCO of 8.2%, irrespective of disease duration [1]. On the other hand our data are in agreement with a study documenting that FVC values within the first 3 years after disease onset strongly predict SSc-ILD outcome [24].

GCs were used most frequently in 58% of the patients in high proportions and even at dosages >10 mg/day and >20 mg/day. This comes as a surprise and has to be questioned, as the effect of GCs on lung function was marginal at best and only slightly positive in patients with > 75% of predicted FVC who might as well continue...
without any IS at all. Furthermore, it is well-established that this treatment regimen is associated with higher rates of infection and scleroderma renal crisis [25]. Of note, patients receive combinations of GC with MTX, AZA, MMF or CYC regardless of lung function parameters or NYHA class. Collectively, our data show that combining GCs with another IS therapy reflects the standard of care in many centres worldwide.

The second most frequently used therapy was CYC, as recommended by the EUSTAR guidelines for patients with severe and progressive SSc-ILD. Two meta-analyses failed to show a significant benefit of CYC on SSc-ILD on lung function tests [26]. However, a statistically non-relevant improvement might still represent a patient-relevant effect on quality of life as reflected by the Short Form-36 (SF-36) data evaluated within the first sclerosis lung study [4]. In our analysis, patients treated with CYC monotherapy or CYC/GC started with the worst DLCO values, worst NYHA class, highest frequencies of restrictive defects and PH, and the highest mRSS. More than 60% of these patients showed signs of active inflammation reflected by high ESR, CRP elevation or ground glass opacifications on HRCT. Stratification of these patients by their starting values did not result in differences in the slope of DLCO or FVC values compared to all other patients. Interestingly, Becker et al. describe the highest SSc-ILD response rates assessed by FVC and DLCO in patients with low FVC values prior to CYC therapy [27] indicating a potential for reversal of fibrosis.

MMF, often regarded as the potential maintenance therapy in SSc-ILD, was used as monotherapy in moderate or - combined with GC - severe lung impairment, in our analysis. A prospective open-label trial on MMF describes early and significant improvement in DLCO, non-significant improvement in FVC and reduction in ground glass opacifications in five patients with disease duration between 1.5 and 3 years [28]. A meta-analysis argues along these lines, suggesting that MMF may stabilise lung function [29]; however, the superiority of MMF compared to CYC was not verified [7]. The very recent randomized controlled, double-blind, parallel group trial comparing MMF with oral CYC shows significant improvement in pre-specified measures of lung function over 2 years. It did not reach its primary endpoint, i.e. MMF to be more effective than CYC; however, MMF had a better side-effect profile [8].

An uncontrolled study of AZA maintenance therapy after 1-year induction with CYC showed stabilising effects of AZA in SSc-ILD, but involved only 13 patients [30]. Retrospective data on 36 patients with SSc-ILD comparing oral CYC with AZA shows significant effects of AZA on DLCO and FVC, yet no effects of CYC [12]. Our data cannot confirm this as AZA had only a very slightly positive effect on DLCO in patients starting with DLCO >75%, thus being almost equal to the effect of “never IS”.

Studies analyzing the effects of MTX on SSc-ILD are rare. This might be due to the fact that ILD is one of the possible side effects of MTX and hence physicians might be hesitant to prescribe it to patients with SSc-ILD. Indeed, there is one study showing no effects of MTX on lung function despite trends towards positive effects on the mRSS [31]. However, this study was small (n = 29) and covered a relatively short timeframe (24 weeks). A study with 11 patients taking MTX describes subjective improvement in dyspnoea in 5 patients, no change in another 5 and worsening in 1 patient [32]. In our data, MTX was used in patients that resembled those of the never IS group except for higher mRSS and more frequent ground glass opacifications. Comparing MTX + GC to MTX alone displayed significant differences in mRSS, DLCO, FVC, FEV-1 and rates of ground glass opacifications. Nevertheless, its effect on the course of PFTs was negligible.

