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Clinical science

Anti-acid therapy in SSc-associated interstitial lung disease: long-term outcomes from the German Network for Systemic Sclerosis

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Abstract

Objectives: Gastroesophageal reflux disease (GERD) occurs frequently in patients with SSc. We investigated whether the presence of GERD and/or the use of anti-acid therapy, specifically proton-pump inhibitors (PPIs), are associated with long-term outcomes, especially in SSc-associated interstitial lung disease (SSc-ILD).

Methods: We retrospectively analysed patients with SSc and SSc-ILD from the German Network for Systemic Sclerosis (DNSS) database (2003 onwards). Kaplan–Meier analysis compared overall survival (OS) and progression-free survival (PFS) in patients with GERD *vs* without GERD (SSc

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and SSc-ILD), and PPI *vs* no PPI use (SSc-ILD only). Progression was defined as a decrease in either percentage predicted forced vital capacity of ≥10% or single-breath diffusing capacity for carbon monoxide of ≥15%, or death.

Results: It was found that 2693/4306 (63%) registered patients with SSc and 1204/1931 (62%) with SSc-ILD had GERD. GERD was not associated with decreased OS or decreased PFS in patients in either cohort. In SSc-ILD, PPI use was associated with improved OS *vs* no PPI use after 1 year [98.4% (95% CI: 97.6, 99.3); $n=760$ *vs* 90.8% (87.9–93.8); $n=290$] and after 5 years [91.4% (89.2–93.8); $n=357$ *vs* 70.9% (65.2–77.1); $n=106$; $P<0.0001$]. PPI use was also associated with improved PFS *vs* no PPI use after 1 year [95.9% (94.6–97.3); $n=745$ *vs* 86.4% (82.9–90.1); $n=278$] and after 5 years [66.8% (63.0–70.8); $n=286$ *vs* 45.9% (39.6–53.2); $n=69$; $P<0.0001$].

Conclusion: GERD had no effect on survival in SSc or SSc-ILD. PPIs improved survival in patients with SSc-ILD. Controlled, prospective trials are needed to confirm this finding.

Keywords: anti-acid, reflux, interstitial lung disease, proton pump inhibitors, SSc

Rheumatology key messages

- We assessed the effects of gastroesophageal reflux disease (GERD) and proton-pump inhibitor (PPI) use on overall survival/progression-free survival (OS/PFS) in SSc and SSc-ILD.
- PPI use was associated with improved OS and PFS in patients with SSc-ILD.
- The presence of GERD had no effect on OS or PFS in SSc or SSc-ILD.

Introduction

SSc is a rare and complex autoimmune disease, characterized by immune dysregulation, microvascular damage and progressive fibrosis [1]. SSc affects multiple organ systems and can lead to interstitial lung disease (ILD), which is a leading cause of death among patients with SSc [2–5]. SSc-associated ILD (SSc-ILD) results in significant pulmonary symptoms, such as exertional dyspnoea and cough, as well as impaired quality of life [6, 7].

Current evidence suggests that 20–30% of patients with SSc-ILD will develop progressive disease, i.e. worsening lung function [8–10]. Certain patient characteristics and biomarkers are associated with disease progression in SSc-ILD, though predicting which patients will progress remains challenging. Risk factors for progression include male sex, older age, elevated CRP, positive anti-Scl-70 (anti-topo I) status, negative ACA status, pulmonary arterial hypertension, dcSSc, arthritis, lower peripheral oxygen saturation after exercise, lower diffusing capacity of the lung for carbon monoxide (DLco), exertional dyspnoea, and non-productive cough [11–14].

