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Open questions on the management of targeted therapies for the treatment of systemic sclerosis-interstitial lung disease: results of a EUSTAR survey based on a systemic literature review

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***Abstract*:**

Background: The results of randomized controlled (RCT) and retrospective studies have expanded the armamentarium of drugs for systemic sclerosis (SSc) – interstitial lung disease (ILD) treatment. The correct positioning of these drugs is not yet clarified.

Objectives: Systemic literature review (SLR) on rituximab (RTX), tocilizumab (TCZ), nintedanib and abatacept (ABT) for the treatment of SSc-ILD. The results of the SLR were used to create a dedicated survey.

Design: The study was performed as a systematic review.

Data sources and methods: the SLR was performed using the following terms: "(systemic sclerosis OR scleroderma) AND (interstitial lung disease OR lung fibrosis OR pulmonary fibrosis) AND (rituximab OR tocilizumab OR abatacept OR nintedanib)". The results of the SLR were integrated in a survey including 8 domains. These were sent to all EUSTAR members and to the participants of the 2020 Scleroderma World Congress.

Results: 41 studies (34 on RTX, 5 on TCZ, 2 on ABT, and 1 on nintedanib) were identified. RCTs supported the use of TCZ and nintedanib, while retrospective studies supported the use of RTX for SSc-ILD. No clear data were obtained about ABT. The survey showed that RTX is the most available option (96%) whereas the most frequent reason for targeted therapy introduction is lung progression while on csDMARDs (86% RTX, 59% TCZ and 63% nintedanib). Combination therapy was the most frequently mentioned therapeutic scheme for nintedanib (75%) and RTX (63%). Physicians' perception of safety was similar for all drugs, while drug efficacy was the same for RTX and nintedanib, followed by TCZ (4.8 ± 2). The most frequently raised concerns pertained to efficacy, safety and combination regimens.

Conclusion: Our SLR supports the use of RTX, TCZ and nintedanib for SSc-ILD patients and underlines the need for more data about upfront combination versus monotherapy. It also highlighted the need to identify predictors supporting drug choice according to both pulmonary and extra-pulmonary manifestations.

Keywords: abatacept, combination therapy, efficacy, interstitial lung disease, nintedanib, rituximab, safety, systemic sclerosis, tocilizumab

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Introduction

Systemic sclerosis (SSc) is a complex autoimmune condition, and its pathogenesis is characterized by a variable combination of vasculopathic, inflammatory, and fibrotic changes.[1] Among organ complications, the development of interstitial lung disease (ILD)[2] carries important implications for the patients' morbidity,[3] mortality,[4]

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and quality of life.[5] Recently, an European consensus agreed on the application of chest high-resolution computed tomography (HRCT) as the gold standard diagnostic tool for SSc-ILD.[6] In addition, HRCT is also used to follow-up SSc-ILD patients, allowing the quantification of changes in ILD patterns and disease extent.[7] In order to obtain functional information, other tools such as pulmonary function tests (PFTs), 6-min walking test (6MWT), and patient-reported outcomes questionnaires are recommended as a monitoring algorithm,[8] also aiming at detecting progressive patients.[9]

The most recent update on the recommendations for the treatment of SSc-ILD included cyclophosphamide and hematopoietic stem cell transplantation, as both showed positive results in stabilizing lung function in the context of randomized clinical trials (RCTs).[10] Although not included in the recommendation, there is also evidence for stabilizing effect of mycophenolate mofetil (MMF), which was compared to cyclophosphamide still in a RCT.[11] Since then, an increasing amount of evidence was progressively generated from other RCTs and cohort studies[12] and tocilizumab (TCZ) has been approved as a treatment for SSc-ILD by the Food and Drug Administration (FDA).[13] Among the RCTs, the SENSCIS study[14] has led to the approval of nintedanib, a tyrosine kinase inhibitor, for the treatment of SSc-ILD. In addition to nintedanib and TCZ, other biological disease-modifying antirheumatic drugs (DMARDs; including rituximab[15,16] and abatacept)[17,18] have been discussed for the treatment of SSc-ILD.

Therefore, our aims were to (1) summarize the current data on the 'SSc-ILD targeted treatments' performing a systematic literature review (SLR) and to (2) collect information from SSc-ILD caring physicians on availability, knowledge and confidence with efficacy and treatment profiles, drivers of prescription, current practice, and open questions regarding the same molecules in the light of the SLR results.

Materials and methods

An SLR was performed on the Web of Science Core Collection, Embase *via* Embase.com, Medline *via* PubMed, and Cochrane Reviews. The following search terms were used: '(systemic sclerosis OR scleroderma OR sclerosis) AND (interstitial lung disease OR lung fibrosis OR pulmonary fibrosis) AND (rituximab OR tocilizumab OR abatacept OR nintedanib)', for papers published from inception to 31 March 2020. The reporting of this study conforms to the PRISMA statement (the PRISMA checklist is available as supplemental material)[19]. The review was not registered.

Studies in English, which specifically focused on the treatment of SSc-ILD with the above-mentioned four treatments, including at least five patients aged over 16 years as part of interventional RCTs, observational retrospective or prospective cohorts, registries, or case series, were identified. We excluded manuscripts on pre-clinical, *in vitro*, and animal model studies, with patients affected by overlap syndromes as defined by international criteria, not including SSc patients or in which SSc patients' data could not be extrapolated, not presenting outcome data on functional, radiological, or mortality outcome, not published as full paper or for which the full texts were not available. Reviews were excluded, but their references list was checked to include manuscripts eventually not captured by the search across the four databases.

PEO (Population Exposed Outcome) questions on specific Population (adult SSc patients), Exposure (any of the molecules listed above), and Outcome (mortality, change in radiological or functional findings) were formulated.

All the identified manuscripts were assessed according to the inclusion and exclusion criteria, through two rounds of evaluation (title and abstract, then full-text evaluations) by two pairs of assessors (C.C. and E.Z., G.D.L., and M.G.L.). A third evaluator (C.B.) was consulted in case of disagreement and evaluated title, abstract, and full text of the manuscript.

Data on study nature, inclusion criteria, number of patients, age, definition of ILD, and number of patients with ILD were collected during full-text evaluation round. Data on treatment (target molecule, concomitant therapy with csDMARD), functional outcomes [forced vital capacity (FVC)%, total lung capacity (TLC)%, diffusion capacity for carbon monoxide (DLCO)% or their changes between timepoints], radiological outcomes (patterns and radiological ILD extent), safety (adverse events, infections, treatment interruption, need for escape therapy), and survival (mortality rates) at baseline and 3 months/12 weeks, 6 months/24 weeks, 12 months/48–52 weeks, 24 months/96 weeks, or

last available follow-up were collected. Level of evidence was assessed according to the Oxford scale.

A dedicated survey was created including eight domains: general information, drug availability (specifically the possibility of prescribing the targeted therapy for patients with SSc), safety (both global and lung-specific), efficacy, timing of treatment initiation, monotherapy or combination, drivers of drug choice and of target population (see Supplementary File 1). Perceived safety, efficacy, and confidence were investigated with a 0–10 scale, with increasing values representing more positive ratings.

The extracted data were analyzed and presented in terms of prevalence (percentage) for categorical variables and mean (standard deviation) or median (interquartile range) for continuous variables according to distribution. The quantitative data were analyzed with SPSS version 20.0. The answers to the open questions were imported into the software Dedoose to undergo qualitative analysis: answers were coded manually by a single researcher (C.B.) using the themes discussed and agreed between the authors. The generated thematic codes were counted and used as a basis to create unmet needs/future research questions.

