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Therapeutic management of fibrosis in systemic sclerosis patients – an analysis from the Swiss EUSTAR cohort

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Summary

OBJECTIVES: Systemic sclerosis is a chronic autoimmune connective tissue disease leading to microvascular and fibrotic manifestations in multiple organs. Several treatment options and recommendations from different European countries are available. In this study, for which the ambit is Switzerland specifically, we aim to describe the treatment patterns of systemic sclerosis patients with fibrotic manifestations.

METHODS: Systemic sclerosis patients were selected from six Swiss tertiary centres recorded in the multicentre, prospective European Scleroderma Trials and Research (EUSTAR) registry. Patients fulfilling the 2013 ACR/EULAR systemic sclerosis classification criteria at baseline were included. To determine the differences in treatment of varying degrees of fibrosis, four groups were identified: (1) patients with a modified Rodnan skin score (mRSS) >0; (2) those with mRSS ≥7; (3) those with interstitial lung disease (SSc-ILD), diagnosed by either chest X-Ray or high-resolution computed tomography; and (4) patients fulfilling one of the additional criteria for extensive interstitial lung disease, defined as interstitial lung disease involvement of >20% in high-resolution computed tomography, dyspnea NYHA-stage 3/4, or a predicted forced vital capacity (FVC) of <70%.

RESULTS: A total of 590 patients with systemic sclerosis fulfilled the inclusion criteria. In this cohort, 421 (71.4%) had mRSS >0, of whom 195 (33.1%) had mRSS ≥7; interstitial lung disease was diagnosed in 198 of 456 (43.4%), of whom 106 (18.0 %) showed extensive interstitial lung disease. Regarding non-biologic disease-modifying medications (DMARDs), the most frequently prescribed was methotrexate, followed by hydroxychloroquine and mycophenolate mofetil. Rituximab and tocilizumab were most frequently used among the biologic DMARDs. Specifically, 148/372 (39.8%) of treated patients with skin fibrosis received methotrexate, mycophenolate mofetil or rituximab, and 80/177 (45.2%) with interstitial lung disease received cyclophosphamide, mycophenolate mofetil, tocilizumab or rituximab. Most patients received a proton-pump inhibitor, and few patients underwent hematopoietic stem cell transplantation.

CONCLUSION: Overall, in Switzerland, a wide range of medications is prescribed for systemic sclerosis patients. This includes modern, targeted treatments for which randomised controlled clinical trial have been recently reported.

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Introduction

Systemic sclerosis is an autoimmune connective tissue disease characterised by increased deposition of extracellular matrix, resulting from fibroblast dysfunction, microvasculopathy, and autoimmunity [1–5]. The organ manifestations and clinical course of systemic sclerosis vary greatly, and this complicates its monitoring and treatment [4, 6].

Recommendations regarding its treatment have been published by both the European League Against Rheumatism (EULAR) and the European Scleroderma Trials and Research (EUSTAR) groups in 2009 and were then updated in 2017 [6, 7]. Furthermore, other national societies, such as the British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR), have also published recommendations for treating systemic sclerosis [8, 9]. Despite significant agreement between both guidelines, especially regarding organ manifestations, the BSR guidelines offer more suggestions regarding non-pharmacologic treatment; they also cover topics like calcinosis, musculoskeletal, and cardiac symptoms [8]. In addition, consensus guidance for SSc-ILD management has been published by European experts [10].

For systemic sclerosis-related skin fibrosis, the recommendations suggest that methotrexate may be considered for

early diffuse systemic sclerosis, given its effect on skin fibrosis [6, 8, 11]. However, the evidence behind these recommendations should be interpreted with some caution. A randomised controlled trial of methotrexate versus a placebo in early diffuse systemic sclerosis showed a trend in favour of methotrexate, but it did not indicate statistical significance [12]. Another randomised controlled trial with methotrexate versus a placebo was statistically significant for methotrexate in treating early skin fibrosis, but most patients in the methotrexate group had limited systemic sclerosis with less severe organ involvement; as such, an mRSS reduction could hardly be deemed as clinically relevant [11]. Furthermore, both trials had a relatively small sample size.

The EULAR recommends considering cyclophosphamide for treating progressive SSc-ILD, despite the medication's toxicity [6, 13, 14]. However, studies showed that once cyclophosphamide is discontinued, its beneficial effects decline [15]. Mycophenolate mofetil demonstrated improvement versus baseline similar to cyclophosphamide in a large randomised controlled trial for the following: Forced Vital Capacity (FVC), the transition dyspnea index (TDI), some but not all quantitative measures of lung fibrosis on high-resolution computed tomography, and the modified Rodnan skin score (mRSS) for skin fibrosis [16–19].

In the two trials, it was observed that randomised placebo-controlled trials with tocilizumab indicated a trend of improving skin fibrosis and had a strong effect on stabilizing interstitial lung disease [20–22]. There was also a non-significant, but consistent directionality of efficacy regarding skin and interstitial lung disease in the EUSTAR real-life cohort treated with tocilizumab [23]. The RECITAL trial revealed that rituximab was not superior to cyclophosphamide, but it did suggest comparable effects to cyclophosphamide when treating patients diagnosed with connective tissue disease with associated interstitial lung disease, including systemic sclerosis [24, 25]. Similarly, a recent single country, smaller double blind, placebo-controlled, randomised trial with rituximab showed a significant improvement of skin sclerosis and lung function in systemic sclerosis without major safety concerns [26].