Overall, our data describe treatment patterns in patients with SSc-ILD that are used across European centres yet are only partially in accordance with EUSTAR recommendations. Most clinicians chose intensive IS in active lung disease. Common choices were not only CYC+/−GC as recommended by current guidelines, but also MMF + GC. None of the specific types of IS was clearly superior to another in influencing the course of lung function in any DLCO or FVC group. The only positive trends seen were in patients in the never IS group and patients taking GC, starting with >75% of predicted FVC, and in the never IS group, patients taking AZA and MTX starting with >75% of predicted DLCO all had a reduced rate of deterioration over time. Thus, if carefully monitored for changes in lung function, patients with SSc-ILD with only small PFT impairment might benefit from on-demand IS instead of ongoing IS.

Our study has some limitations: The retrospective design leaves us with some missing data, reducing the large number of patients within this data set to small groups when addressing specific questions of immunosuppressive treatment. Furthermore, changes in the prescription pattern might be missed, and data on when and why the immunosuppressive treatment was changed are lacking. Additional prospective data are urgently warranted. The prospective observational trial of the Seventh Framework Programme (FP7) project “DeSScipher” (a study to decipher the optimal management of systemic sclerosis) launched in 2012 will allow assessment of the dynamics of SSc-ILD-related treatment patterns in terms of escalation and de-escalation and to evaluate their efficacy.
Conclusions
IS is broadly prescribed in SSc-ILD. Clusters of clinical and functional characteristics guide individualised treatment. The data favour differential decision-making pointing either to watchful waiting and close monitoring in the early stages or start of immunosuppressive treatment in patients with SSc-ILD and moderately impaired lung function. Advantages of specific IS are difficult to depict due to confounding by indication. Data do not support liberal use of GC in SSc-ILD.

Additional file

Additional file 1: EUSTAR co-workers (DOCX 17 kb)

Abbreviations
6MWD: Six minute walk distance; ACA: Anti-centromere antibodies; ACR: American College of Rheumatology; ANA: Anti-nuclear antibodies; a-TNF: Anti-tumour necrosis factor α; AZA: Azathioprine; BMI: Body mass index; CI: Cardiac index; CRP: C-reactive protein; CYC: Cyclophosphamide; dCSC: Diffuse cutaneous systemic sclerosis; DeSScipher: Study to decipher the optimal management of systemic sclerosis; DLCO: Diffusing capacity for carbon monoxide; D-PA: D-penicillamine; ESR: Erythrocyte sedimentation rate; EULAR: European League against Rheumatism; EUSTAR: European League against Rheumatism Scleroderma Trial and Research; FEV1: Forced expiratory volume in one second; FP?: Seventh Framework Programme; FVC: Forced vital capacity; GC: Glucocorticoids; HRCT: High resolution computed tomography; IILD: Interstitial lung disease; IMA: Imatinib; IS: Immunosuppressive treatment; ISSc: Limited systemic sclerosis; LVEF: Left ventricular ejection fraction; MMF: Mycophenolate mofetil; mRSS: Modified Rodnan skin score; MTX: Methotrexate; NYHA: New York Heart Association; O2: Oxygen; PAPmean: Mean pulmonary arterial pressure; PAPsys: Systolic pulmonary arterial pressure; PFT: Pulmonary function test; PM SCL: Polymyositis and Scleroderma antibody; PVR: Pulmonary vascular resistance; PWP: Pulmonary wedge pressure; RNA: Ribonucleic acid; RTX: Rituximab; RVSP: Right ventricular systolic pressure; SCL 70: Anti-topoisomerase 1; SSC: Systemic sclerosis; TCZ: Tocilizumab; TLP: Total lung capacity; U1RNP: U1-small nuclear ribonucleoprotein particle; VDA: Valenti disease activity index

Acknowledgements
We appreciate the work of all members of the participating EUSTAR centres represented by the list of co-workers on behalf of the DeSScipher project research group within the EUSTAR network, which is provided as Additional file 1.

Funding
This work was funded by the EU research grant HEALTH-FS-2012-305495 and by the research funds of the Department of Rheumatology, Immunology and Allergology, University of Bern, Switzerland.

Availability of data and materials
Data that support the findings of this study were extracted from the EUSTAR database and were used under license for the current study, and so are not publicly available. Data are available upon reasonable request.

Authors’ contributions
SA and DH extracted and analysed the data and drafted and edited the manuscript. ES analysed the data and edited the manuscript. YA, LZ, FDG, CD, OD, MF, MMC, UML, IT, GV and UW were involved in analysis and interpretation of the data and revised the manuscript. PV analysed and interpreted the data and drafted and edited the manuscript. GR designed the study, analysed and interpreted the data and edited the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, and gave final approval of the version to be published.

