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Original Article

Clinical science

Preventive effects of early immunosuppressive treatment on the development of interstitial lung disease in systemic sclerosis

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Abstract

Background: Hypothesizing that early treatment yields improved prognosis, we aimed to investigate how the timing of immunosuppressive treatment relates to interstitial lung disease (ILD) development and the course of pulmonary function in systemic sclerosis (SSc).

Methods: A cohort was created using data from the EUSTAR database and Nijmegen Systemic Sclerosis cohort, including adult patients who started their first immunosuppressive treatment (i.e. mycophenolate mofetil, methotrexate, cyclophosphamide, tocilizumab or rituximab) after SSc diagnosis, and no signs of ILD on high-resolution CT. ILD-free survival and the course of forced vital capacity (FVC) % predicted were assessed for up to 5 years' follow-up comparing patients who started early (disease duration ≤3 years) *vs* late with immunosuppression.

Results: 1052 patients met the eligibility criteria. The early treatment group ($n = 547$, 52%) showed a higher prevalence of male sex, diffuse cutaneous subtype (53.1% *vs* 36.5%), and anti-topoisomerase-I antibody (ATA, 51.1% *vs* 42.7%). Most patients were treated with methotrexate (60.1%), whereas only a few patients were treated with biologics (1.7%). The incidence of ILD was 46.6% after mean (S.D.) 3.6 (1.4) years; the hazards ratio for ILD in the early treatment group was 1.13 (95% CI: 0.93, 1.38) after adjustment for confounders. FVC % predicted trajectories were comparable between groups.

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Conclusion: Our findings did not confirm a preventive role of early initiation of immunosuppressive therapy *vs* late initiation on ILD development. However, our findings should be interpreted with caution, considering the high inflammatory, ATA-positive enriched nature of the cohort, confounding by indication, and that very few patients were treated with biologics.

Keywords: systemic sclerosis, interstitial lung disease, early treatment.

Rheumatology key messages

- Early immunosuppressive treatment is not associated with prevention of ILD compared with late treatment.
- The course of pulmonary function is comparable between patients starting early or late with immunosuppressive treatment.

Introduction

SSc is a heterogeneous auto-immune disease characterized by a triad of inflammation, vascular damage and fibrosis [1]. Although the cause of SSc is unknown to date, the hypothesis is that microvascular damage triggers an autoimmune response and inflammation causing fibrosis [2]. Different organ systems may be affected to a varying degree, causing increased morbidity and mortality [3]. Interstitial lung disease associated to SSc (SSc-ILD) is an important organ complication that leads to reduced quality of life and represents the most frequent cause of disease-related mortality [4].

The clinical course of ILD is highly variable, ranging from patients with long-term stability of pulmonary function to patients with rapid decline. A recently published analysis of the European Scleroderma Trials And Research (EUSTAR) database showed that 67% of all systemic sclerosis associated interstitial lung disease (SSc-ILD) patients experience progression of ILD at any time in a 5-year follow-up period. Interestingly, this study showed that periods of stabilization alternate with periods of progressive decline in pulmonary function and that only a minority of patients showed a pattern of rapid, continuous decline [5]. To date, clinical practice is to monitor pulmonary function in SSc patients with high-resolution CT (HRCT) scan-confirmed absence of ILD. This monitoring is especially performed in early stages to identify new onset ILD or progression of existing disease, followed by a HRCT scan to confirm the new diagnosis or the progression [6].

Current consensus statements recommend treating patients with severe and progressive SSc-ILD with immunosuppressive therapies such as mycophenolate mofetil or cyclophosphamide [7, 8]. Other immunosuppressive agents used for the treatment of ILD previously included methotrexate and azathioprine, whereas more recently rituximab and tocilizumab have been used [9, 10]. For patients with mild SSc-ILD without signs of progression, a wait-and-see approach might be considered [6, 7]. However, several recent studies, such as the tocilizumab trials, have shown that starting immunosuppressive treatment in mild and moderate ILD might also have a favourable effect on the disease course compared with placebo [11–14], which is further supported by a recent retrospective cohort analysis [12].