Results

Systematic literature review

The databases search identified 917 manuscripts, out of which 609 duplicated were removed. Among 308 abstracts selected, 234 were excluded, mostly as not including SSc patients. Finally, 74 full texts were evaluated, and 41 of them were selected for full data extraction. Of these, one paper was duplicated in the results as its two cohorts of patients were treated with either TCZ or abatacept (ABT),[19] whereas two papers were merged as one of them included only longer follow-up data on the same cohort of patients.[20,21] Ultimately, our SLR included 25 cohort studies, 7 case–control studies, 5 randomized controlled trials, 3 case series, and 1 cross-sectional study (see Figure 1). ACR/EULAR 2013 classification criteria were used in 12 papers, while 10 papers considered ARA 1987 classification criteria, and in 2 papers both ACR/EULAR 2013 criteria were used; SSc criteria were not specified in 17 papers. The median number of patients per study was 18 (10–37), with a mean age ranging from 35 to 61 years and a median percentage of female patients per study of 81.5% (73–89%). The median percentage of ILD patients included per study was 100% (63–100%). The mean age of ILD patients ranged from 35 to 59 years, with a median percentage of female ILD patients of 83% (76–92%) and the median percentage of limited cutaneous SSc (lcSSc) patients included per study of 24% (0–46%). In 17 studies (40.5%), a control group was included. A total of 34 studies (81%) investigated rituximab (RTX), 5 studies (12%) TCZ, 2 studies (5%) ABT, and 1 study (2%) nintedanib. The results of our SLR are summarized in Table 1.

Rituximab. Among the 34 studies investigating the role of RTX in SSc,[15,19–52] a total of 1001 patients (691 SSc-ILD patients) were evaluated: median number of 18 patients per study (11–30). The overall level of evidence for RTX in SSc-ILD patients is low as most of the studies were classified as level 3b and level 4 according to the Oxford scale, only the RCT[45] was classified as level 2b. Characteristics of the studies are summarized in Table 1.

Inclusion criteria were presence of ILD (71%), early disease (21%), dcSSc (18%), and anti-topoisomerase I (ATA) positivity (1%). Exclusion criteria were specified in 13 studies and were mostly concomitant infectious diseases (54%), cancer (46%), and heart failure (38%). The concomitant use of MMF therapy was reported in 59 studies, whereas in 20 studies patients were also treated with other concomitant immunosuppressive therapies. Four different RTX treatment regimens were described. A control group was present in 14 studies (41%) which included standard of care medications,[19,29,31–33,39,42,47] cyclophosphamide,[20,38,48,49] and placebo.[45] In one study, the control group included the same group of patients before RTX therapy.[30] Baseline and follow-up data are summarized in Table 2.

The 3-month follow-up was available in four studies (12%).[19,24,33,38] A statistically significant improvement of the predicted delta FVC was observed in a single study,[38] whereas a statistically significant change of the median predicted DLCO was reported in only two studies[24,38] (a decrease and an improvement in delta predicted DLCO of 8.5%, respectively).

The 6-month follow-up was available in 14 studies (42%).[22–24,27,30,32,36,38–41,43,46,48] In seven studies,[22,30,32,36,38,46,49] a statistically significant

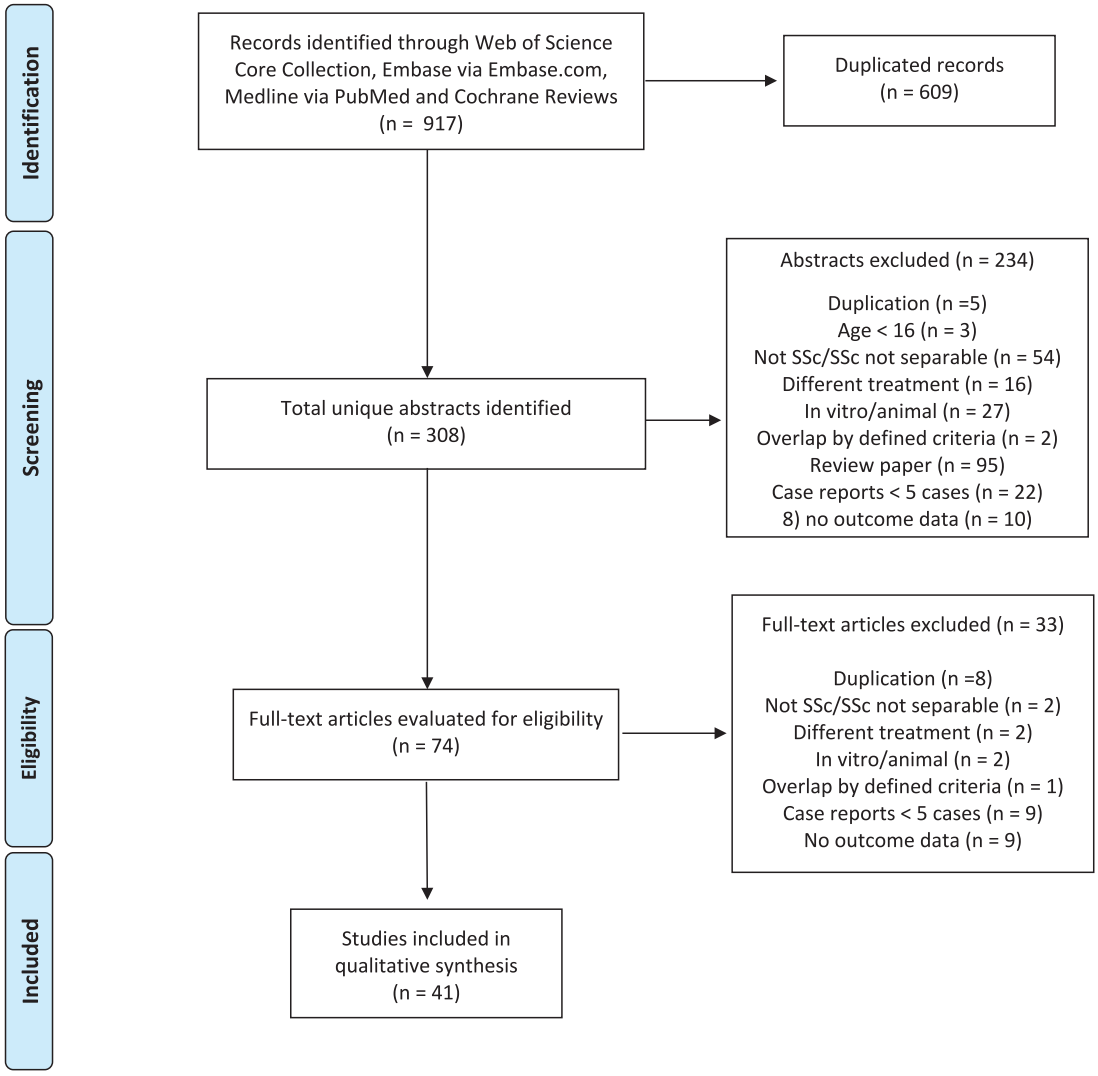

Figure 1. PRISMA flow diagram of the systematic literature review.

improvement of the predicted FVC was reported, as compared to baseline ($n=3$) and control groups ($n=1$) and to both baseline and controls ($n=1$). A 6.6% increase of the mean predicted delta FVC compared to both baseline and controls was reported in one study, whereas a 1.5% decrease compared to controls was observed in another study.

