

## CLINICAL SCIENCE

# Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practice: a prospective cohort study

Muriel Elhai,<sup>1</sup> Marouane Boubaya,<sup>2</sup> Oliver Distler,<sup>3</sup> Vanessa Smith,<sup>4,5</sup> Marco Matucci-Cerinic,<sup>6</sup> Juan José Alegre Sancho,<sup>7</sup> Marie-Elise Truchetet,<sup>8</sup> Yolanda Braun-Moscovici,<sup>9</sup> Florenzo Iannone,<sup>10</sup> Pavel I Novikov,<sup>11</sup> Alain Lescoat,<sup>12</sup> Elise Siegert,<sup>13</sup> Ivan Castellví,<sup>14</sup> Paolo Airó,<sup>15</sup> Serena Vettori,<sup>16</sup> Ellen De Langhe,<sup>17</sup> Eric Hachulla,<sup>18</sup> Anne Erler,<sup>19</sup> Lidia Ananieva,<sup>20</sup> Martin Krusche,<sup>21</sup> F J López-Longo,<sup>22</sup> Jörg H W Distler,<sup>23</sup> Nicolas Hunzelmann,<sup>24</sup> Anna-Maria Hoffmann-Vold,<sup>25</sup> Valeria Ricciari,<sup>26</sup> Vivien M Hsu,<sup>27</sup> Maria R Pozzi,<sup>28</sup> Codrina Ancuta,<sup>29</sup> Edoardo Rosato,<sup>30</sup> Carina Mihai,<sup>31</sup> Masataka Kuwana,<sup>32</sup> Lesley Ann Saketkoo,<sup>33</sup> Carlo Chizzolini,<sup>34</sup> Roger Hesselstrand,<sup>35</sup> Susanne Ullman,<sup>36</sup> Sule Yavuz,<sup>37</sup> Simona Rednic,<sup>38</sup> Cristian Caimmi,<sup>39</sup> Coralie Bloch-Queyrat,<sup>40</sup> Yannick Allanore,<sup>41</sup> for EUSTAR network

**Handling editor** Josef S Smolen

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/annrheumdis-2018-214816>).

For numbered affiliations see end of article.

## Correspondence to

Dr Muriel Elhai, Rheumatology A Department, Paris Descartes University, Cochin Hospital, Paris 75014, France; [muriel-elhai@hotmail.fr](mailto:muriel-elhai@hotmail.fr)

Received 24 November 2018

Revised 7 February 2019

Accepted 28 February 2019



© Author(s) (or their employer(s)) 2019. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** Elhai M, Boubaya M, Distler O, et al. *Ann Rheum Dis* Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2018-214816

## ABSTRACT

**Objective** To assess the safety and efficacy of rituximab in systemic sclerosis (SSc) in clinical practice.

**Methods** We performed a prospective study including patients with SSc from the European Scleroderma Trials and Research (EUSTAR) network treated with rituximab and matched with untreated patients with SSc. The main outcomes measures were adverse events, skin fibrosis improvement, lung fibrosis worsening and steroids use among propensity score-matched patients treated or not with rituximab.

**Results** 254 patients were treated with rituximab, in 58% for lung and in 32% for skin involvement. After a median follow-up of 2 years, about 70% of the patients had no side effect. Comparison of treated patients with 9575 propensity-score matched patients showed that patients treated with rituximab were more likely to have skin fibrosis improvement (22.7 vs 14.03 events per 100 person-years; OR: 2.79 [1.47–5.32];  $p=0.002$ ). Treated patients did not have significantly different rates of decrease in forced vital capacity (FVC)  $>10\%$  (OR: 1.03 [0.55–1.94];  $p=0.93$ ) nor in carbon monoxide diffusing capacity (DLCO) decrease. Patients having received rituximab were more prone to stop or decrease steroids (OR: 2.34 [1.56–3.53],  $p<0.0001$ ). Patients treated concomitantly with mycophenolate mofetil had a trend for better outcomes as compared with patients receiving rituximab alone (delta FVC: 5.22 [0.83–9.62];  $p=0.019$  as compared with controls vs 3 [0.66–5.35];  $p=0.012$ ).