Although there are no data on possible preventive mechanisms, an exploratory stratified analysis of a recent retrospective study revealed that mycophenolate mofetil might play a preventive action on the development of ILD in SSc [15]. There are no data available on the time to treatment and any preventive mechanisms of immunosuppressive treatment. We hypothesize that early treatment, defined as treatment started in the first 3 years after first non-Raynaud phenomenon symptom, reduces the risk to develop ILD and has a positive effect on the course of pulmonary function.

Therefore, our primary objective was to analyse the association between the timing of immunosuppressive treatment and the development of ILD. Furthermore, the secondary aim of this study was to analyse the association of timing of immunosuppressive treatment on the course of pulmonary function [defined as forced vital capacity (FVC) % predicted] regardless of the development of ILD, given the variability in screening for SSc-ILD [16] and the difficulty in defining the timing of ILD onset [17, 18].

Methods

Patients and study design

We performed a post-hoc analysis of prospectively collected data extracted from two databases, namely the EUSTAR database and Nijmegen Systemic Sclerosis cohort. There was no overlap in patients within the two databases. A detailed description of the structure of the databases, the collected data set and definitions of clinical variables have been described earlier [4, 19–21]. In compliance with local regulations, the pre-existing databases were approved by the Ethical Committees at each centre and patients provided written informed consent. According to Dutch law and regulations, this observational, non-interventional study was exempt from the requirement of approval by a medical ethics committee. Data were extracted from the registries in April 2021 and December 2022 for the EUSTAR database and Nijmegen Systemic Sclerosis cohort, respectively.

After cleaning and structuring the data (for details see Supplementary Table 1 available at *Rheumatology* online), we constructed a database using data of patients meeting the following criteria: (i) age ≥18 years, (ii) treated with at least 3 months' immunosuppressive drugs (i.e. mycophenolate mofetil, cyclophosphamide, methotrexate, tocilizumab or rituximab), (iii) absence of ILD defined as an HRCT scan negative for ILD at or within 2 months of start of first immunosuppressive treatment, (iv) documented visit at start of immunosuppressive treatment ±12 months to characterize study population, (v) no prior treatment with a biologic or antifibrotic therapy in the preceding year, and (vi) at least 1 year follow-up. Patients entered the study at start of immunosuppressive treatment and were followed for a period of up to 5 years. Azathioprine was not included in our analysis since it is mostly used as maintenance therapy after cyclophosphamide induction [9].

Baseline data were derived from visits with a maximum difference of 1 year from first start of immunosuppressive treatment. We used data on demographic and disease characteristics including subsets of SSc according to LeRoy criteria, antibody status, fulfilment of ACR/EULAR criteria [22], pulmonary function tests, New York Heart Association (NYHA) functional

class, organ involvement and CRP status (elevated *vs* normal according to laboratory cut-off values of each centre).

As patients with an unfavourable prognostic phenotype are more likely to start early with immunosuppressive treatment, we defined a priori established disease predictors through literature search and identified the following confounders based on authors consensus: i.e. gender, diffuse cutaneous subtype, Caucasian ethnicity, presence of anti-topoisomerase-I antibodies, presence of anti-RNA polymerase III antibodies, higher age, lower FVC % predicted and lower diffusing capacity of the lung for carbon monoxide (DLCO) % predicted [23].

Patients were analysed according to the first prescribed immunosuppressive drug. No adjustments were performed for treatment changes or discontinuation of immunosuppressive drug.

Patient and public involvement

Patients were not involved with this analysis.

Statistical analysis

Patients were dichotomized into an early and late treatment group based on disease duration from first non-Raynaud phenomenon symptom at start of immunosuppressive treatment using a threshold of 3 years in line with the criteria used for early disease, while developing the ACR/EULAR criteria [22].

Baseline demographic and clinical characteristics were compared with an independent Student's *t*-test, Mann–Whitney *U*-test or Fisher's exact test as appropriate on cases with known date of first non-Raynaud phenomenon symptom between the early and late treatment group. For multivariable analysis, missing baseline values were imputed using chained imputations and predictive mean matching. Based on the maximum fraction of missing data (FMI) and coefficient of variation (standard error) [CV(SE)], we calculated that 42 imputations were needed. All statistical tests were performed two-sided ($\alpha = 0.05$). The analyses were carried out using Stata statistical software version 17 (StataCorp, College Station, TX, USA).