The 12-month follow-up was available in 20 studies (59%).[15,20–26,31,36,38–40,42–46,51,52] In 11 studies,[15,21,22,31,36,38,40,42,43,46,51] a statistically significant change of the mean predicted FVC was reported, as compared to baseline ($n=9$), controls ($n=1$), and both baseline and controls ($n=1$). Seven studies[15,22,23,38,40,42,46] (20.6%) reported a statistically significant improvement of the predicted DLCO; as compared to baseline ($n=6$), and compared to both baseline and controls ($n=1$), and compared to controls ($n=1$).

The 24-month follow-up was available in nine studies (26%).[20,21,24,26,38–40,43–45] In two studies[39,40] (22%), a statistically significant improvement of the mean predicted FVC was reported, as compared to baseline and to controls ($n=1$), or only to baseline ($n=1$).[10] Two studies (22%) reported a statistically significant improvement of the predicted DLCO.[39,40]

The latest follow-up of RTX studies ranged from 3 to 7 years in six studies (17%). In five studies[25,28,29,31,37] (14.7%), a statistically significant improvement of the mean predicted FVC was

Table 1. Characteristics of studies included in the systemic literature review investigating rituximab, tocilizumab, abatacept, and nintedanib in SSc-ILD patients.

	Rituximab	Tocilizumab	Abatacept	Nintedanib
Number of studies	34	5	2	1
Number of studies with control group	14 (41%)	3 (60%)	0	1
Number of RCTs	1 (3%)	3 (60%)	0	1 (100%)
Number of patients	1001	232	34	288
Number of ILD patients	691	41	21	288
Age of patients (range of median age, years)	35–59	51–57	61 and 55	Mean 54 ± 12
Age of ILD patients (range of median age)	35–59[a]	57[b]	–	Mean 54 ± 12
Female patients, % (range)	82 (71–89)	83.5 (79.5–90)	93 and 71	75
ILD female patients, % (range)	83 (76–91)	100[b]	–	75
Number of control patients	9825	181	0	288
Limited SSc (% median, range)	13 (0–42)	0–47[c]	67 and 57	48
Disease duration, years (range)	0.6–11.4[d]	0.7–1.5[e]	7 and 13	3.4 (0.3–7.1)[f]
Definition of ILD (number of studies)	24 (72%)	2 (40%)	2 (100%)	1 (100%)
HRCT	11 (46%)	1 (50%)	2 (100%)	0
PFT	0	1 (50%)	0	0
Both	13 (54%)	0	0	1 (00%)
ILD duration (range of median, months)	7–100[g]	7[b]	–	–
Concomitant immunosuppression				
MMF (number of studies)	17/29 (59%)	1/4 (25%)	0	1 (100%)
MMF (% of patients in included studies)	28 (11–45)	100	–	48.3
MTX, AZA, Steroid > 10, CYC (number of studies)	20/34 (59%)	2/4 (50%)	2 (100)	1 (100%)
MTX, AZA, Steroid > 10, CYC (% of patients in included studies)	39 (11–75.5)	57–78	67–71	8

(Continued)

Table 1. (Continued)

	Rituximab	Tocilizumab	Abatacept	Nintedanib
Dose regimens/number of studies	Available in 28 studies: • 1 g 2 weeks apart/19 studies (68%) • 375 mg/m^2 weekly for 4 weeks/11 studies (39%) • 500 mg 2 weeks apart/5 studies (18%) • 1 g monthly/1 studies (4%) • Multiple/6 studies (21%)	Available in all studies: • 162 mg weekly sc/3 studies (60%) • 8 mg/kg monthly ev/2 studies (40%)	Available in all studies • 10 mg/kg ev monthly (79%) • 125 mg/weekly sc (21%)	1 study • 150 mg twice daily per os
Follow-up time (range of mean, months)	6–84	6–24	11–28	12

AZA, azathioprine; b, *versus* baseline; c, *versus* controls; CYC, cyclophosphamide; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; MMF, mycophenolate mofetil; MTX, methotrexate; PFT, pulmonary function tests; RCT, randomized clinical trials; SSc, systemic sclerosis; –, not available.
[a]Available in 11 (32%) studies.
[b]Available in a single study (20%).
[c]Available in 4 studies (80%).
[d]Available in 28 (82%) studies.
[e]Available in 3 studies (60%).
[f]Minimum, maximum.
[g]Available in 10 (29%) studies.

reported compared to baseline ($n = 4$) and to control ($n = 1$). Two studies[25,37] (5.8%) reported a statistically significant improvement of the predicted DLCO compared to baseline.

Adverse events at different timepoints are summarized in Table 2.

RTX could be taken into consideration for the treatment of patients with SSc-ILD, especially in combination with other csDMARDs (MMF above all), but the level of evidence of the studies precludes from strong conclusions. The regimen of 1 g 2 weeks apart 6 monthly was the commonly used one. Adverse events are common but severe adverse events affect only up to roughly 10% of patients. Long-term data, up to 7 years, are available. RTX is not approved for the treatment of SSc-ILD patients.

Abatacept. Two cohort studies without control group evaluated the role of ABT in SSc for a total of 34 patients.[19,53] The level of evidence for ABT in SSc-ILD patients is extremely low as both studies were classified as level 4. A significant percentage of patients was treated with concomitant immunosuppressive therapies. ABT was used intravenously (i.v.) with a dosage of 10 mg/kg monthly in 27 (79%) patients and subcutaneously (s.c.) with a dosage of 125 mg weekly in the remaining patients. Baseline and follow-up data are summarized in Table 2. No efficacy data were available at 3 months.

The 6-month follow-up was available in both studies. No study reported a statistically significant change of the predicted FVC value. One study reported a statistically significant worsening of the mean predicted DLCO.

The 12-month follow-up was available in one study[53] (50%): statistically significant modification in the lung function test (FVC or DLCO) was not observed. Adverse events at different timepoints are summarized in Table 2.

Our SLR does not support the use of abatacept for patients with SSc-ILD due to the absence of significant efficacy data. Overall drug safety was satisfactory but even in this case the level of evidence is extremely poor. ABT is not approved for the treatment of SSc-ILD patients.

Tocilizumab. Among the five studies evaluating the role of TCZ[19,54–57] in SSc, three (60%) were RCTs and two (40%) cohort studies. The level of evidence for TCZ in SSc-ILD patients is high as two RCTs were classified as level 1b, one RCT was classified as level 2b, and the other studies

Table 2. Baseline and follow-up data of studies included in the systemic literature review investigating rituximab, tocilizumab, abatacept, and nintedanib in SSc-ILD patients.