In carefully selected patients with rapidly progressive systemic sclerosis and a risk of organ failure, hematopoietic stem cell transplantation should also be considered [6]. Studies showed substantial improvement in skin fibrosis and a general stability of internal organ involvement, which is estimated to extend at least three years and was associated with significantly improved quality of life [7, 8, 27–30]. Nevertheless, haematopoietic stem cell transplantation is still associated with high treatment-related mortality of around 10% [29, 30].

This study's aim was to analyse the therapeutic management of systemic sclerosis patients in the Swiss EUSTAR cohort in light of current recommendations, with a focus on advanced skin fibrosis and systemic sclerosis-related-interstitial lung disease.

Patients and methods

Study population and criteria

Systemic sclerosis patients from all six EUSTAR Swiss expert centres (Aarau, Basel, Bern, Geneva, Lausanne, and Zurich) were extracted from the multicentre, prospective EUSTAR database and included in this analysis (exported on 26.07.2019). Characteristics of the Swiss EUSTAR cohort have been reported recently [31]. All Swiss centres obtained ethics approval and all patients signed informed consent forms. The Cantonal Ethics Committee Zurich (BASEC Nr.2017-02102) approved the data analysis.

In the present study, only systemic sclerosis patients' visits between 2013 and 2019 were analysed, namely because the extended data on patients' treatments were collected from 2013 onwards in the EUSTAR database.

The European Scleroderma Trials and Research group (EUSTAR)is an international research network, which was launched in 2004, that seeks to raise the awareness, understanding, research, and management of systemic sclerosis throughout Europe and worldwide. The main research tool is a multicentre online registry with prospectively collected data. More than 100 clinical, laboratory, and demographic data are collected annually, with patients having signed informed consent forms first. Over 200 international centres have contributed since 2004. Patients had to fulfil the 2013 ACR/EULAR systemic sclerosis classification criteria at baseline [32].

Furthermore, eligible patients were sub-categorised according to the extent of their skin and interstitial lung disease at baseline. Regarding skin fibrosis, two different patient groups were formed. The first cohort was comprised of all patients with a modified Rodnan skin score (mRSS) >0, identifying those with skin fibrosis in general; the second was comprised of those with more advanced skin fibrosis, indicated by a mRSS of ≥7. This threshold was chosen because it reflects the lowest value classifiable as diffuse cutaneous systemic sclerosis [4, 33].

The presence of interstitial lung disease was determined by either chest X-Ray or high-resolution computed tomography, as listed in the EUSTAR database. The expert radiologist from the local centres, following the method described by either Goh et al or by local practice, assessed the extent of interstitial lung disease [34]. A patient was presumed to have more advanced interstitial lung disease if, in addition to showing interstitial lung disease on chest X-Ray or high-resolution computed tomography, one of the following criteria applied: interstitial lung disease extent of >20% on high-resolution computed tomography, dyspnea by New York Heart Association (NYHA) stage 3/4, or predicted FVC of <70%.

Treatment analysis

Potentially disease-modifying medications prescribed for each patient at the baseline visit were recorded. These medications, DMARDs, included immunomodulatory medications (hydroxychloroquine, intravenous immunoglobulins), conventional immunosuppressives (azathioprine, cyclosporin A, cyclophosphamide, D-penicillamine, leflunomide, methotrexate, mycophenolate mofetil, and glucocorticoids [e.g., prednisone, sul-

fasalazine]), and biological DMARDs (abatacept, rituximab, TNF-alpha antagonists, and tocilizumab). Prednisone was considered a DMARD in doses >10 mg/d [35].

In addition, haematopoietic stem cell transplantation lung transplantation, oxygen supplementation and proton-pump inhibitor usage were recorded, the latter because gastro-oesophageal reflux disease is hypothesised to initiate and progress interstitial lung disease [6, 8, 36, 37]. The use frequency of each treatment was compared with the above-mentioned sub-groups.

Statistical analysis

For this observational descriptive study, sample size calculation was not performed. All available data from Swiss EUSTAR centres were used for this analysis. All statistical analyses were performed using SPSS statistics version 25 software (IBM). Data were expressed as frequencies and percentages for categorical variables, or as a median and interquartile range (IQR) for continuous variables according to their distribution. Continuous variables were compared with the Mann–Whitney U test or t-test, and categorical variables with Chi-square test or Fisher's exact test, as applicable.

Results

Study population

Patient selection is summarised in figure 1.

Among 812 Swiss patients in the EUSTAR database, 590 were eligible and their demographic and clinical characteristics are listed in table 1. The population was predominantly female (79.8%) with a median age of 68.0 (57–77) years. The median disease duration was 6.0 (2–13) years, and most patients had been diagnosed with limited cutaneous systemic sclerosis (74%).