**Conclusion** Rituximab use was associated with a good safety profile in this large SSc-cohort. Significant change was observed on skin fibrosis, but not on lung. However, the limitation is the observational design. The potential stabilisation of lung fibrosis by rituximab has to be addressed by a randomised trial.

## Key messages

### What is already known about this subject?

- Some efficacy of rituximab in systemic sclerosis (SSc) has been suggested by few small-sized uncontrolled studies. Large controlled studies were lacking.

### What does this study add?

- Rituximab is safe in SSc.
- Treatment with rituximab improves skin fibrosis, which is a marker of disease activity and severity as compared with untreated control-patients.
- No significant change was observed on lung fibrosis in the whole cohort.
- Secondary analyses suggest that combination therapy with mycophenolate mofetil might be more effective for treating lung fibrosis.

### How might this impact on clinical practice or future developments?

- A clue for the future to get a better impact on SSc outcomes might be combination therapy, which should be further studied.

## INTRODUCTION

Systemic sclerosis (SSc) is an orphan disease that is characterised by fibrosis of the skin and internal organs, autoimmunity and vasculopathy.<sup>1</sup> SSc has the highest cause-specific mortality among connective tissue diseases.<sup>2</sup> Progressive interstitial lung disease (ILD) is the leading cause of death in SSc.<sup>3</sup> Despite the fatal burden associated with this condition, treatment options for SSc remain limited.<sup>4</sup> Preliminary case-reports and series have suggested that rituximab, a chimeric monoclonal antibody targeting B cells, could improve

## Systemic sclerosis

**Table 1** Baseline characteristics of patients with SSc treated with rituximab and untreated SSc-controls from EUSTAR database

	Total (n=9829)	Non-treated (n=9575)	Treated (n=254)	P value
Sex (Female)	8437 (85.8%)	8256 (86.2%)	181 (71.3%)	<0.0001
Age, Mean±SD	54.4±13.8	55 (45–65)	51 (44–58)	<0.0001
Diffuse cutaneous form	3022 (31%)	2866 (30.2%)	156 (63.9%)	<0.0001
Disease duration (years), Median (Q1–Q3)	5.2 (2:11.1)	5.2 (2–11.1)	4.2 (1.9–9.7)	0.046
ANA	9053 (94.6%)	8813 (94.5%)	240 (98%)	0.026
Anti-Scl70	3123 (33.9%)	2994 (33.4%)	129 (52.9%)	<0.0001
ACA	3436 (37.4%)	3410 (38.1%)	26 (10.7%)	<0.0001
RNA pol III antibodies	162 (5.3%)	145 (5.2%)	17 (7%)	0.31
Modified Rodnan skin score, Median (Q1–Q3)	(0:86)	7 (3–13)	14 (6–24)	<0.0001
Lung fibrosis (on HRCT)	1686 (43.4%)	1505 (41.4%)	181 (71.3%)	<0.0001
FVC, Mean±SD	94.5±21.7	96 (81–110)	77 (63–95.2)	<0.0001
DLCO, Mean±SD	70.2±23.1	71 (57–84)	57 (43–72.3)	<0.0001
Tender joints count, Median (Q1–Q3)	0 (0:0)	0 (0–0)	0 (0–4)	<0.0001
Swollen joints count, Median (Q1–Q3)	0 (0:0)	0 (0–0)	0 (0–0.8)	<0.0001
CRP, Median (Q1–Q3)	3 (1:7)	2.4 (1–6)	5 (2–14.6)	<0.0001
Previous IS or biologics	1798 (18.3%)	1698 (17.7%)	100 (39.4%)	<0.0001
Steroids			171 (67.3%)	
Prednisone (mg/day), Median (Q1–Q3)	0 (0:5)	0 (0–5)	5 (0–10)	<0.0001
Follow-up (months)	25.1 (18.5:38.1)	25.1 (18.9–38)	24.3 (13.3–41.4)	0.005

Previous IS (immunosuppressive drugs) include methotrexate, mycophenolate mofetil, azathioprine and cyclophosphamide, whereas biologics include anti-TNF alpha, tocilizumab and abatacept.