	Rituximab	Tocilizumab	Abatacept	Nintedanib
Baseline FVC, reported in	In all studies	In 4 (80%)	In all studies	1 study (100%)
• Studies reporting mean or median <80%	21 (62%)	4 (100%)	1 (50%)	1 (100%)
• Studies reporting mean or median <60%	2 (6%)	0	0	0
Baseline DLCO, reported in	25 studies (73%)	4 studies (80%)	2 studies (100%)	1 study (100%)
• Studies reporting mean or median <80%	25 (100%)	4 (100%)	2 (100%)	1 (100%)
• Studies reporting mean or median <60%	21 (76%)	1 (25%)	0	0
3-month FU data (significant change)				
• Number of studies	4 (12%)	1 (20%)	–	–
• Number of patients	58	15	–	–
• Studies showing FVC improvement	1c (25%)	0	–	–
• Studies showing FVC worsening	0	0	–	–
• Studies showing DLCO improvement	1 (25%)	0	–	–
• Studies showing DLCO worsening	1 (25%)	0	–	–
6-month FU data (significant change)				
• Number of studies	14 (42%)	1 (20%)	2 (100%)	–
• Number of patients	262	43	34	–
• Studies showing FVC improvement	1c (7%) and 4b (29%)	–	0	–
• Studies showing FVC worsening	1c (7%)	1c (100%)	0	–
• Studies showing DLCO improvement	3c (21%) and 2b (14%)	–	1c (50%)	–
• Studies showing DLCO worsening	0	–	0	–
12-month FU data (significant change)				
• Number of studies	20 (59%)	3 (60%)	1 (50%)	1 (100%)
• Number of patients	420	173	27	288
• Studies showing FVC improvement	2c (10%) and 10b (50%)	0	0	0
• Studies showing FVC worsening	0	0	0	16.7%
• Studies showing DLCO improvement	2c (10%) and 7b (35%)	2 (66.7%)	0	–
• Studies showing DLCO worsening	0	0	0	–
24-month FU data (significant change)				
• Number of studies	9 (26%)	–	–	–
• Number of patients	144	–	–	–

(Continued)

Table 2. (Continued)

	Rituximab	Tocilizumab	Abatacept	Nintedanib
• Studies showing FVC improvement	1c (11%) and 4b (44%)	–	–	–
• Studies showing FVC worsening	0	–	–	–
• Studies showing DLCO improvement	1c (11%) and 2b (22%)	–	–	–
• Studies showing DLCO worsening	0	–	–	–
• Latest FU data (significant change)	Range 3–7 years	–	–	–
• Number of studies	6 (17%)	–	–	–
• Number of patients	457	–	–	–
• Studies showing FVC improvement	1c (17%) and 4b (67%)	–	–	–
• Studies showing FVC worsening	0	–	–	–
• Studies showing DLCO improvement	2b (33%)	–	–	–
• Studies showing DLCO worsening	0	–	–	–
3-month FU data				
• Number of studies	1 (3%)	1 (20%)	1 (50%)	–
• Number of patients	18	15	27	–
• Patients with adverse events	5.5%	13%	33%	–
• Patients with severe adverse events	5.5%	7%	11%	–
• Patients with infections	0	–	22%	–
• Mortality	5.5%	0	0	–
6-month FU data				
• Number of studies	6 (18%)	1 (20%)	2 (100%)	–
• Number of patients	166	43	34	–
• Patients with adverse events	22.3%	88%	21%	–
• Patients with severe adverse events	10.8%	21%	0	–
• Patients with infections	10.8%	40%	34%	–
• Mortality	3%	2%	0	–
12-month FU data				
• Number of studies	8 (23.5%)	2 (40%)	1 (50%)	1 (100%)
• Number of patients	159	193	27	288
• Patients with adverse events	20.8%	–	15%	98%
• Patients with severe adverse events	5%	26%	3.7%	24%
• Patients with infections	5%	14%	3.7%	11.5%
• Mortality	2.5%	4.3%	0	3.5%

(Continued)

Table 2. (Continued)

	Rituximab	Tocilizumab	Abatacept	Nintedanib
24-month FU data				
• Number of studies	4 (44.4%)	–	–	–
• Number of patients	144	–	–	–
• Patients with adverse events	79%	–	–	–
• Patients with severe adverse events	22.9%	–	–	–
• Patients with infections	9%	–	–	–
• Mortality	2.8%	–	–	–
Latest follow-up time (months)				
• Number of studies	5 (14.7%)	–	–	–
• Number of patients	110	–	–	–
• Patients with adverse events	24%	–	–	–
• Patients with severe adverse events	10.9%	–	–	–
• Patients with infections	10%	–	–	–
• Mortality	2.6%	–	–	–

b, *versus* baseline; c, *versus* controls; DLCO, diffusion capacity for carbon monoxide; FU, follow-up; FVC, forced vital capacity; –, not available.

were classified as level 2b and 4. The number of ILD patients evaluated, specified in three (60%) studies, was 41. Inclusion criteria were early disease in two (40%) studies with a disease duration <5 years, presence of ILD resistant to DMARDs or RTX in one (20%) study, and dcSSc subset in two (40%) studies. The concomitant use of MMF therapy was reported only in one (20%) study with all patients being on concomitant MMF therapy. In two (40%) studies, patients were also treated with other concomitant immunosuppressive therapies. TCZ treatment regimen was 162 mg s.c. weekly in three (60%) and 8 mg/kg i.v. monthly in two (40%) studies. Baseline and follow-up data are summarized in Table 2. No efficacy data were available at 3 months.

The 6-month follow-up was available in one study[55] (20%). A statistically significant smaller reduction of the mean FVC was reported compared to controls.

The 12-month follow-up was available in three studies[55–57] (60%). In one study, a statistically significant worsening of the predicted FVC compared to baseline was observed and, in another study, a statistically significant drop of the mean predicted FVC >10% compared to controls was observed in three (10%) patients. Adverse events at different timepoints are summarized in Table 2.

Tocilizumab at a dose of 162 mg weekly subcutaneously was shown to be effective in SSc-ILD patients in two RCTs in monotherapy. Its use in combination with csDMARDs is extremely poorly studied. Side effects, especially infections, can be common in up to one quarter of patients. No long-term data exist. TCZ is approved for the treatment of SSc-ILD patients.

Nintedanib. Nintedanib was used in a single 52-week randomized placebo-controlled trial classified as level 1b, including 576 SSc patients all with SSc-ILD.[13] Inclusion criteria were <7-year disease duration from onset of first non-Raynaud's symptom, ILD defined by HRCT with at least 10% extent, FVC at least 40%, and DLCO

between 30% and 89%. Patients were excluded in case of liver of renal dysfunction, significant pulmonary hypertension, >3 digital ulcers, bleeding risk, anticoagulation or high-dose anti-platelets, hemorrhagic events, hematuria, gastrointestinal (GI) bleeding, history of scleroderma renal crisis, uncontrolled systemic hypertension, thrombotic events <12 months, life expectancy <2.5 years, prednisone >10 mg/day, or immunosuppressive therapy except MMF of MTX (at stable dose) in the previous 6 months.

The control group was defined as SSc-ILD patients receiving placebo on top of background therapy (MMF in 48.3% of patients). Nintedanib was administered orally 150 mg twice daily. At 52 weeks, the delta FVC was 41 ml (1.2%) ($p < 0.04$). FVC worsened >10% in 16.7% of patients treated with nintedanib. Delta DLCO was −3.21 ml/min/mmHg. HRCT follow-up data were not reported. The 12-month AEs were reported in 283 (98.3%) of patients, classified as severe in 69 (24%). In 218 patients (77%), the most common AE was diarrhea, infections were recorded in 33 patients (11.5%). In 16 cases, nintedanib was suspended and 10 deaths (3.5%) were recorded.

Nintedanib was studied in a single RCT study which was specifically designed for SSc-ILD and included the largest number of SSc patients among all available trials. Nintedanib was effective in reducing the rate of decline especially when in combination with MMF. Side effects are mainly limited to GI intolerance. No long-term data exist. Nintedanib has been the first drug approved for the treatment of SSc-ILD patients.