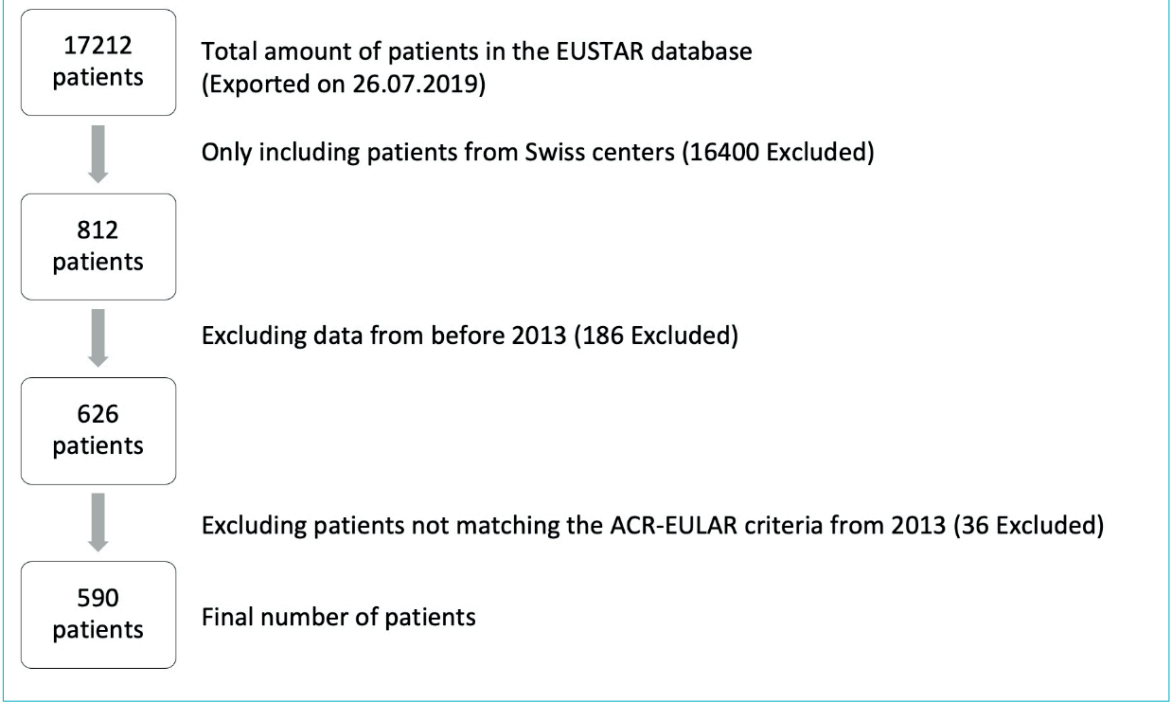
Table 2 presents the subclassification into more advanced skin fibrosis and interstitial lung disease. Of the 590 patients, 421 (71.4%) had an mRSS >0, of whom 195 (33.1%) had an mRSS ≥7. Regarding interstitial lung disease, the database included 198 (43.4%) patients with interstitial lung disease on either chest X-Ray or high-resolution computed tomography, of whom 106 (18%) had more advanced interstitial lung disease.

Treatment

All treatments with potentially disease modifying agents per patient are depicted in figure 2. Regarding non-biologic DMARDs, the most frequently prescribed medication was methotrexate, in 97 (16.4%) patients, followed by hydroxy-/chloroquine, in 67 (11.4%), and mycophenolate mofetil in 55 (9.3%) patients. Among biologic DMARDs, rituximab and tocilizumab were administered most frequently, each in 23 (3.9%) patients. Additionally, 124 (21%) patients were treated with low-dose prednisone (≤10 mg/d). Seven (1.2%) underwent haematopoietic stem cell transplantation and two (0.3%) lung transplantation. Furthermore, 378 (64.1%) received proton-pump inhibitors and 20 (3.4%) required oxygen supplementation.

Individual treatments differ based on the extent of skin and interstitial lung disease, in comparison to the entire cohort, are illustrated in figure 3. Cyclophosphamide was used more frequently among patients with more advanced skin fibrosis and patients with interstitial lung disease, including those with more advanced interstitial lung disease.

Figure 1: Patient selection overview. Of the 17,212 patients in the EUSTAR database at the time of export, 812 were from Swiss EUSTAR centres (Aarau, Basel, Bern, Geneva, Lausanne and Zurich). Because recording extended therapy data began in 2013, only data collected after 2013 were considered for analysis. Finally, patients not meeting the 2013 ACR/EULAR classification criteria were excluded. ACR: American College of Rheumatology; EULAR: European league Against Rheumatism; EUSTAR: European Scleroderma Trial and Research Group.



There was a higher prescription rate of methotrexate for patients with more advanced skin fibrosis. Mycophenolate mofetil's prescription rate was higher among patients with interstitial lung disease and even greater for those with more advanced interstitial lung disease. The data also indicate a higher prescription rate for patients with more advanced skin fibrosis [38]. Rituximab was more a widely used among patients with more advanced skin fibrosis or interstitial lung disease. Furthermore, tocilizumab was used more frequently among patients with more extended skin fibrosis and with advanced interstitial lung disease.