Association between disease duration at first start of immunosuppressive treatment and time to ILD diagnosis

ILD diagnosis was defined as an HRCT scan showing the presence of ILD, honeycombing, lung fibrosis, ground glass opacification, reticular changes, tractions or bullae. Patients with a visit-free interval of ≥2 years were censored on their last visit date.

First, we assessed ILD-free survival in the early and late treatment groups by unadjusted Kaplan–Meier analysis on complete cases. Then, we performed a Cox proportional hazards analysis to correct for confounding by indication on imputed data. The base Cox proportional hazards model was defined using the a priori selected set of confounders as specified above. The other baseline characteristics were assessed for potential confounding using a 'change-in-estimate' (CIE) approach using a cut-off point of 10% [24, 25].

In addition, the association between first start of immunosuppressive treatment and ILD development was analysed using disease duration as a continuous variable and after stratification by first prescribed immunosuppressive agent. Furthermore, all-cause mortality was assessed in both groups.

Association between start of first immunosuppressive treatment and the course of pulmonary function during 5-year follow-up irrespective of the ILD-status

For this analysis, data of patients with at least two PFTs during follow-up were used. The difference in the trajectory of FVC % predicted between early *vs* late treatment was estimated by a multilevel mixed linear regression analysis on imputed data using the predefined confounders and the CIE approach.

Next, where data were available, the change in PFT was categorized in every 12-month period using the following previously reported definition: 'significant decline' (absolute FVC decline >10%), 'moderate decline' (absolute FVC decline 5–10%), 'stable' (absolute FVC change <5%) and 'improvement' (absolute FVC improvement of ≥5%) [5]. A margin of 3 months was allowed for the PFT at the beginning and end of each 12-month period.

Sensitivity analysis

All described analyses were repeated excluding patients diagnosed with ILD in the interval 2–12 months after first start of immunosuppressive treatment to exclude patients with potentially undiagnosed ILD at baseline.

Sample size calculation

While this study lacks a formal power calculation, it aligns with the general guideline for Cox regression models, which suggests a minimum of 10 events per predictor variable to ensure adequate power [26].

Results

Patient population

Within the two included databases, 4612 patients with a documented start date of a prescribed immunosuppressive agent were identified (Fig. 1). After applying the eligibility criteria, 1052 patients without ILD at baseline were included in our analyses. Demographic and clinical characteristics of all eligible patients are shown in Table 1 (see online Supplementary Table 2, available at *Rheumatology* online, for details about missing data rate).

The mean age of the overall population was 51.8 years, with a male to female ratio of 1:3. A total of 95.0% of patients fulfilled the ACR/EULAR criteria and 46.1% had dcSSc, with a mean (S.D.) modified Rodnan skin score (mRSS) value of 11.7 (9.5). With respect to antibody status, 27.3% were positive for anticentromere antibodies, 47.7% were positive for anti-topoisomerase I antibodies, and 9.4% were positive for RNA polymerase III antibodies.

Patients in the early treatment group were more frequently male, had a higher frequency of dcSSc and had more frequently anti-topoisomerase I and anti-RNA polymerase III antibodies. The mean mRSS values and the prevalence of elevated CRP were higher in the early treatment group. In both groups, MTX was the most frequently prescribed immunosuppressive agent.

The follow-up duration in the total population was median (IQR) 3.8 (2.2–5.0) years and not different between the two subgroups [mean (S.D.): early group: 3.6 (1.4); late group: 3.7 (1.4)]. All-cause mortality was 5.6% in the total population (4.9% in the early treatment group and 6.7% in the late treatment group, $P = 0.31$).