Survey

In the survey, 168 of 945 physicians (18%) replied. We observed no gender prevalence among the repliers (50.6% females) and a higher frequency in the age range between 31 and 50 years (63.7%). The repliers were predominantly rheumatologists (73.8%), but also clinical immunologists (10.1%), internal medicine specialist (7.7%), pneumologists (4.8%), or others (3.6%, including dermatology, pediatrics, and gastroenterology). Most physicians worked at a University Hospital with >5 years of experience (81%) and with an average number of monthly follow-up of SSc patients >11 in 75% of cases. Two thirds of the repliers were European and almost half belonged to an EUSTAR center.

The availability of targeted therapies for SSc-ILD patients varied, the highest being RTX (96%), followed by TCZ (92%) and nintedanib (80%) and the lowest was ABT (18%). The main indication for RTX, TCZ, and nintedanib introduction at the time of the survey was as rescue therapy in SSc patients with ILD progression while on conventional disease-modifying antirheumatic drugs (cDMARDs; 86%, 59%, and 63%, respectively). The second most common indication was functional progression of ILD independently of concomitant therapies (44%, 37%, and 57%, respectively). Interestingly, none of the proposed options included in the survey (ILD diagnosis, ILD progression on HRCT, ILD functional progression, ILD progression while on conventional drugs) was selected as the most common indication for ABT introduction (45%). Combination therapy (targeted therapy + cDMARD) was the most commonly identified therapeutic scheme for nintedanib (75%) followed by RTX (63%) and finally TCZ (47%). Monotherapy was the most commonly reported as a potential treatment option for TCZ (47%) and the least commonly reported for nintedanib (12%). Physicians' perception of global safety and lung safety for the four medications in SSc-ILD patients was comparable among all drugs, highest with nintedanib (7.3 ± 1.7 and 8.0 ± 1.6, respectively) and lowest with TCZ (6.8 ± 1.6 and 6.5 ± 1.6, respectively). Physicians' perception of drug efficacy was the same for RTX and nintedanib (6.8 ± 1.6) and only slightly lower for TCZ (6.3 ± 1.6), whereas it was the lowest for ABT (4.8 ± 2). Physicians' confidence on when to initiate a targeted therapy in SSc-ILD patients was comparable between RTX and nintedanib (6.2 ± 2.3 *versus* 6.0 ± 2.2), followed by TCZ (5.3 ± 2.3) and ABT (3.5 ± 2.5).

Physicians were then asked to identify which elements to consider when choosing among one of the four drugs. From our survey, it emerged that the efficacy profile on SSc-ILD and the overall safety profile were the first and second most important and most frequently voted drug-related characteristics for all four drugs. Among disease features, failure of previous DMARD therapy was the most important factor for all four medications, while the following were differently distributed (RTX: myositis and inflammatory arthritis; TCZ: arthritis and increased inflammatory markers; nintedanib: arthritis and high infection risk; ABT: high infection risk and SSc duration). Among ILD features, failure of previous traditional therapies and presence of extensive ILD

(>20% on HRCT) were the two most commonly reported for all drugs.

Unmet needs and future research agenda

Overall, 470 comments or questions (Excerpts) were received from 79 of 168 repliers, covering the 32 pre-defined themes at least once. The most frequently raised concerns pertained to efficacy profile, safety profile, and combination regimens in more than 20% of the excerpts (see Table 3 for further details).

While equally distributed among the drugs for the efficacy domain, safety and combination concerns were expressed mostly for the treatment with nintedanib suggesting that more pieces of information and education are needed to make the physicians more familiar with this drug. Efficacy concerns were directed principally toward monotherapy or combination with other conventional immunosuppressants or bDMARDs. Moreover, a need for more evidence also emerged on long-term treatment duration and outcomes, and predictors supporting drug choice and timing of treatment initiation.

With regard to safety, comments were raised about the use of RTX as a possible determinant of secondary immunodeficiency and low-response to vaccination, with special remarks on the current SARS-CoV-2 pandemic. With comparable entity, extra-pulmonary safety profile (i.e. gastrointestinal) concerns were raised for both TCZ and nintedanib, pointing out the need to identify risk factors for safety events.

Overall, different major points were raised, as bases for future research agenda for the SSc scientific community (see Table 4).

Our survey repliers underlined the need to obtain more data regarding the upfront initiation of combination regimen *versus* monotherapy, as well as in the identification of predictors supporting drug choice according to both pulmonary and extra-pulmonary patient profile. In addition, the concept of timing emerged meaningfully, related to both the patient (i.e. early *versus* long-term disease or ILD) and the drug of choice (including first choice and escalation strategies). Finally, the need for additional data emerged in different topics, including the comparison between monotherapy and combination in particular of nintedanib and bDMARDs. Finally, complementary efficacy and safety data were identified as an unmet need for all the drugs investigated, with real-life data requested for nintedanib and RCT data for the three bDMARDs, in support of the currently available literature.

Discussion

In SSc, ILD is currently a leading cause of morbidity and mortality and, therefore, its treatment represents one of the main objectives in the area of SSc clinical research.[58] Since the ILD course shows a significant variability among patients, increasing efforts have been made to identify predictors of ILD progression[9] and to identify when and which patient should be treated with immunosuppressants.[6] Drug choice is crucial and should be based on different factors (safety and efficacy issues, other organ involved, disease duration, patient' age, comorbidities, patient's preference, etc.).

Since the release of the EULAR guidelines in 2017,[10] several studies have explored other treatments for SSc-ILD besides cyclophosphamide and haematopoietic stem cell transplantation (HSCT).

First, the SLS-II trial, which, although failed to meet the primary endpoint, demonstrated a comparable efficacy for MMF and (cyclophosphamide) CYC, with superiority of MMF in some secondary endpoints, including safety.[11] More recently, the use of biological DMARDs and small molecules has attracted the attention of the SSc medical community. Biological DMARDs that have been explored for SSc-ILD treatment (or more generally SSc) include RTX, TCZ, and ABT that are already approved and routinely used for the treatment of other rheumatic/autoimmune diseases. Among these bDMARDs, only TCZ has been clearly shown to be effective in SSc-ILD patients thanks to the positive results of two RCTs, whereas high-level RCTs showing a clear efficacy and safety profile are still missing for the other two bDMARDs.

Nevertheless, since SSc-ILD management is particularly challenging,[59] a significant number of patients may require a second- or third-line treatment, after the failure of a first-line treatment. Moreover, given the heterogeneity of disease, SSc patients with concomitant organ involvements need a tailored therapeutic strategy for different organs and systems (e.g. ILD plus dcSSc and arthritis). Consequently, clinicians are

Table 3. Queries about the use of rituximab, tocilizumab, nintedanib, and abatacept from the EUSTAR survey according to pre-defined themes.

Themes	*N*	*N* associated with drugs	*N* associated with rituximab	*N* associated with tocilizumab	*N* associated with nintedanib	*N* associated with abatacept
Efficacy	112	100	25	26	27	22
Combination	111	73	11	9	40	13
Safety	103	81	18	18	36	9
Predictors/risk factors	90	65	18	21	14	12
Patient selection	78	62	16	19	12	15
Conventional immunosuppressants	75	51	11	7	26	7
Timing	72	51	12	15	15	9
More data needed	71	58	14	13	14	17
Drug choice	68	39	10	7	15	7
Comparison	67	47	12	10	13	12
Infection	57	49	20	15	4	10
bDMARD	48	21	1	0	20	0
Extra-pulmonary	45	43	2	18	22	1
Treatment duration	39	34	15	8	9	2
Monotherapy	36	18	5	1	10	2
Anti-fibrotics	33	15	4	4	0	7
Prophilaxis/vaccination	21	18	12	2	0	2
Whether to start treatment	19	18	3	4	7	4
Guidelines needed	18	6	1	1	4	0
Maintenance/management	16	14	2	4	7	1
SARS-Cov-2/COVID-19	15	15	9	2	1	3
Dosage	15	24	5	3	4	2
Duration of the disease	15	25	3	5	5	2
Reduction of defense	15	23	12	1	0	0
Outcomes	14	8	4	2	2	2
Quality of life	11	10	2	3	3	2
Special populations	6	4	1	1	3	0
Which drug to start	4	4	1	1	1	1
Prevention	4	4	1	1	1	1
Relapse	3	3	1	1	0	1
Compliance	2	1	0	0	1	0
Stop treatment	2	2	1	1	0	0

bDMARDs, biologic disease-modifying anti-rheumatic drugs.