Of 421 patients with skin fibrosis (mRSS >0), 49 either had taken no medication at all or had only proton-pump inhibitors, while 148/372 (39.8%) received treatment with-methotrexate, mycophenolate mofetil, or rituximab. For the 198 patients with interstitial lung disease, as determined by X-ray or high-resolution computed tomography, 21 were without treatment or had only proton-pump in-

Table 1:
Baseline demographic and clinical characteristics of the study cohort (n = 590). Definitions of items and organ manifestation align with EUSTAR [7]. Data of listed variables are presented as number (n)/total cases with available data (N) (%). Disease duration was calculated as the difference between the dates of the baseline visit and the first non-Raynaud's symptom of the disease, as reported by the patient. Pulmonary hypertension was judged on right heart catheterisation (RHC). Active disease was defined as a score >3, determined by calculating European Scleroderma Study Group disease activity indices for systemic sclerosis, as proposed by Valentini [56].

Demographics		**Median (IQR)**	**Frequency (n/N) (%)**
Age, years (n = 590)		68.0 (57–77)	
Disease duration, years (n = 538)		6.0 (2–13)	
Female			471/590 (79.8%)
Male			119/590 (20.2%)
Limited cutaneous systemic sclerosis			328/443 (74.0%)
Diffuse cutaneous systemic sclerosis			115/443 (26.0%)
Skin/vascular	mRSS (n = 590)	3 (0–9)	
	Raynaud's Phenomenon		563/586 (96.1%)
	Digital ulcers		189/516 (36.6%)
	Active digital ulcers		66/516 (12.8%)
	Pitting scars		200/498 (40.1%)
	Scleredema		297/508 (58.5%)
	Telangiectasia		327/516 (63.4%)
	Abnormal nailfold capillaroscopy		411/479 (85.8%)
Musculoskeletal	Tendon friction rubs		42/565 (7.4%)
	Joint synovitis		87/580 (15.0%)
	Joint contractures		170/573 (29.7%)
	Muscle weakness		71/578 (12.3%)
Gastrointestinal	Esophageal symptoms		315/582 (54.1%)
	Stomach symptoms		160/569 (28.1%)
	Intestinal symptoms		180/574 (31.4%)
Cardiopulmonary	Dyspnea NYHA stage 1/2		486/543 (89.5%)
	Dyspnea NYHA stage 3/4		57/543 (10.5%)
	Diastolic dysfunction		150/481 (31.2%)
	Pericardial effusion		19/500 (3.8%)
	Conduction blocks		55/425 (12.9%)
	LVEF <45%		4/521 (0.8%)
	PAH by RHC		11/244 (4.5%)
	Interstitial lung disease on high-resolution computed tomography		198/456 (43.4%)
	Lung function		
	FVC, % predicted	98 (83–111)	
	FEV1, % predicted	94 (82–106)	
	TLC, % predicted	100 (85–112)	
	DLCO, % predicted	75 (61–88)	
	FVC <70% predicted		54/529 (10.2%)
	DLCO <70% predicted		199/513 (38.8%)
Kidney	Renal crisis		12/584 (2.1%)
Laboratory parameters	ANA positive		525/537 (97.8%)
	ACA positive		230/490 (46.9%)
	Anti-Scl-70 positive		140/507 (27.6%)
	Anti-RNA-polymerase III positive		51/433 (11.8%)
	Creatinine kinase elevation		61/536 (11.4%)
	Proteinuria		55/542 (10.1%)
	ESR >25 mm/h		114/526 (21.7%)
	CRP elevation		113/558 (20.3%)
	Active disease (VAI >3) (56)		166/363 (45.7%)

ACA: anti-centromere antibody; ANA: antinuclear antibody; Anti-Scl-70: anti-topoisomerase antibody; CRP: C-reactive protein; DLCO: diffusing capacity for carbon monoxide; ESR: erythrocyte sedimentation rate; FEV1: forced expiratory volume in 1 sec; FVC: forced vital capacity; LVEF: left ventricular ejection fraction; mRSS: modified Rodnan skin score; NYHA: New York Heart Association; TLC: total lung capacity; VAI: Valentini activity index.

hibitors; 80/177(45.2%) received therapy with cyclophosphamide, mycophenolate mofetil, tocilizumab, or rituximab (figure 4).

Low-dose prednisone (≤10 mg/d) was used and often and, even more frequently so, among patients with any type of interstitial lung disease. This was particularly the case for patients with advanced interstitial lung disease patients. Finally, the prescription rates for both proton-pump inhibitors and oxygen supplementation were higher in the

Table 2:
Fibrotic manifestations of systemic sclerosis patients in Switzerland (total Swiss cohort n = 590). Classification according to severity of skin and interstitial lung disease. Data of listed variables are presented as number (n)/total cases with available data (N) (%). Skin fibrosis was defined as mRSS >0, and more advanced skin fibrosis as mRSS ≥7. The presence of interstitial lung disease was determined by either chest X-Ray or high-resolution computed tomography. Advanced interstitial lung disease was defined by the parameters shown above.

		Frequency (n/N)	(%)
Skin	mRSS >0	421/590	(71.4)
	mRSS ≥7	195/590	(33.1)
Lung	Interstitial lung disease on CXR or high-resolution computed tomography	198/456	(43.4)
	Advanced interstitial lung disease	106/590	(18.0)
	High-resolution computed tomography, fibrosis >20%	20/91	(21.9)
	Dyspnea NYHA stage 3/4	57/543	(10.5)
	FVC predicted <70%	54/529	(10.2)

CXR: Chest X-Ray; FVC: Forced vital capacity; mRSS: modified Rodnan skin score; NYHA: New York Heart Association.