Values are median (IQR) or mean±SD or numbers (%) of observations.

Lung fibrosis was diagnosed on HRCT.

ACA, anticentromeres; ANA, antinuclear antibodies; DLCO, diffusing capacity of lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution CT; RNA pol III, RNA polymerases III antibodies; SSc, systemic sclerosis.

skin and lung fibrosis in SSc.<sup>5–19</sup> However, these studies were mostly limited by small samples sizes, lack of control arms, single centre designs, discrepancies in study designs and short durations of follow-up. In a previous European Scleroderma Trials and Research (EUSTAR) report on 63 patients with SSc, rituximab treatment was associated with improvement in skin fibrosis, particularly in the diffuse cutaneous form, together with a stabilisation of pulmonary functional testing.<sup>20</sup> Though rituximab demonstrated a good safety profile, but this was limited by 6 months follow-up; and only nine of these patients had restrictive SSc-ILD, thus preventing any firm conclusions.

The aim of our study was to investigate larger population with longer follow-up and including more patients with lung involvement to better assess the effect of rituximab on SSc and establish a side effect profile specific for SSc.

## METHODS

### Data source

The ongoing EUSTAR is an international, multicentre, prospective registry managed by physicians (list of authors and online supplementary appendix I) and organised centrally by its committee.<sup>20</sup>

For controls, we interrogated the EUSTAR database at the end of July 2017, providing information on 14 239 patients, from 142 participating centres, fulfilling the 2013 criteria for SSc<sup>21</sup> (Strobe Checklist in online supplementary appendix II). Patients without follow-up (n=4664) and patients with previous autologous stem cell transplantation were excluded. The structure of the database, the minimum essential data set and the inclusion criteria have been described in detail previously.<sup>22</sup>