Ethics approval and consent to participate
Prior to inclusion into the database each patient gave informed consent. Ethics approval was obtained from local ethics committees prior to start of the evaluation. Local ethics committees are represented by the locations listed after each author’s name and after each co-worker’s name as provided in Additional file 1.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details
1Department of Rheumatology, Immunology and Allergology, University Hospital and University of Bern, Freiburgstrasse 4, 3010 Bern, Switzerland. 2German Rheumatism Research Center, A Leibniz Institute, Berlin, Germany. 3Department of Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, Germany. 4Department of Rheumatology A, Descartes University, APHP, Cochin Hospital, Paris, France. 5Department of Rheumatology and Immunology, University of Pecs, Pecs, Hungary. 6University of Leeds, Leeds, UK. 7UCL Division of Medicine, Centre for Rheumatology, Royal Free Hospital, London, UK. 8Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland. 9Department of Rheumatology and Clinical Immunology, Osteology and Physical Therapy, Justus-Liebig-University Giessen, Kerckhoff Klinik, Bad Nauheim, Germany. 10Department Experimental and Clinical Medicine, Division of Rheumatology AOUC, University of Florence, Florence, Italy. 11Department of Rheumatology, Second University of Naples, Naples, Italy. 12Department of Rheumatology, University of Basel, Basel, Switzerland. 13Department of Rheumatology, University Medical Center Schleswig-Holstein, Kiel, Germany.

Received: 27 July 2017 Accepted: 11 January 2018

Published online: 30 January 2018

References
1. Khanna D, Tseng CH, Farmani N, Steen V, Furst DE, Clements PJ, et al. Clinical course of lung physiology in patients with scleroderma and interstitial lung disease: analysis of the Scleroderma Lung Study Placebo Group. Arthritis Rheum. 2011;63(10):3078–85.
2. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis. 2007;66(7):940–4.
3. Kowal-Bielecka O, Landewe R, Avouac J, Chwierko S, Micielli I, Cizkaj L, et al. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). Ann Rheum Dis. 2009;68(5):620–8.
4. Tashkin DP, Elashoff R, Clements PJ, Roth MD, Furst DE, Silver RM, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. Ann Intern Med. 2008;149(1):102–6.
5. Nithyanova SI, Brough GM, Black CM, Denton CP. Mycophenolate mofetil in diffuse cutaneous systemic sclerosis—a retrospective analysis. Rheumatology (Oxford). 2007;46(5):442–5.
6. Koutrompas A, Zigos A, Alexiou I, Barouta G, Sakkas L. Mycophenolate mofetil in systemic sclerosis-associated interstitial lung disease. Clin Rheumatol. 2010;29(10):1167–8.
7. Panopoulos ST, Bounia VK, Trakada G, Giavri I, Kostopoulos C, Sfikakis PP. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4(9):708–19.
8. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kierup EC, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-associated interstitial lung disease (SLS I): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4(9):708–19.
9. Raghu G, Depaso WJ, Cain K, Hammar SP, Wetzel CE, Dreis DF, et al. Azathioprine combined with prednisone in the treatment of idiopathic
pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial. Am Rev Respir Dis. 1991;144(2):291–6.

10. Poomrogmhir H, Rezaei N, Sheidae Z, Almasi AR, Moradi-Lakeh M, Almasi S, et al. Systemic sclerosis: comparison of efficacy of oral cyclophosphamide and azathioprine on skin score and pulmonary involvement—a retrospective study. Rheumatol Int. 2014;34(12):1691–9.

11. Nadashkevich O, Davis P, Fritzler M, Kovalenko W. A randomized unblinded trial of cyclophosphamide versus azathioprine in the treatment of systemic sclerosis. Clin Rheumatol. 2006;25(2):205–12.

12. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum. 2006;54(12):3962–70.

13. Walker KM, Pope J, participating members of the Scleroderma Clinical Trials C, Canadian Scleroderma Research G. Treatment of systemic sclerosis complications: what to use when first-line treatment fails—a consensus of systemic sclerosis experts. Semin Arthritis Rheum. 2012;42(1):42–55.