Figure 2: Treatment with potentially disease modifying agents in Swiss systemic sclerosis patients, illustrated alphabetically as drugs per patient at baseline visit. Numbers and percentage refer to Switzerland's total patient population. Exact numbers are listed in table S1 in the appendix.

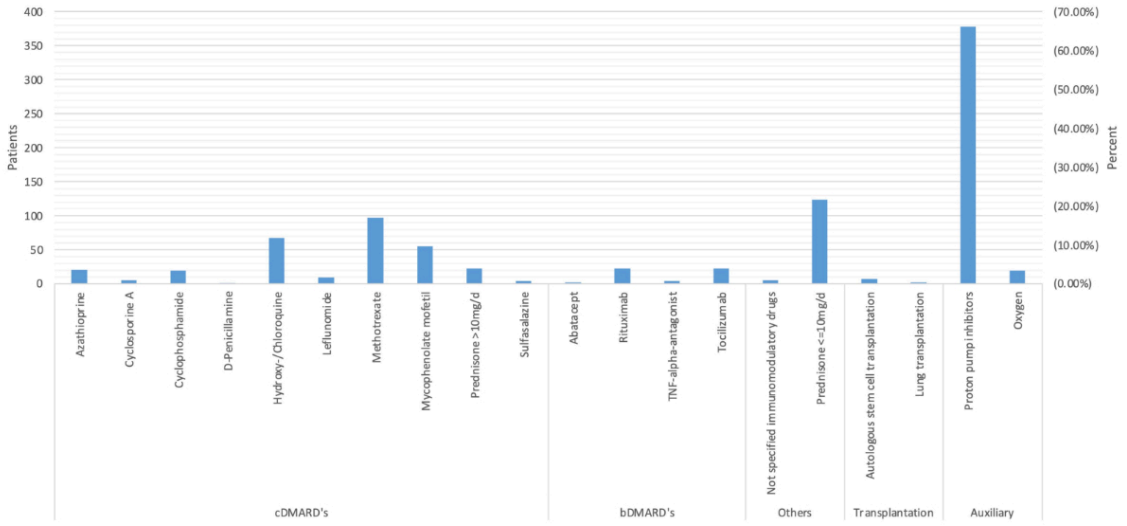
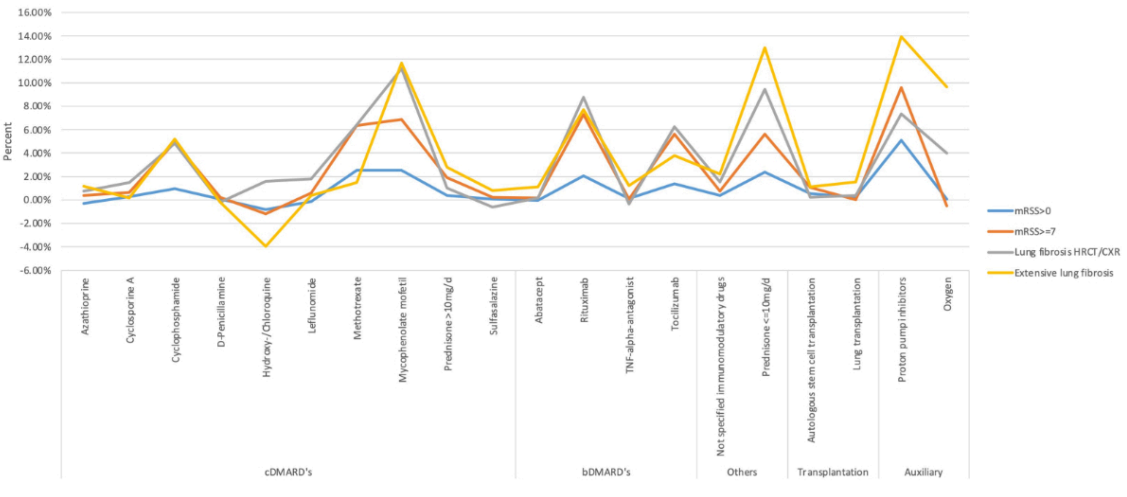


Figure 3: Treatment differences among SSc patients according to severity of skin fibrosis and interstitial lung disease, compared to the average baseline treatments of the study's cohort. CRX: Chest X-Ray; HRCT: High-resolution computed tomography; mRSS: modified Rodnan skin score; TNF: Tumor necrosis factor.



group of patients with advanced interstitial lung disease compared to the other cohorts.

Only seven systemic sclerosis patients were eligible for haematopoietic stem cell transplantation. They were younger than the average population, with a median age of 57.0 (50.5–62.5), yet the median disease duration had already been 5.0 (3–10) years. Most patients (66.7%) were diagnosed with diffuse systemic sclerosis, had reported more vascular and cardiopulmonary problems, and had worse lung function parameters; 40% had an active disease score (VAI >3). More detailed information is listed in table S2 in the appendix.

A total of 315 patients had recorded gastrooesophageal reflux disease and 251 (79.7 %) were treated with proton-pump inhibitors (figure 4).