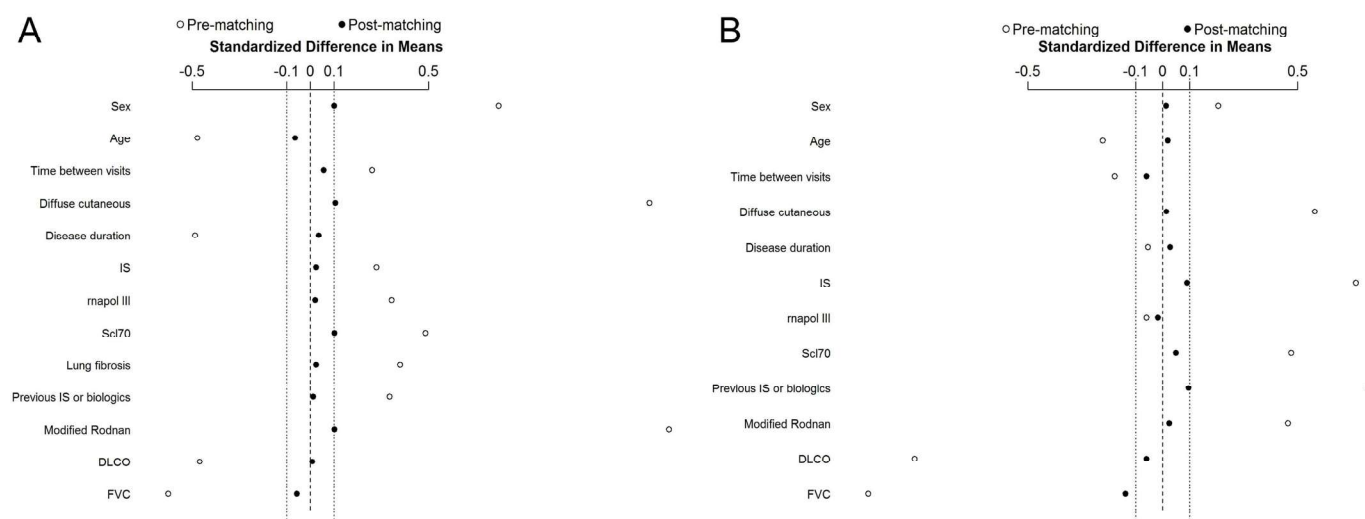
### Design and analytic sample

From March to September 2017, we queried the database and sent a call for observations in the EUSTAR network regarding rituximab use. Out of 14 239 patients recorded in the database, 254 were recruited because of rituximab use (37 centres). We sent a questionnaire to each centre with at least one rituximab-treated patient. For each patient, we collected in addition to the database content, the main indication for initiating the treatment, previous treatments received and dosage. The following baseline and follow-up information were also queried: modified Rodnan skin score (mRSS), presence and extent of lung fibrosis on CT, FVC (% predicted), DLCO (% predicted), presence of digital ulcers, overlap disease (defined by co-occurrence of another autoimmune disease),<sup>23</sup> number of tender and swollen joints (/28), DAS-28 ESR/CRP scores, joint contracture and tendon friction rubs, morning stiffness, visual analogic scale for articular pain, HAQ-DI score, presence of lower and upper gastrointestinal symptoms and CRP (mg/L). The number of infusions and dosage were recorded. Concomitant treatments and dosage were also collected.

### Outcomes

The occurrence of any adverse event (including hypogammaglobulinemia,<sup>24</sup> infection (and need for hospitalisation), scleroderma renal crisis [SRC]), serious adverse event and discontinuation because of an adverse event was collected. In case of death, we asked the relationship between the death and rituximab: (1) not related, (2) unlikely related, (3) possibly related, (4) probably related and (5) definitely related.

Outcomes were assessed at last observation under treatment (median follow-up [IQR]: 24.3 [13.3–41.4] months) responders for skin fibrosis were defined as patients with ≥5 points and 25% of improvement in mRSS.<sup>25</sup> mRSS is frequently used as a primary outcome in clinical trials, therefore we assessed rituximab effect also in patients without a ‘skin indication’ and limited the analysis to patients with a mRSS ≥10 (n=131) consistently with distribution of skin involvement in Eustar.<sup>3</sup> For lung fibrosis worsening, we used the following cut-offs: ≥10% decrease in FVC and ≥15% decrease in DLCO.<sup>26</sup> Evolution of articular involvement was assessed: tender and swollen joints counts (/28), DAS-28 ESR/CRP scores, joint contracture, tendon friction rubs, duration of morning stiffness, articular pain,



**Figure 1** Quality of the matching: Matching 1:4 for skin (A) and for lung involvement (B). Matching allows comparability of cases and controls with less than 10% of difference between all variables studied. Data, presented as mean±SEM, are from the first imputed and matched (ratio 1:4) dataset. DLCO, diffusing capacity of lung for carbon monoxide; FVC, forced vital capacity.

HAQ-DI score and CRP (mg/L). Concomitant steroid use and dosage were collected.

### Covariates

Covariates used in the model to calculate propensity score were baseline characteristics: sex, age, cutaneous form, anti-nuclear antibodies (ANA), anticentromere antibodies (ACA), anti-Scl70 antibodies, RNA polymerases III (RNA pol III) antibodies, disease duration, region (Western and Eastern Europe, North and South America, Africa and Asia), time between two visits (time between the baseline and final visit under rituximab), previous and concomitant use of immunosuppressant (IS) or biologics, mRSS, DLCO, FVC and lung fibrosis. IS drugs included methotrexate, mycophenolate mofetil, azathioprine and cyclophosphamide, whereas biologics included TNF alpha inhibitors, tocilizumab and abatacept.

### Statistical analysis

Categorical results are presented as counts and percentages. Non-normally distributed variables are presented as median with IQR and normally distributed variables as means±SD. Comparison of characteristics of treated and non-treated patients was performed by  $\chi^2$  test and Student's t-test or the Mann-Whitney test, according to the distribution of the variable. Side effects during treatment with rituximab were summarised by the frequency and percentage. To evaluate efficacy of rituximab for skin fibrosis in SSc, a propensity score approach was used. This score was estimated using a logistic regression with adjustment on regions. The analysis of responders was based on propensity score matching with a ratio 1:4 and a calliper of 0.05 SD of the logit propensity score. To account for missing data, analyses were conducted using multiple imputations by chained equations with 50 imputations obtained after 10 iterations.<sup>27</sup> The variables considered in the imputation models were all characteristics used in propensity score. For each complete imputed data set, propensity score was estimated and association between decrease in the mRSS and treatment was evaluated using conditional logistic regression. Results were aggregated by pooling estimates obtained on each imputed dataset according to Rubin's rules.<sup>28</sup> Balance in potential confounders was assessed by standardised mean differences.<sup>29</sup> Sensitivity analyses were performed using