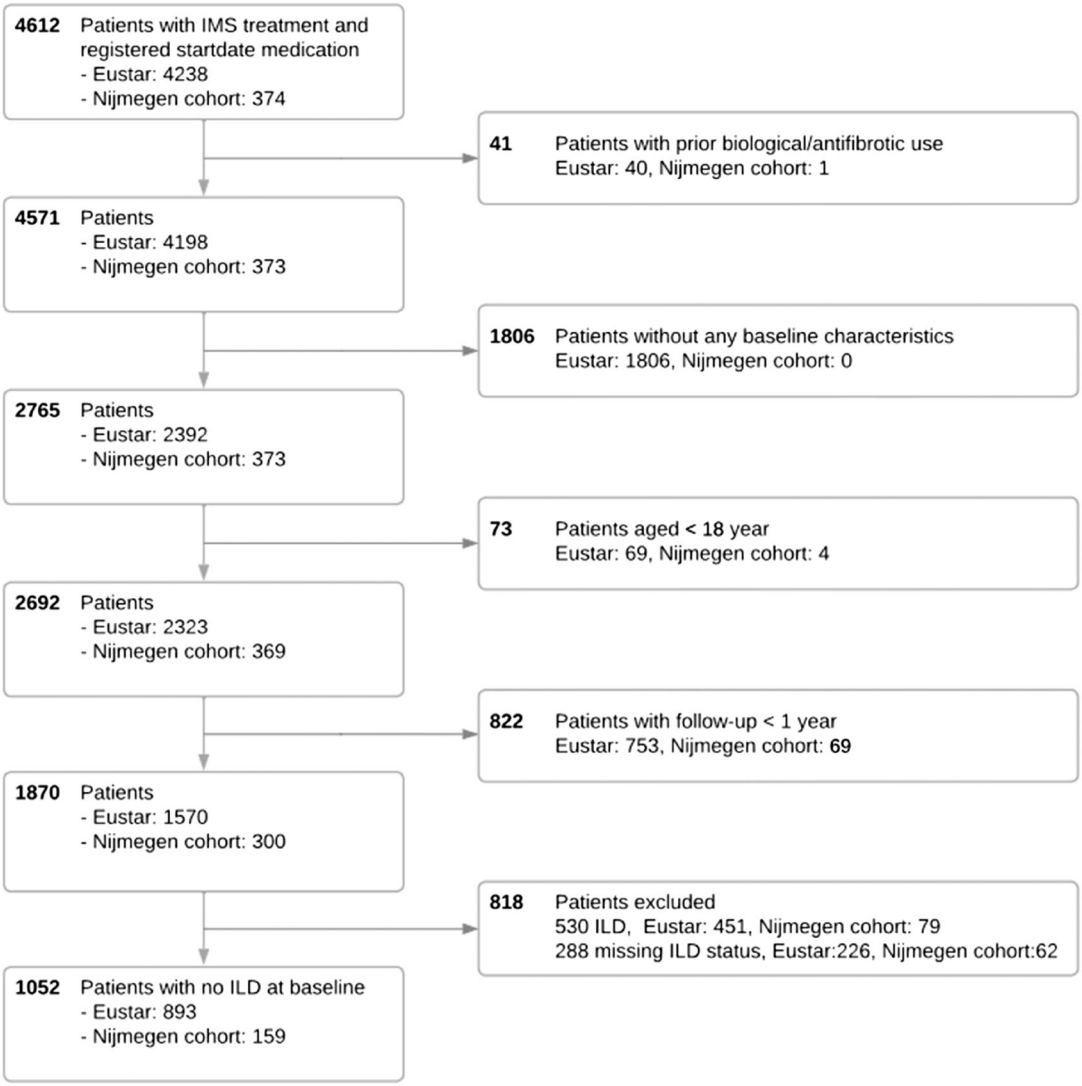

Figure 1. Flowchart of patient selection from combined cohort of the EUSTAR database and Nijmegen Systemic Sclerosis cohort

ILD-free survival after the start of immunosuppressive treatment

We observed 490 (46.6%) new ILD cases after mean (S.D.) 3.6 (1.4) years of treatment. Fig. 2 displays the unadjusted Kaplan–Meier survival curve on cases complete for disease duration showing no differences in ILD-free survival rates at each given time point during the 5 year follow-up period for both groups.