Discussion

Overall, a wide range of medications is prescribed for systemic sclerosis patients in Switzerland, nevertheless with consistent adherence to guidelines. Overall, 81 patients (13.7 %) did not receive any medication and 39 (6.6 %) had only proton-pump. It must be account for that treatment decisions are derived by means of a complex process, with many influencing factors (e.g., contraindications, patient preferences, financial considerations, etc.), which cannot be analysed from registry data.

In detail, cyclophosphamide was used more frequently among patients with advanced interstitial lung disease or with interstitial lung disease in general than among the average patient population; this aligns with EULAR recommendations and other guidelines [6, 8]. In addition, 27.2% of this group fulfils the criteria for advanced interstitial lung disease. Furthermore, skin fibrosis is associated with an increased risk of internal organ manifestations [16].

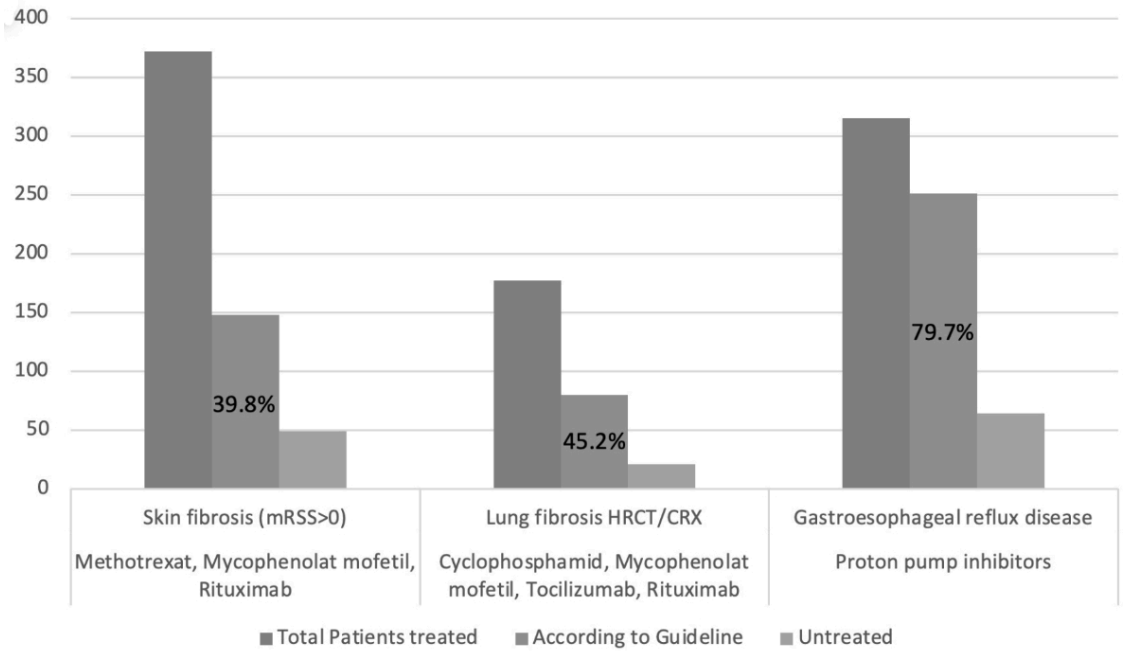
We also ascertained that methotrexate was used more commonly among patients with advanced skin fibrosis [6, 8].

While not yet recommended by EUSTAR, newer studies and BSR and BHPR guidelines recommend mycophenloate mofetil to be used frequently among those in our study cohort for interstitial lung disease, as well as for advanced skin fibrosis among Swiss systemic sclerosis patients [8, 16, 17, 39].

In Switzerland, there is a tendency to use rituximab for treating systemic sclerosis patients with more advanced skin and lung fibrosis. Although it remains a subject of current research, observational studies and smaller randomised controlled clinical trials indicate that anti-CD20 mediated B cell depletion positively effects both skin and lung involvement [35, 40–45]. Recent data from the RECITAL trial showed similar effects of rituximab compared to cyclophosphamide on FVC in patients with connective-tissue disease associated interstitial lung disease, including systemic sclerosis [46]. This explains the wide use of rituximab despite it not yet being recommended by EUSTAR and being only vaguely mentioned in BSR and BHPR guidelines [6, 8]

Tocilizumab use among patients with interstitial lung diseace can be generally explained by the findings of the faSScinate trial; the outcomes indicated a beneficial effect on stabilizing lung function regarding FVC [20, 47]. This is consistent with the more recent randomised placebo-controlled phase III focuSSced trial of tocilizumab in systemic sclerosis, which led to the Federal Drug Administration (FDA) of the United States approving tocilizumab for treating SSc-ILD [48]. These studies also showed a nu-

Figure 4: Percentages of patients treated according to the EULAR/BSR Guidelines. For systemic sclerosis-related skin fibrosis, the recommendation is either methotrexate, mycophenolate mofetil, or rituximab; for systemic sclerosis-related lung fibrosis, the recommendation is cyclophosphamide, mycophenolate mofetil, tocilizumab, or rituximab. Patients with gastrooesophageal reflux disease, for whom proton pump inhibitors have been recommended for treatment, have also been listed. CRX: Chest X-Ray; HRCT: High-resolution computed tomography; mRSS: modified Rodnan skin score; BSR: British Society of Rheumatology.



meric, but not statistically significant, reduction in mRSS changes at week 24. In the phase III trial, in which systemic sclerosis patients received subcutaneous tocilizumab for 48 weeks, there was again a numeric, but not significant, difference between tocilizumab and a placebo in the primary endpoint mRSS at week 48 [21, 47, 48].