Table 4. Concerns and unanswered questions about the use of rituximab, tocilizumab, nintedanib, and abatacept from our EUSTAR survey.

Concerns on safety	Rituximab	Concerns with the use of the drug in patient with hypogammaglobulinemia Concern regarding need for prophylaxis/vaccination against infections or regarding response to vaccination Concerns with use in COVID-19 era Concerns about long-term treatment duration Concerns about combination with conventional IMS *versus* monotherapy Need for identification of risk factors
	Tocilizumab	Concerns about infections Concerns about extra-pulmonary safety Need for identification of risk factors
	Nintedanib	Concerns about extra-pulmonary safety Concerns about combination with conventional IMS Concerns about drug management Concerns about long-term treatment duration Need for identification of risk factors
	Abatacept	No major concerns
Concerns on efficacy	Rituximab	Concerns about combination with conventional IMS *versus* monotherapy Concerns about treatment duration/long-term efficacy Need for identification of predictors
	Tocilizumab	More data needed, in particular in different patient subsets different from RCT Concerns about treatment duration/long-term efficacy Need for identification of predictors
	Nintedanib	Concerns about treatment duration/long-term efficacy Concerns about extra-pulmonary efficacy
	Abatacept	Concerns about efficacy in general, more data needed
Overall questions	Whether to start	Combination with IMS *versus* monotherapy at the time of initiation Need for identification of predictors to support drug choice
	When to start	Need for identification of predictors to support personalized treatment, in terms of Timing, including both (A) Patient Timing – early *versus* longer duration SSc or SSc-ILD (B) Drug Timing – which to choose first, escalation strategy
	Which to choose	Need for identification of predictors to support drug choice according to extra-pulmonary features
	General questions	More data needed about: • Comparison between monotherapy and combination with IMS • Combination of nintedanib with bDMARDs • Overall efficacy on other patient cohorts (non-RCT) • Need for RCT data specifically oriented on SSc-ILD (when missing)

bDMARDs, biologic disease-modifying anti-rheumatic drugs; ILD, interstitial lung disease; IMS, immunosuppressants; RCT, randomized controlled trial; SSc, systemic sclerosis.

increasingly using new drugs in SSc patients in their everyday clinical practice, notwithstanding the lack of formal consensus recommendations and the significant differences in drug availability among countries.

Given this background, the aim of our study was first to perform a SLR on the efficacy and safety of the four targeted therapies (RTX, nintedanib, ABT, and TCZ) in SSc-ILD and to investigate the clinical practice of clinicians devoted to

SSc-ILD patients to understand what questions are still unanswered. The majority of the patients involved in these studies were dcSSc which was often the reason for targeted therapy introduction in observational studies or it represented an inclusion criterion in RCTs. Of note, lcSSc patients were more represented in the nintedanib study (43%) as compared to studies on both RTX and TCZ. The inclusion of lcSSc in RCTs evaluating drug efficacy in SSc-ILD is of particular interest as it was recently reported that the pulmonary outcome is similar between lcSSc and dcSSc patients.[60] In this regard, it should also be mentioned that, contrarily to the INBUILD trial which included only a small number of SSc-ILD patients,[61] the possibility of identifying a clear progressive phenotype in SSc-ILD patients is yet to be determined and this topic is still a matter of debate.

Patients included in the SLR studies were also receiving concomitant immunosuppressive therapy in 59% of studies on RTX, with MMF being the most frequent (28% of patients per study). This is in line with the common clinical practice of combining RTX and MMF in extensive ILD.[15,16,36] In our SLR, we also observed that while the two RCTs showed an efficacy of TCZ monotherapy in SSc-ILD patients, the use of TCZ combination therapy was frequently reported in retrospective studies. A high percentage of combination therapy was also reported in studies with ABT (67% and 71%) and with Nintedanib (48% of patients on MMF).[13]

Regarding efficacy, our SLR data do not support ABT use since the level of evidence of the studies was extremely poor and no significant changes in predicted FVC values at 6 and 12 months were observed. Conversely, data from our SLR were promising for RTX, TCZ, and nintedanib. About RTX, it should though be noticed that the level of evidence of data supporting the role of RTX in SSc-ILD was poor as only a single moncentric RCT with a limited number of patients was included in the SLR and the majority of data were extrapolated from case–control or cohort studies. Nonetheless, a significant improvement in SSc-ILD patients treated with RTX in predicted FVC compared to baseline and controls was observed in about half of studies with available follow-up at 6 and 12 months (7/14 and 11/20 studies, respectively), with a lower percentage of DLCO improvement (3/14 and 7/20 at 6 and 12 months, respectively).

Of note, disease duration was shorter in patients treated with TCZ, as compared to those treated with RTX as this bDMARD has traditionally been used in SSc-ILD cases refractory to conventional treatment, although recent level of evidence 2 data seem to suggest that RTX should also be considered as an early treatment option in SSc-ILD.[49] Nintedanib efficacy in reducing FVC decline in a 52-week period has been clearly demonstrated.[13]

Safety was a major objective of our SLR. As expected, infection was the most frequently reported adverse event, in particular with TCZ and RTX, while, in line with previously reported data in (idiopathic pulmonary fibrosis) IPF, diarrhea was the main side effect recorded for nintedanib. In all studies, the rate of drug discontinuation was generally low, with no treatment discontinuation recorded in the ABT study, which is consistent with the safety profile demonstrated in RA.

After the SLR, our study proceeded with a survey that was designed to capture the real-life experience of clinicians with these drugs in the treatment of SSc-ILD. Survey repliers also received a summary of the above-mentioned SLR results, and they were encouraged to make inquiries on specific issues.

The survey was answered by 168 physicians mainly from Europe and working in academic settings. The survey highlighted a high variability in the availability of the targeted drugs for the treatment of SSc-ILD, with RTX being available in almost all centers. Even though nintedanib has only been recently added for the treatment of SSc-ILD, physicians reported a good confidence in determining when to start nintedanib as well as a high perception of its efficacy, with rates similar to RTX. Nintedanib safety profile was also considered good. Surprisingly, while the level of evidence supporting the use of TCZ in SSc-ILD was high and this therapy is approved by the FDA specifically for SSc-ILD, we observed a slightly lower perception of TCZ efficacy compared to nintedanib and RTX maybe reflecting the lack of lung-specific primary endpoints in the two published TCZ RCTs.