Gastroesophageal reflux disease (GERD) is frequent in SSc (prevalence range 30–96%) [15–17]. Increased oesophageal diameter on high-resolution CT (HRCT) is associated with more severe radiographic ILD, lower lung volume and worse lung function [18, 19]. In addition, oesophageal dysmotility and absent contractility are associated with worse lung function [20, 21]. In one study of 145 patients with SSc-ILD, oesophageal diameter and hiatal hernia were independently associated with disease severity and mortality, but not with progression of ILD [22]. GERD occurs with higher frequency and greater severity in SSc-ILD (both dcSSc and lcSSc subsets) than in SSc without ILD [23]. However, it is not known whether GERD is associated with an increased risk of disease progression or death in SSc or SSc-ILD.

GERD is due to an insufficiency of the lower oesophageal sphincter and can be managed through lifestyle modification, or pharmacologically with anti-acid therapy (AAT), which mainly consists of proton-pump inhibitors (PPIs) [24, 25]. No large-scale, randomized controlled trials of AATs in general, and PPIs in particular, in SSc have been conducted, and the limited outcome data available suggest that PPI use is associated with short-term relief of GERD symptoms but not with long-term benefits [26, 27]. Data on the effect of PPIs on disease progression in idiopathic pulmonary fibrosis (IPF) (the archetypal progressive fibrosing ILD) are conflicting [28–33], and in SSc-ILD are non-existent. Therefore, there is a need to investigate the potential association between PPI use and disease progression in patients with SSc-ILD.

The objectives of this analysis of the registry of the German Network for Systemic Sclerosis (DNSS) were to assess whether (1) the progression of SSc and SSc-ILD is associated with the presence of GERD, and (2) the progression of SSc-ILD is associated with the use of PPIs.

Methods

Study design and study population

The DNSS is an interdisciplinary collaboration of hospitals and research centres with a special interest in SSc as previously described [34]. In this study, we retrospectively analysed patients with SSc registered in the DNSS from 2003 onwards. Two sets of patients were analysed: Set 1 included all patients with SSc or SSc-ILD, and all visits since the initial diagnosis of SSc were analysed; Set 2 included all patients with SSc-ILD, and all visits prior to the diagnosis of ILD were excluded, and is a subset of Set 1. Set 1 was categorized by the presence of GERD (yes/no) (Objective 1), and Set 2 was categorized by the use of PPIs (yes/no) (Objective 2). GERD was defined as oesophageal dysphagia and reflux by patient-reported symptoms such as difficulty swallowing liquid or hard food as well as intermittent heartburn [34].

Following inclusion into the registry, a four-page disease- and organ-specific questionnaire containing >110 items was completed for each patient. These items included patient data on current signs and symptoms, gender, year of birth, characteristic laboratory data (autoantibodies, clinical chemistry), SSc subsets, symptoms, organ involvement, modified Rodnan Skin Score (mRSS), as well as treatment with CSs, immunosuppressants, vasoactive drugs and prescription of physical therapy. Follow-up visits and respective investigations [e.g. echocardiography, ECG, pulmonary function tests (PFTs)] were recommended at least once per year. No specific patient-reported outcome questionnaires were used; symptoms were either self- or physician-reported. At the time of the initiation of the registry in 2003, there was no generally accepted

definition of ILD progression based on DLco and/or forced vital capacity (FVC) thresholds. While data on DLco were recorded in the initial case report form (CRF), data on FVC were not systematically included before 2014.

Outcome definition

Overall survival (OS) was defined as the time from initial SSc diagnosis (Set 1), or first visit with an ILD diagnosis (Set 2), to death from any cause (recorded on the CRF by the respective centre) or last visit (censoring). Progression-free survival (PFS) was defined as the time from first DNSS registry visit (Set 1), or first visit with an ILD diagnosis (Set 2), to either death or disease progression [defined as a decrease in predicted FVC (FVC pred) of $\geq$10% or a decrease in predicted single-breath DLco (DLco-SB pred) of $\geq$15%], in line with definitions of progression used in previous real-world studies [9, 35], and IPF where comparable data on PPI exist [29].