Glucocorticoids, such as prednisone, are frequently used for treating systemic sclerosis despite their efficacy being supported by limited evidence [49, 50]. Often, there is no correlation between the prescription pattern and the clinical signs of inflammation [50]. In Switzerland, this pattern is also reflected by prescriptions given to systemic sclerosis patients. As seen in figure 2, especially daily, low-prednisone doses (≤10 mg/d) are frequently prescribed for patients with systemic sclerosis-related interstitial lung disease and advanced skin fibrosis. There is also a tendency to prescribe doses higher than 10 mg per day among the advanced interstitial lung disease cohort. Higher prednisone doses are usually avoided due to a risk of scleroderma renal crisis.

Regarding haematopoietic stem cell transplantation, there was a slight tendency to offer this treatment for patients with more advanced interstitial lung disease. Among the entire Swiss patient population, there were only seven who underwent haematopoietic stem cell transplantation at the baseline visit, or short afterwards. EUSTAR recommends haematopoietic stem cell transplantation only in carefully selected patients with rapidly progressive systemic sclerosis; this accounts for the high risk of treatment-related morbidity and mortality [6]. Following EUSTAR recommendations, in Switzerland, systemic sclerosis patients were younger, the majority of whom had diffuse systemic sclerosis with worse lung parameters; 40% had active disease.

Finally, proton-pump inhibitors were prescribed most commonly of the analysed medications among our study population. Accordingly, both EUSTAR and BSR/BHPR guidelines recommend using proton-pump inhibitors in cases of systemic sclerosis-related gastro-oesophageal reflux disease (GERD), despite there being a dearth of specific randomised controlled trials [6, 8]. Most of our study population (66.4%) had recorded oesophageal symptoms. Another reason, especially for the additional use of proton-pump inhibitors among patients with advanced interstitial lung disease, why proton-pump inhibitors are frequently used among patients with interstitial lung disease could be because of a suspected causal correlation between interstitial lung disease and GERD [36, 37, 51].

Regarding the limitations of our study, these are inevitable due to missing values based on the observational, multicentre nature of the registry. This study captured neither non-pharmacologic treatments, nor alternative medicines. At the time of exporting data from the EUSTAR database, nintedanib (a drug more recently approved for SSc-ILD treatment, both in Switzerland and worldwide) was not recorded in the EUSTAR database [52]. Thus, such treatments could not be analysed using the current dataset. Data were drawn in 2019, and the treatment landscape may have changed since then. Notably, we have no indications that general adherence to guidelines and recommendations has changed since then; as such, we have strong reason to believe that this study's general conclusions remain valid. Finally, we did not have longitudinal data available to assess treatment duration.

In conclusion, in Switzerland, systemic sclerosis patients are being prescribed a wide range of medications. This includes modern, targeted treatments for which randomised controlled clinical trial have been recently reported. Future research could therefore focus on treatment for other manifestations of systemic sclerosis, such digital vasculopathy, pulmonary arterial hypertension, or systemic sclerosis-related gastrointestinal disease. New guidelines and recommendations, which are expected to be published soon, will have increasing complexity due to the high number of new medications citing strong evidence for efficacy. This will challenge their implementation in clinical practice. It is to be noted that the Swiss EUSTAR database has proven useful in monitoring this process.

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We thank all patients for allowing us to collect their data and for providing informed consent. Primary data are available upon reasonable request, submitted to the corresponding author, following EUSTAR rules.We thank all patients for allowing us to collect their data and for providing informed consent. Primary data are available upon reasonable request, submitted to the corresponding author, following EUSTAR rules.

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Potential competing interests

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Appendix

Table S1:
Numbers of systemic sclerosis patients treated with potentially disease modifying agents in the Swiss EUSTAR cohort (total Swiss cohort n = 590). The exact numbers and percentage values referred to in figure 2 are listed below.

		Number (n/N; [%])
Disease modifying anti-rheumatic drugs	Azathioprine	21/590 (3.6%)
	Cyclosporine A	5/590 (0.9%)
	Cyclophosphamide	20/590 /590 (3.4%)
	D-Penicillamine	1/590 (0.2%)
	Hydroxy-/Chloroquine	67/590 (11.4%)
	Leflunomide	9/590 (1.5%)
	Methotrexate	97/590 (16.4%)
	Mycophenolate mofetil	55/590 (9.3%)
	Prednisone (>10 mg/d)	23/590 (3.9%)
	Sulfasalazine	4/590 (0.7%)
B Disease modifying anti-rheumatic drugs	Abatacept	2/590 (0.3%)
	Rituximab	23/590 (3.9%)
	TNF-alpha-antagonists	4/590 (0.7%)
	Tocilizumab	23/590 (3.9%)
Other Immunosuppressants	Prednisone (≤10 mg/d)	124/590 (21.1%)
	Not specified immunomodulatory drugs	5/590 (0.9%)
Transplantations	Autologous stem cell transplantation	7/590 (1.2%)
	Lung transplantation	2/590 (0.3%)
Auxiliary drugs	Oxygen supplementation	20/590 (3.4%)
	Proton pump inhibitor	378/590 (64.1%)

TNF: Tumor necrosis factor.