Many repliers raised questions about the risk of infections in patients treated with TCZ and RTX, especially in those presenting hypogammaglobulinemia and in light of the COVID-19 pandemic,

possibly due to reported cases of more severe SARS-CoV-2 infection in SSc patients on RTX therapy.[62] Several points were raised about nintedanib, its long-term use, and the combination with other immunosuppressants, especially bDMARDs (the SENSCIS trial provided data on combination therapy with MMF only). Repliers were also keen on having more data or drug-specific predictors of response and expressed concerns about treatment duration/long-term efficacy. Among specific drug-related questions, the most frequent was about TCZ efficacy in patients with a different subset than that included in the faSScinate/focuSSced trial.[14] For Nintedanib, the main question was about its efficacy on extra-pulmonary manifestations.[13] In fact, some experts have been trying to create an algorithm for SSc-ILD treatment by inputting different clinical scenarios (e.g. presence or absence of extra-pulmonary SSc manifestations).[63] Several other questions focused on the time-to-treatment initiation, in particular when comparing monotherapy *versus* combination therapy. The identification of predictors of drug response is without doubt the most important unmet need raising the issue of precision medicine for SSc patients.

Our study has clearly some limitations. First, our SLR included papers published up to March 2020; therefore, more recent studies, including real-life evidences on nintedanib efficacy and safety, were not included. Second, due to the small presence of non-university hospitals, early career doctors, non-rheumatologists, and non-European repliers, our survey might have been limited in its representativeness.

In conclusion, this is the first study providing SLR data on SSc-ILD targeted treatments investigating also the real-life experience of clinicians with these new drugs. The information collected may thus provide significant suggestions and indications for the design of future studies dedicated to improve the treatment of SSc-ILD.

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Not applicable.

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Not applicable.

Author contributions

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References
1. Varga J, Trojanowska M and Kuwana M. Pathogenesis of systemic sclerosis: recent insights of molecular and cellular mechanisms and therapeutic opportunities. *J Scleroderma Relat Disord* 2017; 2: 137–152.
2. Nihtyanova SI and Denton CP. Pathogenesis of systemic sclerosis associated interstitial lung disease. *J Scleroderma Relat Disord* 2020; 5(Suppl. 2): 6–16.
3. Volkmann ER and Fischer A. Update on morbidity and mortality in systemic sclerosis–related interstitial lung disease. *J Scleroderma Relat Disord* 2021; 6: 11–20.
4. Elhai M, Meune C, Boubaya M, *et al*. Mapping and predicting mortality from systemic sclerosis. *Ann Rheum Dis* 2017; 76: 1897–1905.
5. Saketkoo LA, Scholand MB, Lammi MR, *et al*. Patient-reported outcome measures in systemic sclerosis–related interstitial lung disease for clinical practice and clinical trials. *J Scleroderma Relat Disord* 2020; 5(Suppl. 2): 48–60.
6. Hoffmann-Vold A-M, Maher T, Philpot E, *et al*. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. *Lancet Rheumatol* 2020; 2: e71–e83.
7. Volkmann ER, Chung A and Tashkin DP. Managing systemic sclerosis-related interstitial lung disease in the modern treatment era. *J Scleroderma Relat Disord* 2017; 2: 72–83.
8. Hoffmann-Vold A-M, Allanore Y, Bendstrup E, *et al*. The need for a holistic approach for SSc-ILD – achievements and ambiguity in a devastating disease. *Respir Res* 2020; 21: 1–13.
9. Distler O, Assassi S, Cottin V, *et al*. Predictors of progression in systemic sclerosis patients with interstitial lung disease. *Eur Respir J* 2020; 55: 1902026.

10. Kowal-Bielecka O, Fransen J, Avouac J, *et al.* Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis* 2017; 76: 1327–1339.

11. Tashkin DP, Roth MD, Clements PJ, *et al.* Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *Lancet Respir Med* 2016; 4: 708–719.

12. Campochiaro C and Allanore Y. An update on targeted therapies in systemic sclerosis based on a systematic review from the last 3 years. *Arthritis Res Ther* 2021; 23: 155.

13. Khanna D, Lin CJF, Furst DE, *et al.* Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2020; 8: 963–974.

14. Distler O, Highland KB, Gahlemann M, *et al.* Nintedanib for systemic sclerosis–associated interstitial lung disease. *N Engl J Med* 2019; 380: 2518–2528.

15. Elhai M, Boubaya M, Distler O, *et al.* Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practice: a prospective cohort study. *Ann Rheum Dis* 2019; 78: 979–987.

16. Campochiaro C, De Luca G, Lazzaroni MG, *et al.* Safety and efficacy of rituximab biosimilar (CT-P10) in systemic sclerosis: an Italian multicentre study. *Rheumatology* 2020; 59: 3731–3736.

17. Lescoat A, Lelong M, Jeljeli M, *et al.* Combined anti-fibrotic and anti-inflammatory properties of JAK-inhibitors on macrophages in vitro and in vivo: perspectives for scleroderma-associated interstitial lung disease. *Biochem Pharmacol* 2020; 178: 114103.

18. Bruni C, Praino E, Allanore Y, *et al.* Use of biologics and other novel therapies for the treatment of systemic sclerosis. *Expert Rev Clin Immunol* 2017; 13: 469–482.

19. Elhai M, Meunier M, Matucci-Cerinic M, *et al.* Outcomes of patients with systemic sclerosis-associated polyarthritis and myopathy treated with tocilizumab or abatacept: a EUSTAR observational study. *Ann Rheum Dis* 2013; 72: 1217–1220.

20. Koneva O, Ananyeva LP, Garzanova L, *et al.* OP0187 Rituximab and cyclophosphamide comparison for efficacy and safety in the patients with systemic sclerosis associated with interstitial lung disease. *Ann Rheum Dis* 2019; 78: 169.

21. Garzanova L, Ananyeva L, Koneva O, *et al.* OP0173 Reduction of skin fibrosis in systemic sclerosis on rituximab treatment. Long-term follow-up. *Ann Rheum Dis* 2021; 80: 104.

22. Moazedi-Fuerst FC, Kielhauser SM, Brickmann K, *et al.* Rituximab for systemic sclerosis: arrest of pulmonary disease progression in five cases. Results of a lower dosage and shorter interval regimen. *Scand J Rheumatol* 2014; 43: 257–258.

23. Melsens K, De Keyser F, Decuman S, *et al.* Assessment of sensitivity to change of the European Scleroderma Study Group activity index. *Clin Exp Rheumatol* 2016; 34: 148–151.

24. Melsens K, Vandecasteele E, Deschepper E, *et al.* Two years follow-up of an open-label pilot study of treatment with rituximab in patients with early diffuse cutaneous systemic sclerosis. *Acta Clin Belg* 2018; 73: 119–125.

25. Lumetti F, Spinella A, Colaci M, *et al.* AB0212 Long-term treatment with rituximab in systemic sclerosis management: an overview of the clinical experience from a real-life setting. *Ann Rheum Dis* 2019; 78: 1563.

26. Lepri G, Avouac J, Airò P, *et al.* Effects of rituximab in connective tissue disorders related interstitial lung disease. *Clin Exp Rheumatol* 2016; 34: 181–185.

27. Lafyatis R, Kissin E, York M, *et al.* B cell depletion with rituximab in patients with diffuse cutaneous systemic sclerosis. *Arthritis Rheum* 2009; 60: 578–583.

28. Koneva O, Desinova O, Ovsyannikova O, *et al.* FRI0484 impact of anti-B-cell therapy with rituximab on pulmonary function of the patients with systemic sclerosis and interstitial lung disease. *Ann Rheum Dis* 2015; 74: 603–604.

29. Koneva O, Ananieva L, Garzanova L, *et al.* Comparison of the rituximab (RTM) efficacy in monotherapy regimen and in combination with immunosuppressants in systemic sclerosis (SSC) with interstitial lung disease (ILD). *Chest* 2020; 157: A374.