Ethics approval

All patients in the registry provided written informed consent, and the Ethics Committee of the coordinating centre, Cologne University Hospital, approved the patient information and consent form for the registry (No. 04–43). This was used as the basis for approval from local ethics committees by all participating centres prior to registering patients.

Inclusion and exclusion criteria

Eligible patients were aged $\geq$18 years and had a diagnosis of SSc according to classification criteria published by the ACR 1980 criteria [36] or, from 2014, the ACR/European League Against Rheumatism 2013 criteria [37] for SSc. Classification of patients with dcSSc *vs* lcSSc was informed by criteria established by Le Roy *et al.* [38]. SSc-overlap syndrome was defined as a disease occurring with clinical aspects of SSc (according to the ACR criteria) or main symptoms of SSc simultaneously with those of other CTDs/autoimmune diseases such as DM, SS or SLE, as previously described [1, 34, 38–41]. In the original inclusion criteria, patients were defined as having SSc-ILD if bilateral fibrosis was visible on chest X-ray or HRCT scans and other possible causes of lung fibrosis were excluded [34]. Following a revision of the CRF in 2014, only patients with ILD confirmed on HRCT were accepted. No minimum duration of PPI treatment was specified as part of the eligibility criteria (any use of PPIs was sufficient for inclusion).

Statistics

Statistical analyses were conducted using SPSS Statistics 23.0.0.3 64-Bit software (IBM Corp., Armonk, NY, USA). In the analysis of patient characteristics, *P* values were calculated using the Pearson's Chi-squared test for categorical data. For continuous data, *P* values were calculated parametrically using the *t* test, since the sample distribution was assumed to be normal due to the large sample size. The requirement of homogeneous variance between the groups for performing the *t* test was checked using Levene's test; if the assumption was violated, the degrees of freedom were adjusted accordingly. We did not adjust for multiple testing due to the exploratory nature of this study.

For Set 1, data recorded between the first and last visits were aggregated (in order to capture all follow-up data) using the following coding system: dichotomous variables (ever/never), ordinal and continuous variables (worst value: minimum or maximum value), and irreversible symptoms and characteristics (value at last visit). For Set 2, data were taken from the first visit with an ILD diagnosis. Kaplan–Meier analysis compared OS and PFS between (1) patients with SSc and SSc-ILD with *vs* without GERD (Set 1), and (2) patients with SSc-ILD receiving *vs* not receiving PPIs (Set 2). Missing data were imputed using available data from other visits, where possible. No further imputation of missing data was performed.

Cox regression analyses were performed to evaluate the relationship between GERD/PPI use and survival. A univariable analysis including the variables affecting survival in SSc-ILD (baseline FVC, age, sex, baseline mRSS) was also performed. To estimate the effect of GERD on OS and PFS, univariable and multivariable Cox regression models were performed. In addition to GERD, univariable models were fitted for clinically relevant covariates, i.e. age (years), gender, SSc subtype, Scl-70 positive, ACA positive, AAT use, immunosuppressive therapy, pulmonary hypertension (OS and PFS); DLco-SB%, FVC% (OS only), and time since SSc diagnosis (years; PFS only). As FVC pred was only included in the registry from 2014, only a smaller subset has FVC pred values. In univariable analysis, a higher FVC pred value showed improved survival ($P = 0.005$). FVC pred was not included in the multivariable analysis of OS. The remaining covariates were included in the original multivariable model along with GERD/PPI. While GERD/PPI was kept as the primary outcome variable in the model, covariates were selected using the backward elimination method based on $P > 0.1$ (Wald statistic). For Cox regression models, hazard ratios, corresponding 95% CIs, and *P* values (Wald test) are reported.