In addition, we found no clinically relevant difference in ILD-free survival between the groups on imputed data after adjusting for a priori defined confounders; mean incidence ILD 0.45 (95% CI: 0.40, 0.50) in the early group and 0.46 (95% CI: 0.43, 0.51) in the late group. Using a CIE approach, no additional confounder to the predefined base Cox proportional hazards model was identified (see Supplementary Table 3, available at *Rheumatology* online). Thus, after adjustment for sex, age, Caucasian ethnicity, diffuse cutaneous subtype, presence of anti-topoisomerase I antibodies, presence of anti-RNA polymerase III antibodies, FVC % predicted and DLCO % predicted, the hazard ratio (HR) for ILD in the early treatment group *vs* the late treatment group was 1.13 (95% CI: 0.93, 1.38). Performing the same analysis for methotrexate, cyclophosphamide and mycophenolate mofetil separately yielded HR (95% CI) of 1.04 (0.76, 1.43), 1.25 (0.87, 1.79) and 1.33 (0.88, 1.98), respectively. No separate analysis was performed for tocilizumab and rituximab, given the limited number of patients receiving these drugs. In addition, the HR (95% CI) for ILD survival with disease duration as a continuous variable was 0.99 (0.98, 1.01) (Supplementary Tables 4–7, available at *Rheumatology* online, for detailed models).

Course of pulmonary function after start of immunosuppressive treatment

We identified 789 patients fulfilling the eligibility criteria for this research question. As shown in Fig. 3, the estimated course of pulmonary function on imputed data adjusted for confounders is not different between groups. Over the 5-year follow-up period, the FVC % predicted in the early treatment group was not higher [ΔFVC (95% CI): 1.36% (−0.52, 3.25), $P = 0.16$]. Classifying the magnitude of change in FVC % predicted in every consecutive follow-up year showed that the proportion of patients with a major or significant decline in FVC % predicted varied over the years between 25% and 38% for the early treatment group and between 19% and 30% for the late treatment group (see Table 2).

Table 1. Overall baseline demographic and clinical characteristics of all SSc patients and characteristics stratified by early treatment and late treatment group

Characteristic	Total sample ($n = 1052$)	Early group ($n = 547$)	Late group ($n = 376$)	*P*-value
Age, mean (S.D.), years	51.8 (13.2)	50.4 (13.2)	53.0 (12.5)	**0.004**
Male, %	24.6	29.6	17.3	**<0.001**
Caucasian ($n = 1001$), %	79.6	81.5	77.5	0.17
Disease characteristics				
ACR/EULAR criteria fulfilled ($n = 1037$), %	95.0	93.2	95.0	**0.01**
Disease duration[a] ($n = 923$), median (IQR), years	2.1 (0.7–6.7)	0.8 (0.4–1.7)	8.4 (5.1–13.8)	**<0.001**
Diffuse cutaneous SSc ($n = 927$), %	46.1	53.1	36.5	**<0.001**
Limited cutaneous SSc ($n = 927$), %	49.6	42.5	59.0	
Antinuclear antibodies ($n = 1047$), %	97.7	97.6	97.9	1.00
Anti-centromere Ab ($n = 1012$), %	27.3	19.0	39.4	**<0.001**
Anti-topoisomerase I Ab ($n = 1028$), %	47.7	51.1	42.7	**0.01**
Anti-RNA polymerase III Ab ($n = 705$), %	9.4	12.4	5.3	**0.003**
Lung characteristics				
FVC % predicted ($n = 867$), mean (S.D.)	93.9 (20.3)	94.9 (19.2)	94.0 (21.6)	0.55
DLCO % predicted ($n = 857$), mean (S.D.)	70.4 (20.3)	71.6 (20.3)	69.6 (20.6)	0.10
Other characteristics				
mRSS ($n = 784$), median (IQR)	9 (4–18)	12 (6–19)	7 (3–14)	**<0.001**
Oesophageal symptoms ($n = 884$), %	56.6	53.2	63.0	**0.01**
Arthritis ($n = 906$), %	87.5	86.4	88.5	0.45
Tendon friction rubs ($n = 919$), %	11.1	12.3	9.6	0.26
Pulmonary hypertension ($n = 693$), %	10.1	8.8	11.7	0.28
Elevated CRP ($n = 772$), %	25.6	30.7	22.3	**0.02**
Ever smoker ($n = 885$), %	41.8	43.9	38.9	0.16
First prescribed immunosuppression				0.90
Cyclophosphamide, %	18.7	19.7	19.4	
Methotrexate, %	60.1	59.6	57.5	
Mycophenolate mofetil, %	19.5	19.0	21.0	
Rituximab, %	0.4	0.4	0.5	
Tocilizumab, %	1.3	1.3	1.6	