14. Arakawa H, Yamashita M, Kurishita Y, Yamada H, Nakajima Y. Methotrexate-induced pulmonary injury: serial CT findings. J Thorac Imaging. 2003;18(4):231–6.

15. Lepri G, Avouac J, Airo P, Anguita Santos F, Bellando-Randone S, Blagoevic J, et al. Effects of rituximab in connective tissue disorders related interstitial lung disease. Clin Exp Rheumatol. 2016;34 Suppl 1005(5):181–5.

16. De Lauretis A, Sestini P, Pantelidis P, Hoyles R, Hansell DM, Goh NS, et al. Serum interleukin 6 is predictive of early functional decline and mortality in interstitial lung disease associated with systemic sclerosis. J Rheumatol. 2013;40(4):435–46.

17. Khanna D, Denton CP, Jaheis A, van Laar JM, Frech TM, Anderson ME, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet. 2016;387(10038):2630–40.

18. Steen VD, Medsger Jr TA. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. Arthritis Rheum. 1998;41(9):1613–9.

19. Mouthon L, Berezné A, Guélinvin L, Valeyre D. Therapeutic options for systemic sclerosis related interstitial lung diseases. Respir Med. 2010;104 Suppl 1:559–69.

20. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76(8):1327–1339.

21. Rodnan GP, Medsger TA, Altman RD, D’Angelo WA, Fries JF, LeRoy EC, Kirsner AB, MacKensie AH, MacShane DJ, Myers AR, Sharp GC. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum. 1980;23(5):581–90.

22. Steen VD, Conte C, Owens GR, Medsger Jr TA. Severe restrictive lung disease in systemic sclerosis. Arthritis Rheum. 1994;37(9):1283–9.

23. Walker UA, Tyndall A, Czirjak L, Denton C, Farge-Bancel D, Kowal-Bielecka O, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis. 2007;66(6):754–63.

24. Morgan C, Knight C, Lunt M, Black CM, Silman AJ. Predictors of end stage lung disease in a cohort of patients with scleroderma. Ann Rheum Dis. 2003;62(2):146–50.

25. Iudici M, van der Goes MC, Valentini G, Bijlsma JW. Glucocorticoids in systemic sclerosis: weighing the benefits and risks - a systematic review. Clin Exp Rheumatol. 2013;31(2 Suppl 76):157–65.

26. Nannini C, West CP, Erwin PJ, Matteson EL. Effects of cyclophosphamide on pulmonary function in patients with scleroderma and interstitial lung disease: a systematic review and meta-analysis of randomized controlled trials and observational prospective cohort studies. Arthritis Res Ther. 2008;10(5):R124.

27. Becker MO, Schohe A, Weinert K, Huscher D, Schneider U, Burmester GR, et al. Responders to cyclophosphamide as maintenance therapy in early diffuse systemic sclerosis patients. Ann Rheum Dis. 2012;71(12):2061–2.

28. Liossis SN, Bounas A, Andonopoulos AP. Mycophenolate mofetil as first-line treatment improves clinically evident early scleroderma lung disease. Rheumatology (Oxford). 2006;45(8):1005–8.

29. Tzouvelekis A, Galanopoulos N, Bourou E, Kolios G, Zacharis G, Ntollos P, et al. Effect and safety of mycophenolate mofetil or sodium in systemic sclerosis-associated interstitial lung disease: a meta-analysis. Pulm Med. 2012;2012:143637.

30. Paone C, Chiancianza I, Cuomo G, Ruocco L, Vettori S, Menegozzo M, et al. Twelve-month azathioprine as maintenance therapy in early diffuse systemic sclerosis patients treated for 1-year with low dose cyclophosphamide pulse therapy.Clin Exp Rheumatol. 2007;25(4):613–6.

31. van den Hoogen FH, Boerbooms AM, Swaak AJ, Rasker JJ, van Lier HJ, van de Putte LB. Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24-week randomized double-blind trial, followed by a 24 week observational trial. Br J Rheumatol. 1996;35(4):364–72.

32. Krishna Sumanth M, Sharma VK, Khaitan BK, Kapoor A, Tejasvi T. Evaluation of oral methotrexate in the treatment of systemic sclerosis. Int J Dermatol. 2007;46(2):218–23.