Results

Patient characteristics

We identified 4306 patients with SSc, of whom 4214 had available data for GERD, with 3024 (71.8%) recorded as suffering from GERD at any point between their first and last DNSS visit (data extraction: 6 February 2019). Almost half of the patients with SSc (44.8%; $n = 1931$) had SSc-ILD, of which 62.3% (1204 out of 1931 patients) were recorded as having GERD at their first visit with an ILD diagnosis. In the SSc-ILD group, 1117 patients received PPIs and 814 patients did not (Table 1 and Fig. 1). Patients received only PPIs in this study; no other types of AAT were administered. GERD was recorded in 65.9% of patients in the PPI group and 58.1% of patients in the non-PPI group ($P = 0.001$). In patients with SSc and with at least two documented visits, the median follow-up time was 38 months [interquartile range (IQR) 18–86]. In patients with SSc-ILD and at least one follow-up visit after the first visit with an ILD diagnosis, the median follow-up time was 39 months (IQR 19–89). At baseline, mean (S.D.) FVC% pred was lower in the PPI group ($n = 232$) compared with the non-PPI group ($n = 83$) [77.8% (18.9) *vs* 84.9% (19.1); $P = 0.003$]. Mean (S.D.) DL_{CO}%-SB pred was also lower in the PPI group ($n = 824$) compared with the non-PPI group ($n = 442$) [57.8% (19.4) *vs* 63.3% (22.7); $P < 0.001$]. The use of immunosuppressants (CYC, MTX, AZA, MMF or chloroquine/HCQ) was higher in the PPI group *vs* the non-PPI group [550/1109 (49.6%) *vs* 321/746 (43.0%); $P = 0.005$]. Statistically significant differences between the PPI and non-PPI group were also found for several other

Table 1. Baseline patient characteristics in the total SSc cohort, in patients with SSc-ILD and by PPI status

			SSc-ILD		
	SSc ($n = 4306$)	SSc-ILD ($n = 1931$)	Non-PPI ($n = 814$)	PPI ($n = 1117$)	*P* value (non-PPI *vs* PPI)
SSc subtypes, *n*	4306	1873	801	1072	
lcSSc, *n* (%)	2421 (56)	729 (39)	308 (39)	421 (39)	0.88
dcSSc, *n* (%)	1370 (32)	945 (51)	405 (51)	540 (50)	
Overlap, *n* (%)	515 (12)	199 (11)	88 (11)	111 (10)	
Age at SSc diagnosis, *n*	4140	1857	778	1079	
Mean age, years (S.D.)	48.61 (14.55)	48.12 (14.91)	48.36 (15.23)	47.97 (14.67)	0.58
Time since diagnosis, *n*	4189	1877	781	1096	
Mean time, years (S.D.)	7.06 (7.90)	7.69 (8.08)	8.29 (8.71)	7.27 (7.58)	0.08
Males, *n* (%)	799 (19)	432 (23)	168 (22)	264 (25)	0.13
BMI, *n*	3137	1072	248	824	
Mean BMI, kg/m^2 (S.D.)	25 (5)	25 (5)	24 (5)	25 (5)	0.21
Scl-70 positive, *n* (%)	1287 (32)	887 (48)	368 (47)	519 (48)	0.76
ACA positive, *n* (%)	1530 (37)	359 (20)	142 (18)	217 (20)	0.39
GERD, *n* (%)	2693 (63)	1204 (62)	502 (62)	702 (63)	0.63
Steroid use, *n* (%)	1842 (44)	864 (47)	341 (46)	523 (47)	0.50
Immunosuppressant use, *n* (%)[a]	2109 (51)	871 (47)	321 (43)	550 (49)	0.005
DL_{CO}-SB% pred, *n*	3196	1266	442	824	
Mean DL_{CO}-SB pred, % (S.D.)	61 (21)	60 (21)	63 (23)	58 (19)	<0.001
FVC% pred, *n*	1439	315	83	232	
Mean FVC pred, % (S.D.)	86 (22)	80 (19)	85 (19)	78 (19)	0.003
FEV_1% pred, *n*	1514	346	87	259	
Mean FEV_1 pred, % (S.D.)	84 (21)	81 (19)	84 (17)	79 (20)	0.004
mRSS, *n*	4019	1770	715	1055	
Mean mRSS (S.D.)	11 (9)	12 (9)	12 (10)	12 (9)	0.36