[a] Disease duration is calculated from first non-Raynaud phenomenon symptom. Of note, 129 patients could not be subdivided into early and late group, due to missing date of first non-Raynaud symptom. *P*-values in bold are significant. Ab: antibodies; DLCO: diffusing capacity of the lungs for carbon monoxide; FVC: forced vital capacity; IQR: interquartile range; mRSS: modified Rodnan skin score; SSc: systemic sclerosis.

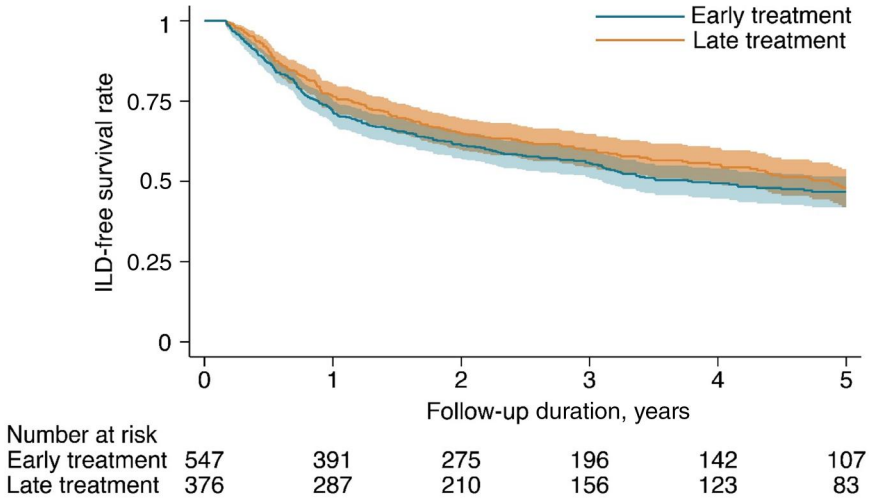

Figure 2. Kaplan–Meier curve of ILD-free survival estimates. Survival rate with 95% confidence interval is shown for the early and late treatment group with the number at risk per follow-up period presented in the table below the figure. ILD: interstitial lung disease

Sensitivity analysis

Repeating all analyses excluding patients diagnosed with ILD in the interval 2–12 months after baseline ($n = 273$) yielded similar results.

The Cox proportional hazards analysis incorporating the additionally identified confounders with the CIE approach for this analysis, i.e. pulmonary arterial hypertension, renal crisis, tender joints, U1RNP antibodies, reduced left ventricular ejection fraction, and dyspnoea NYHA classification showed an HR (95% CI) of 0.86 (0.61, 1.20) for ILD in the early treatment group (Supplementary Tables 8–12 and Supplementary Fig. 1, available at *Rheumatology* online).