other alternative methods of propensity score analysis: ratio 1:1 within a calliper of 0.05 SD of the logit propensity score, stratification on the quintiles of the propensity score and inverse probability of treatment weighting. The analyses of decrease in the FVC of 10%, decrease in the DLCO of 15% and tapering or stopping steroids were performed according the same methodology and same covariates as decrease in mRSS. The variation of FVC as a continuous variable was analysed by a linear mixed-effects model. Exploratory analyses of skin fibrosis improvement and lung fibrosis worsening were focused on diffuse cutaneous form and early disease (<5 years of disease duration).

Factors associated with lung improvement in patients treated with rituximab were determined using univariate and multivariable logistic regression analyses with multiple imputations. Age, disease duration and DLCO were dichotomised according to their median or first quartile for FVC. All variables with  $p < 0.1$  in univariate were included in multivariate analysis with adjustment on regions. The lack of significant interaction between covariates was checked.

All tests were two-sided at a 0.05 significance level. Analyses were carried out using R statistical software V3.3.2.

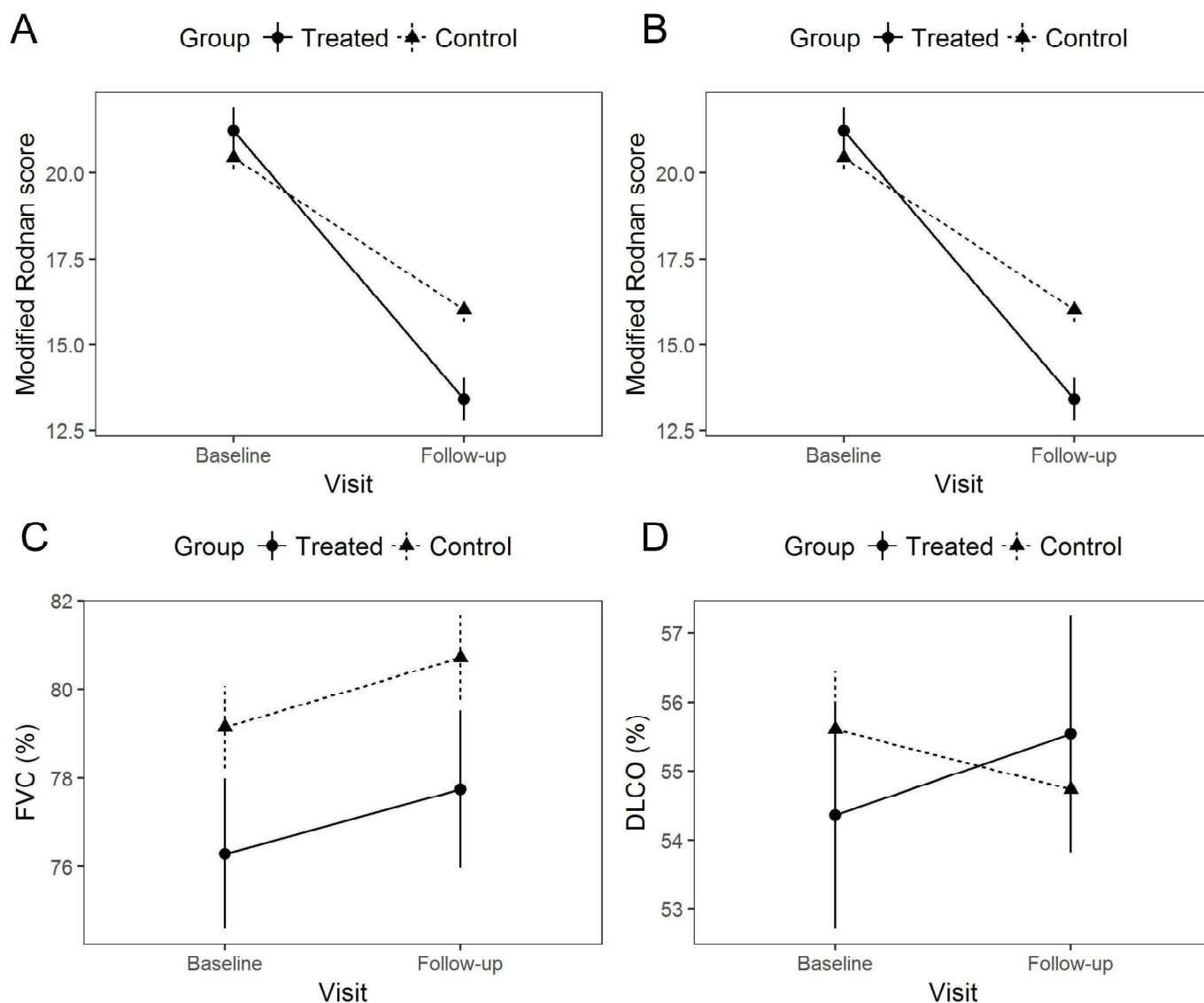
## RESULTS

### Baseline cohort characteristics

From March to September 2017, out of 14 239 patients recorded in the database, 254 were recruited because of rituximab use (37 centres): 71% of female, median age: 51 years, 64% of diffuse cutaneous form and 71% displayed lung fibrosis. Median extent of lung fibrosis on CT was 20%.<sup>10–29</sup> Anti-Scl70 and ACA antibodies were detected in 53% and 11% of the patients, respectively. An overlap syndrome was diagnosed in 26% of the cohort, consistently with previous reports in SSc.<sup>23</sup> Previous treatments included DMARDs in 66/252 (32.5%), biologics in 24/252 (9.5%), cyclophosphamide in 23/252 (9.1%). Further details are provided in table 1 and online supplementary table I and II.