Aggregated data (first to last visit) presented for Set 1 (column 2); data on first visit with ILD diagnosis presented for Set 2 (columns 3–6). Valid *n* for each variable is indicated. *P* values were calculated using the Pearson's Chi-squared test for categorical data, and the Mann–Whitney-*U* test for continuous data. [a]Immunosuppressant use does not include steroid use. GERD: gastroesophageal reflux disease; DL_{CO}-SB: single-breath diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; ILD: interstitial lung disease; IQR: interquartile range; mRSS: modified Rodnan skin score; PPI: proton pump inhibitor; pred: predicted; SSc-ILD: interstitial lung disease associated with SSc.

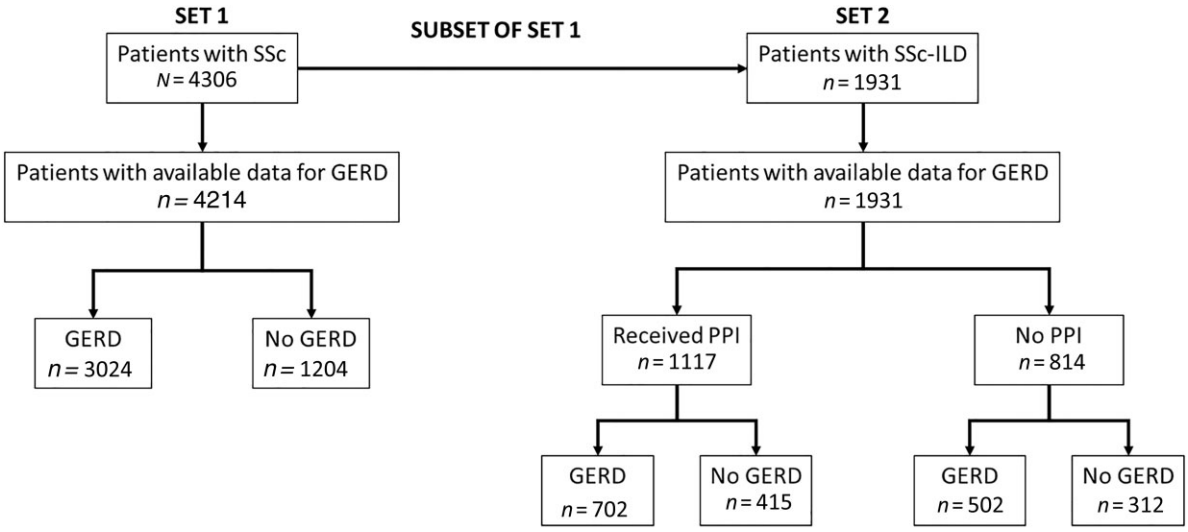


Figure 1. Patient groups in the DNSS analysed in the study. For patients with SSc, data show GERD at any visit. For patients with SSc-ILD, data show GERD at first visit with ILD diagnosis. DNSS: German Network for Systemic Sclerosis; GERD: gastroesophageal reflux disease; PPI: proton pump inhibitor; SSc-ILD: SSc-associated interstitial lung disease

baseline characteristics, including gastrointestinal and renal involvement, as well as use of certain medications (AT1 receptor antagonists, endothelin receptor antagonists, prostanoids, analgesics) (Supplementary Table S1, available at *Rheumatology* online). There were no significant differences between the PPI and non-PPI groups for SSc subtype (lcSSc, dcSSc, overlap), age, sex, antibody status, BMI, mRSS, GERD, or steroid use (Table 1; Supplementary Table S1, available at *Rheumatology* online). A similar proportion of patients with dcSSc (65.3%; $n = 620$) and lcSSc (62.4%; $n = 454$) had GERD at baseline.