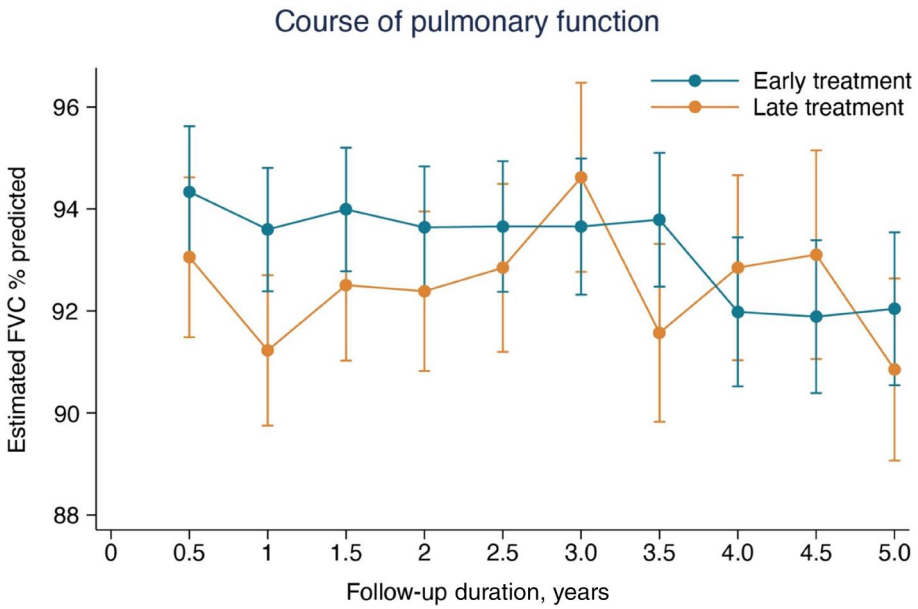

Figure 3. Course of pulmonary function adjusted for confounders. Predicted FVC value (%) based on mixed regression analysis adjusted for gender, diffuse subtype, Caucasian ethnicity, anti-topoisomerase I antibodies, anti-RNA polymerase III antibodies, age at baseline, FVC at baseline and DLCO at baseline. Error bars represent 95% confidence interval. DLCO: diffusing capacity of the lungs for carbon monoxide; FVC: forced vital capacity

Table 2. Descriptive data on the course of pulmonary function in every 12-month consecutive period

	Year 1	Year 2	Year 3	Year 4	Year 5
Early group					
n (95% CI)	239 (238, 240)	121 (121, 122)	84 (83, 84)	55 (54, 55)	42 (42, 42)
Improved PFT, %	26	30	23	18	16
Stable PFT, %	46	42	52	44	51
Moderate decline, %	16	16	16	25	19
Significant decline, %	12	12	9	13	14
Late group					
n (95% CI)	157 (156, 158)	76 (75, 76)	59 (58, 59)	43 (43, 44)	33 (33, 33)
Improved PFT, %	24	22	31	25	29
Stable PFT, %	56	55	40	53	50
Moderate decline, %	10	11	22	10	15
Significant decline, %	9	12	8	12	6

Patients in the early treatment group and in the late treatment group were categorized based on their annual FVC change if present for that interval. The following definition has been used: significant decline: absolute FVC decline of >10%; moderate decline: absolute FVC decline of 5–10%; stable: absolute FVC change of <5%; improvement: absolute FVC improvement of ≥5%. FVC: forced vital capacity; PFT: pulmonary function test.

Discussion

This is the first observational study of prospectively collected data analysing the association between time to intervention in SSc and the risk to develop ILD. In our cohort of 1052 patients with SSc and no ILD receiving immunosuppressive treatment, the incidence of ILD in the first 5 years after initiation of treatment was not different between patients starting with immunosuppressive treatment early in the disease course *vs* patients starting late. Similarly, the timing of start of immunosuppressive treatment did not influence the course of pulmonary function in the first 5 years after initiating treatment.

To date, only one small single centre study ($n = 43$, 80% ILD at baseline) evaluated the influence of time to intervention on disease course [12]. Patients starting with early immunosuppressive treatment had less clinical worsening after 1 year than the late treatment group. Despite a substantial proportion of patients experiencing a worsening of pulmonary function in the early group, the authors of this study suggest that a window of opportunity exists in early SSc. The results of our study do not confirm these findings, for which several explanations are possible. First, we included only patients without ILD, allowing us to focus on preventive mechanisms. Secondly, in contrast to the above-mentioned study we corrected for confounding by indication. Of note, the analysis was not corrected for differences in baseline FVC % predicted, which was higher in the early treatment group [12]. Last, we specifically focused on the development of ILD and did not assess clinical worsening by the first step of the revised ACR-CRISS.

In our cohort, starting early with immunosuppressive treatment did not influence the course of FVC % predicted during follow-up compared with starting late with immunosuppressive treatment, regardless of ILD status. The prevalence of a progressive phenotype varied between 28% and 38% in the early treatment and 19% and 30% in the late treatment group over 5 years, suggesting a slightly higher prevalence of a progressive phenotype in the early treatment group.