Table S2:
A comparison of demographic and clinical characteristics between the total number of patients in the Swiss systemic sclerosis cohort and Swiss patients with recorded haematopoietic stem cell transplantation at baseline visit (seven in total). Definitions of items and organ manifestation align with EUSTAR. Data are presented as number (n)/total valid cases (N) (%). Disease duration was calculated as the difference between the dates of the baseline visit and the first non-Raynaud's symptom of the disease, per patient reports. Pulmonary hypertension was judged based on RHC. Active disease was defined as a score >3, which was derived by calculating European Scleroderma Study Group disease activity indices for systemic sclerosis, as proposed by Valentini [48].

	Total Swiss cohort (n = 590%)			**Haematopoietic stem cell transplantation (n = 7%)**	
		Median (IQR%)	**Frequency (n/N; %)**	**Median (IQR%)**	**Frequency (n/N; %)**
Demographics	Age, years	68.0 (57–77)		57.0 (50.5–62.5)	
	Disease duration, years	6.0 (2–13)		5.0 (3–10)	
	Female		471/590 (79.8%)		5/7 (71.4%)
	Male		119/590 (20.2%)		2/7 (28.6%)
	Limited cutaneous systemic sclerosis		328/443 (74.0%)		2/6 (33.3%)
	Diffuse cutaneous systemic sclerosis		115/443 (26.0%)		4/6 (66.7%)
Skin/Vascular	mRSS	3 (0–9)		2 (1–8)	
	Raynaud's Phenomenon		563/586 (96.1%)		6/6 (100.0%)
	Digital ulcers		189/516 (36.6%)		5/6 (83.3%)
	Active digital ulcers		66/516 (12.8%)		2/6 (33.3%)
	Pitting scars		200/498 (40.1%)		5/5 (100.0%)
	Scleredema		297/508 (58.5%)		1/5 (20.0%)
	Telangiectasia		327/516 (63.4%)		4/5 (80.0%)
	Abnormal nailfold capillaroscopy		411/479 (85.8%)		2/2 (100.0%)
Musculoskeletal	Tendon friction rubs		42/565 (7.4%)		None (0.0%)
	Joint synovitis		87/580 (15.0%)		1/6 (16.7%)
	Joint contractures		170/573 (29.7%)		None (0.0%)
	Muscle weakness		71/578 (12.3%)		None (0.0%)
Gastrointestinal	Esophageal symptoms		315/582 (54.1%)		5/7 (71.4%)
	Stomach symptoms		160/569 (28.1%)		2/6 (33.0%)
	Intestinal symptoms		180/574 (31.4%)		1/6 (16.7%)
Cardiopulmonary	Dyspnea NYHA stage 1/2		486/543 (89.5%)		4/6 (66.6%)
	Dyspnea NYHA stage 3/4		57/543 (10.5%)		2/6 (33.4%)
	Diastolic dysfunction		150/481 (31.2%)		3/4 (75.0%)
	Pericardial effusion		19/500 (3.8%)		1/4 (25.0%)
	Conduction blocks		55/425 (12.9%)		None (0.0%)
	LVEF<45%		4/521 (0.8%)		None (0.0%)
	PAH by RHC		11/244 (4.5%)		2/5 (40.0%)
	Interstitial lung disease on high-resolution computed tomography		198/456 (43.4%)		2/6 (66.7%)
	Lung function				
	FVC, % predicted	98 (83–111%)		73.5 (53.3–93.5)	
	FEV1, % predicted	94 (82–106)		77 (60–96.5)	
	TLC, % predicted	100 (85–112)		81 (63–93.5)	
	DLCO, % predicted	75 (61–88)		55.5 (50.8–61)	
	FVC<70% predicted		54/529 (10.2%)		3/7 (42.9%)
	DLCO<70% predicted		199/513 (38.8%)		4/5 (80.0%)
Kidney	Renal crisis		12/584 (2.1%)		None (0.0%)
Laboratory parameters	ANA positive		525/537 (97.8%)		5/6 (83.3%)
	ACA positive		230/490 (46.9%)		1/6 (16.7%)
	Anti–Scl–70 positive		140/507 (27.6%)		3/6 (50.0%)
	Anti–RNA–polymerase III positive		51/433 (11.8%)		None (0.0%)
	Creatinine kinase elevation		61/536 (11.4%)		1/6 (16.7%)
	Proteinuria		55/542 (10.1%)		4/6 (66.7%)
	ESR >25 mm/h		114/526 (21.7%)		3/6 (50.0%)
	CRP elevation		113/558 (20.3%)		2/7 (28.6%)
	Active disease (VAI >3%)[48]		166/363 (45.7%)		2/5 (40.0%)

ACA: anti-centromere antibody; ANA: antinuclear antibody; Anti-Scl-70: anti-topoisomerase antibody; CRP: C reactive protein; DLCO: diffusing capacity for carbon monoxide; ESR: erythrocyte sedimentation rate; FEV1: forced expiratory volume in 1 sec; FVC: forced vital capacity; LVEF: left ventricular ejection fraction; mRSS: modified Rodnan skin score; NYHA: New York Heart Association; TLC: total lung capacity; VAI: Valentini activity index.