Effect of GERD on outcomes in SSc and SSc-ILD

In patients with SSc, GERD was not associated with a difference in 20-year OS: 86.2% (95% CI: 84.1, 88.3) in the GERD group ($n = 429$) *vs* 87.4% (83.6–91.4) in the non-GERD group ($n = 93$; $P = 0.82$). GERD was also not associated with a difference in 5-year PFS: 66.0% (63.5–68.6) in

the GERD group ($n = 672$) *vs* 68.0% (62.2–74.2) in the non-GERD group ($n = 94$; $P = 0.77$) (Supplementary Fig. S1, available at *Rheumatology* online). Of 612 patients with progression in Set 1, 156 died and 456 had progression based on DLco and/or FVC thresholds.

In the subgroup of patients with SSc-ILD, GERD was not associated with a difference in 20-year OS: 83.4% (80.2–86.8) in the GERD group ($n = 192$) *vs* 79.4% (69.4–90.9) in the non-GERD group ($n = 17$; $P = 0.36$). GERD was also not associated with a difference in 5-year PFS: 62.2% (58.8–65.8) in the GERD group ($n = 374$) *vs* 67.9% (59.3–77.7) in the non-GERD group ($n = 39$; $P = 0.57$) (Supplementary Fig. S2, available at *Rheumatology* online). Of 353 patients with progression in Set 2, 129 died and 224 had progression based on DLco and/or FVC thresholds.

The number of events reported in Supplementary Figs S1B and S2B, available at *Rheumatology* online, is slightly lower, as only patients with additional information on GERD were included in the Kaplan–Meier analyses.

Effect of PPIs on outcomes in patients with SSc-ILD

In patients with SSc-ILD, PPI use was associated with an improved OS and PFS (Fig. 2A and B). One year after the first ILD visit, the rate of OS (95% CI) was 90.8% (87.9, 93.8) in the non-PPI group ($n = 290$) *vs* 98.4% (97.6, 99.3) in the PPI group ($n = 760$); after 5 years, the rate of OS was 70.9% (65.2, 77.1) in the non-PPI group ($n = 106$) *vs* 91.4% (89.2–93.8) in the PPI group ($n = 357$) ($P < 0.0001$). One year after the first ILD visit, the rate of PFS (95% CI) was 86.4% (82.9, 90.1) in the non-PPI group ($n = 278$) *vs* 95.9% (94.6, 97.3) in the PPI group ($n = 745$) ($P < 0.0001$); after 5 years, the rate of PFS (95% CI) was 45.9% (39.6, 53.2) in the non-PPI group ($n = 69$) *vs* 66.8% (63.0, 70.8) in the PPI group ($n = 286$) ($P < 0.0001$).

Regression analyses

Using Cox regression models for OS or PFS, no additional role of potential confounders was identified. The effect of GERD and PPI on OS and PFS remained stable after adjusting for relevant covariates, including immunosuppressive therapy (Supplementary Tables S2–S5, available at *Rheumatology* online).

Discussion

While there is some debate around the potential effects of PPIs on IPF [42, 43], nothing is known about whether (or how) PPIs affect disease progression in SSc-ILD. Our study, the largest of its kind to investigate outcomes associated with PPI use in patients with SSc-ILD, suggests that PPIs may provide some survival benefit (in terms of both OS and PFS) over a 5-year period in this at-risk population. In addition, our findings suggest that the presence of GERD has no association with survival outcomes (20-year OS or 5-year PFS) in patients with SSc or SSc-ILD. Regression analyses confirmed that the effect of GERD and PPIs on OS and PFS remained stable after adjusting for relevant covariates, including immunosuppressive therapy. Thus, our results suggest that a potential survival benefit might be associated with PPI use rather than influenced by other comorbidities or perhaps immunosuppressive therapies.