However, this is likely not a meaningful difference, given our findings that the absolute change in pulmonary function is comparable (Fig. 3), the incidence of ILD is not different in the groups, and the fluctuations in the prevalence of progressive phenotype should be interpreted with caution given the amount of available data. Interestingly, the prevalence of a decline in FVC % ≥10% is comparable to earlier reported annual prevalence of 13–18% in SSc-ILD patients [5]. Our results indicate the need of monitoring of the pulmonary function in SSc regardless of the presence of ILD.

To date, there is no definitive evidence supporting the start of immunosuppressive treatment in an early disease stage in SSc. A systematic review (reporting studies between 2005 and 2018) failed to show an added value of early treatment, but suggested that a window of opportunity exists in SSc based on two patients benefiting from rituximab started in an early disease stage and the positive effects of rituximab in other rheumatic diseases [27]. More recent studies, such as the phase II and phase III tocilizumab studies and a retrospective analysis of the Canadian Scleroderma Research Group registry, have highlighted the importance of initiating immunosuppressive therapy in an early disease stage [11, 13, 14, 28]. In these studies, starting immunosuppressive treatment compared with placebo resulted in a prognostically more favourable disease course of SSc. Regarding the preventive effect of immunosuppressive treatment, data from prospective studies are lacking. Despite the limited evidence, several experts have suggested that it might be beneficial to initiate immunosuppressive treatment in an early disease stage, based on the findings that tocilizumab has shown efficacy in early SSc-ILD and/or on the pathophysiological mechanism that inflammation precedes irreversible fibrosis [18, 29, 30].

Our study does not show an added value of early immunosuppressive treatment compared with late immunosuppressive treatment. However, this does not exclude that a small subset of SSc patients might benefit from early treatment. SSc is a heterogeneous disease, and a recent analysis has shown that only a small proportion of patients in the EUSTAR database fulfil the eligibility criteria of several recent key clinical trials [31]. Our study population was characterized by a high inflammatory profile, which might also explain the observed high incidence of inflammatory arthritis. Future research should therefore focus on classifying patients according to their prognostic phenotype as well as identifying the optimal time to start immunosuppressive treatment in different subsets. In this light, tight control of disease features is also important, which could be accomplished with telemonitoring. In SSc, it has been shown to be feasible to measure pulmonary function and skin score reliably at home [32, 33]. Prospective longitudinal studies are needed to confirm its validity in monitoring disease activity.

A major strength of our study is the large study population of patients with clinical SSc diagnosis from international expert centres and the long follow-up period. Nevertheless, our study has limitations. First, our study is hampered by the potential bias introduced by confounding by indication, due to the post-hoc nature of our analysis. In addition, the follow-up time could have been too short to capture the proportion of patients developing ILD in a later stage. Also, the chosen cut-off point of 3 years in our study is arbitrary; however, our analysis using disease duration as a continuous measure yielded similar results. Furthermore, most of the patients in the primary analysis used methotrexate, while to date there is scarce evidence for efficacy of methotrexate in SSc. Only two small placebo controlled randomized controlled trials, which were underpowered and used different eligibility criteria, showed a limited effect on skin involvement but not on ILD [34, 35]. Nevertheless, re-analysis excluding patients treated with methotrexate yielded similar results as the primary analysis (results not shown). Finally, it is arguable whether all patients in our primary analysis were ILD-free. However, our sensitivity analysis excluded patients who developed ILD in the first year after start of immunosuppressive treatment and showed similar results, confirming the robustness of our data.

To conclude, our study does not show an added value for a preventive immunosuppressive strategy when started early *vs* late in the disease course. However, considering confounding by indication and heterogeneity in the SSc population, an early preventive effect in a subgroup of SSc patients cannot be ruled out. Therefore, more research is needed in early disease stages with specific subsets of patients with different phenotypes, to further unravel disease phenotype and identify patients benefiting from early treatment.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data are available from the corresponding author on reasonable request

Contribution statement

Substantial contributions to study conception and design: A. V., M.F.R.B., C.B., O.D., C.H.M.E., M.V.

Substantial contributions to acquisition of data: all authors. Substantial contributions to analysis and interpretation of data: all authors. Drafting the article or revising it critically for important intellectual content: all authors. Final approval of the version of the article to be published: all authors.

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