30. Rituximab in progressive, refractory to conventional treatment, interstitial lung disease. A24. Autoimmune interstitial lung disease, https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2016.193.1_MeetingAbstracts.A1147 (accessed 13 November 2021).

31. Kiryttopoulos P, Michailidis T, Papchianou E, *et al.* FRI0412 The positive effect of rituximab in pulmonary fibrosis of systemic sclerosis. *Ann Rheum Dis* 2017; 76: 643.

32. Jordan S, Distler JH, Maurer B, *et al.* Effects and safety of rituximab in systemic sclerosis: an

analysis from the European Scleroderma Trial and Research (EUSTAR) group. *Ann Rheum Dis* 2015; 74: 1188–1194.

33. Guzelant G, Melikoglu M, Musellim B, *et al.* AB0634 rituximab in systemic sclerosis-interstitial lung disease, a case series of 18 patients. *Ann Rheum Dis* 2017; 76: 1274.
34. Giuggioli D, Lumetti F, Colaci M, *et al.* Rituximab in the treatment of patients with systemic sclerosis. Our experience and review of the literature. *Autoimmun Rev* 2015; 14: 1072–1078.
35. Fasano S, Giacco V, Riccardi A, *et al.* SAT0274 The effect of rituximab on lung function and skin score in systemic sclerosis-associated interstitial lung disease. Long-term observation. *Ann Rheum Dis* 2019; 78: 1213–1214.
36. Fraticelli P, Fischetti C, Salaffi F, *et al.* Combination therapy with rituximab and mycophenolate mofetil in systemic sclerosis. A single-centre case series study. *Clin Exp Rheumatol* 2018; 36: S142–S145.
37. Fitzgerald DB, Moloney F, Twomey M, *et al.* Efficacy and safety of rituximab in connective tissue disease related interstitial lung disease. *Sarcoidosis Vasc Diffuse Lung Dis* 2015; 32: 215–221.
38. Ebata S, Yoshizaki A, Fukasawa T, *et al.* Rituximab therapy is more effective than cyclophosphamide therapy for Japanese patients with anti-topoisomerase I-positive systemic sclerosis-associated interstitial lung disease. *J Dermatol* 2019; 46: 1006–1013.
39. Daoussis D, Melissaropoulos K, Sakellaropoulos G, *et al.* A multicenter, open-label, comparative study of B-cell depletion therapy with rituximab for systemic sclerosis-associated interstitial lung disease. *Semin Arthritis Rheum* 2017; 46: 625–631.
40. Daoussis D, Liossis SN, Tsamandas AC, *et al.* Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis. *Clin Exp Rheumatol* 2012; 30: S17–S22, https://www.clinexprheumatol.org/abstract.asp?a=4752 (accessed 13 November 2021).
41. Silva Vilela V, Maretti GB, Marques Da L, *et al.* Rituximab for the therapy of systemic sclerosis: a series of 10 cases in a single center. *Rev Bras Ortop (English Ed)* 2016; 56: 458–463.
42. Daoussis D, Liossis SN, Tsamandas AC, *et al.* Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology* 2010; 49: 271–280.
43. Bosello SL, De Luca G, Rucco M, *et al.* Long-term efficacy of B cell depletion therapy on lung and skin involvement in diffuse systemic sclerosis. *Semin Arthritis Rheum* 2015; 44: 428–436.
44. Bosello S, Angelucci C, Lama G, *et al.* Characterization of inflammatory cell infiltrate of scleroderma skin: B cells and skin score progression. *Arthritis Res Ther* 2018; 20: 75.
45. Boonstra M, Meijs J, Dorjée AL, *et al.* Rituximab in early systemic sclerosis. *RMD Open* 2017; 3: e000384.
46. Koenig M, Senécal J-L, Vincent C, *et al.* FRI0264 Treatment with rituximab in patients with systemic sclerosis. *Ann Rheum Dis* 2013; 71: 403.
47. Thiebaut M, Launay D, Rivière S, *et al.* Efficacy and safety of rituximab in systemic sclerosis: French retrospective study and literature review. *Autoimmun Rev* 2018; 17: 582–587.
48. Second Mexican-Canadian Congress of Rheumatology Cancun, Mexico, February 10–15, 2011. *J Rheumatol* 2011; 38: 1132.
49. Sircar G, Goswami RP, Sircar D, *et al.* Intravenous cyclophosphamide vs rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial. *Rheumatology* 2018; 57: 2106–2113.
50. Sari A, Guven D, Armagan B, *et al.* Rituximab experience in patients with long-standing systemic sclerosis-associated interstitial lung disease: a series of 14 patients. *J Clin Rheumatol* 2017; 23: 411–415.
51. Efficacy of rituximab in systemic sclerosis with interstitial lung disease. In: *ACR Meeting Abstracts*, https://acrabstracts.org/abstract/efficacy-of-rituximab-in-systemic-sclerosis-with-interstitial-lung-disease/ (accessed 13 November 2021).
52. Naidu G, Sharma S, Dhir V, *et al.* AB0633 rituximab in scleroderma related interstitial lung disease: a single centre experience from North India. *Ann Rheum Dis* 2017; 76: 1273–1274.
53. Castellví I, Elhai M, Bruni C, *et al.* Safety and effectiveness of abatacept in systemic sclerosis: the EUSTAR experience. *Semin Arthritis Rheum* 2020; 50: 1489–1493.
54. Narváez J, Lluch J, Alegre Sancho JJ, *et al.* Effectiveness and safety of tocilizumab for the treatment of refractory systemic sclerosis associated interstitial lung disease: a case series. *Ann Rheum Dis* 2019; 78: e123.
55. Khanna D, Denton CP, Jahreis A, *et al.* Safety and efficacy of subcutaneous tocilizumab in

adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. *Lancet* 2016; 387: 2630–2640.

56. Denton CP, Lin CJF, Goldin J, *et al*. Lung function preservation in a phase 3 trial of tocilizumab (TCZ) in systemic sclerosis (SSc). *Eur Respir J* 2019; 54: RCT1883.
57. Khanna D, Denton CP, Lin CJF, *et al*. Extended report: safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate). *Ann Rheum Dis* 2018; 77: 212.
58. Roofeh D, Distler O, Allanore Y, *et al*. Treatment of systemic sclerosis–associated interstitial lung disease: lessons from clinical trials. *J Scleroderma Relat Disord* 2020; 5: 61–71.
59. Vonk MC, Walker UA, Volkmann ER, *et al*. Natural variability in the disease course of SSc-ILD: implications for treatment. *Eur Respir Rev* 2021; 30: 200340.
60. Frantz C, Huscher D, Avouac J, *et al*. Outcomes of limited cutaneous systemic sclerosis patients: results on more than 12,000 patients from the EUSTAR database. *Autoimmun Rev* 2020; 19:102452.
61. Flaherty KR, Wells AU, Cottin V, *et al*. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019; 381: 1718–1727.
62. Avouac J, Airó P, Carlier N, *et al*. Severe COVID-19-associated pneumonia in 3 patients with systemic sclerosis treated with rituximab. *Ann Rheum Dis* 2021; 80: e37.
63. Lescoat A, Murphy SL, Roofeh D, *et al*. Considerations for a combined index for limited cutaneous systemic sclerosis to support drug development and improve outcomes. *J Scleroderma Relat Disord* 2020; 6: 66–76.