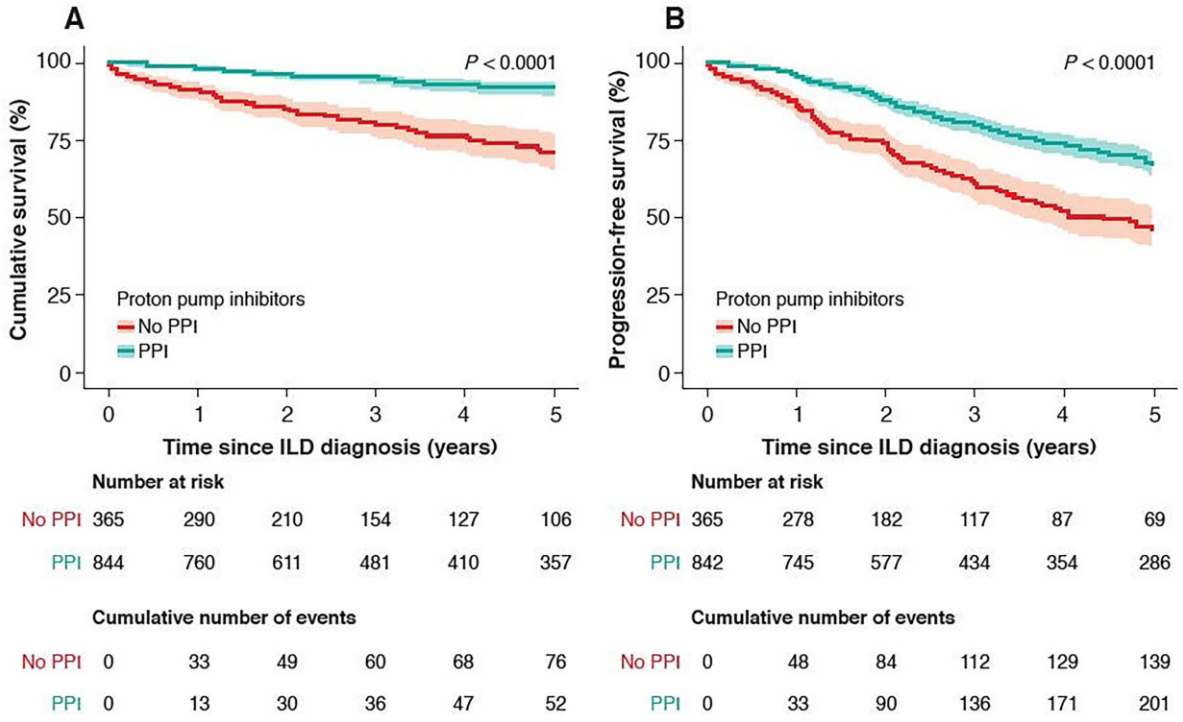
Improved survival in the PPI group could have been influenced by the type of treatment centre visited by patients, i.e. specialist centres may have been more likely to prescribe PPIs to patients with SSc-ILD and may have provided better all-round care. However, since the type of treatment centre was not documented as part of the DNSS database, the potential influence of this factor is unknown. In addition, data on the specific doses of PPI received by patients are also unavailable, preventing a more granular interpretation of the effect of PPIs on survival. Higher doses of PPIs may have resulted not only in different survival outcomes, but also in different safety outcomes, e.g. higher infection rates. Lastly, the number of patients with available and consistent data from serial PFTs was too low to analyse any potential association between pulmonary function decline (change in FVC% pred and DL_{CO}) and survival outcomes over the 5-year observation period.

It is also possible that the favourable survival outcomes in the PPI group were due to other, indirect effects of PPIs on acidic micro-aspiration (the unintentional aspiration of very small amounts of acidic reflux material) [44, 45]. It has been hypothesized that in IPF, persistent inflammation of the lung tissue infrastructure caused by micro-aspiration (discussed by Wang *et al.* [44]) could accelerate disease progression. However, this is yet to be proven, and no studies have investigated the possible effect of PPIs on the acidic component of micro-aspiration.

While it is possible that any use of PPIs could bias our findings, only regularly prescribed drugs were recorded in the CRF. Therefore, a single dose or 1-week course of therapy was not recorded. It should also be noted that GERD in patients with SSc is a chronic disease and shows no remission, therefore regular dosage is likely once initiated.

DLco was reduced both in patients with SSc-ILD and in those with SSc without ILD. This may be due to pulmonary hypertension, or indicate patients at risk of developing pulmonary hypertension [46, 47]. In the Cox regression models for OS or PFS, no additional role of potential confounders was found, and the effect of GERD and PPIs remained stable after adjusting for relevant covariates, including pulmonary hypertension.

Despite these interesting findings, this study is subject to several limitations. Patient characteristics varied between the PPI and non-PPI groups. In the PPI group, patients had worse lung function (lower FVC% pred and DL_{CO}) and higher immunosuppressant use than patients in the non-PPI group. As such, patients in the PPI group (with more advanced disease) may have been less likely to cross the pre-specified thresholds of progression (FVC $\geq$10% or DL_{CO} $\geq$15%), which could have biased the PFS results in favour of PPIs. However, this line of reasoning would also suggest that OS should be shorter in the PPI group, which is not what we observed. Furthermore, lack of standardization of PFTs is a typical limitation of registry data. Although the types of immunosuppressant used were recorded in the database, low patient numbers and changing patterns of use across the study period prevent stratification of our analysis by immunosuppressant type. The frequency of steroid and immunosuppressant therapy may be higher in Germany than in other countries. However, the frequencies are in line with those previously reported for this registry [48], or are similar or lower than those reported in a EUSTAR cohort analysis [49]. In addition, because the PPI subgroup in the SSc-ILD analysis set included patients both with (65.9%) and without (58.1%) GERD, it is not possible to make any conclusions about the association between PPI



	Overall survival				Progression-free survival			
	Years	Proportion	95% CI		Years	Proportion	95% CI	
No PPI	1	90.8	87.9	93.8	1	86.4	82.9	90.1
	5	70.9	65.2	77.1	5	45.9	39.6	53.2
PPI	1	98.4	97.6	99.3	1	95.9	94.6	97.3
	5	91.4	89.2	93.8	5	66.8	63.0	70.8

Figure 2. Kaplan–Meier curve for overall survival (A) and progression-free survival (B) according to use of PPIs in patients with SSc-ILD. Analysis of Set 2. Progression defined as decline in FVC of ≥10%, decline in DL_{CO} of ≥15%, or death. Shading represents confidence intervals. DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; ILD: interstitial lung disease; PPI: proton-pump inhibitor; SSc-ILD: SSc-associated interstitial lung disease

use and survival outcomes in patients with SSc-ILD and GERD specifically. Finally, at the time of data capture, novel therapies such as antifibrotic drugs were not used in the included patients. Their effect on OS and PFS cannot, therefore, be assessed.

Building on our research, prospective studies evaluating PPI alone *vs* in combination with other novel approaches to the management of GERD would be of clinical interest. One such approach that has recently shown promise in IPF is laparoscopic surgical treatment, which had a clinically meaningful impact on lung function in patients with IPF and GERD in a Phase II study [50]. To date, no such study has been conducted in patients with SSc-ILD.

Conclusion

Overall, our findings in this retrospective analysis of a large, prospective, observational cohort suggest that PPI use may provide a survival benefit over 5 years in patients with SSc-ILD. However, further randomized controlled trials are urgently needed to shed more light on the possible effects of PPIs on outcomes in SSc-ILD.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data presented in this study are derived from an independent German registry of patients with SSc (the DNSS network). For all data-related queries, please contact the last author, N.H.

Contribution statement

All authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors

(ICMJE). All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; and contributed substantially to the study design, data analysis, and interpretation and writing of the manuscript.

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