The leading indication for rituximab was lung involvement in 146/254 (58%) cases, skin in 81/254 (32%) cases and in 108/254 (42%) musculoskeletal involvement (flowchart in online supplementary figure 1). Concomitantly to rituximab, patients received steroids for 67.3% (median dose: 10 mg/day [IQR: 5–10]). Total 136 (53.7%) were treated in parallel with DMARDs (methotrexate





**Figure 2** Evolution of skin and lung fibrosis among propensity score-matched patients treated and untreated with rituximab. (A,B) evolution of modified Rodnan skin score between baseline and last visit (under treatment) in patients and propensity score-matched patients from EUSTAR: (A) in patients with skin indication for the treatment; (B) in patients with modified Rodnan skin score at baseline  $\geq 10$ ; (C) evolution of forced vital capacity between baseline and last visit (under treatment) in patients with a lung indication for the treatment and propensity score-matched patients from EUSTAR; (D) evolution of DLCO between baseline and last visit (under treatment) in patients with a lung indication for the treatment and propensity score-matched patients from EUSTAR. Data, presented as mean  $\pm$  SEM, are from the first imputed and matched (ratio 1:4) dataset. DLCO, diffusing capacity of lung for carbon monoxide; EUSTAR, European Scleroderma Trials and Research; FVC, forced vital capacity.

for 75, mycophenolate mofetil for 45, azathioprine for 14 and cyclophosphamide for 6).

### Safety analysis

After a median follow-up of 2 years, nearly 70% of patients (175/254) had no reported side effect, 43 (17%) had minor side effects and 36 (14%) were considered as severe by investigating centre. This led to discontinuation of the treatment in 24 patients (9%). During follow-up, six deaths were recorded: four unrelated to the treatment (two sudden deaths, one sepsis attributed to decubitus ulcers, one heart failure) and two possibly related (two respiratory insufficiencies in the context of lung carcinoma). In all, five cancers were reported during the follow-up. There was no association between occurrence of infections and previous or concomitant treatment with IS or hypogammaglobulinemia. Further details are provided in online supplementary table III.

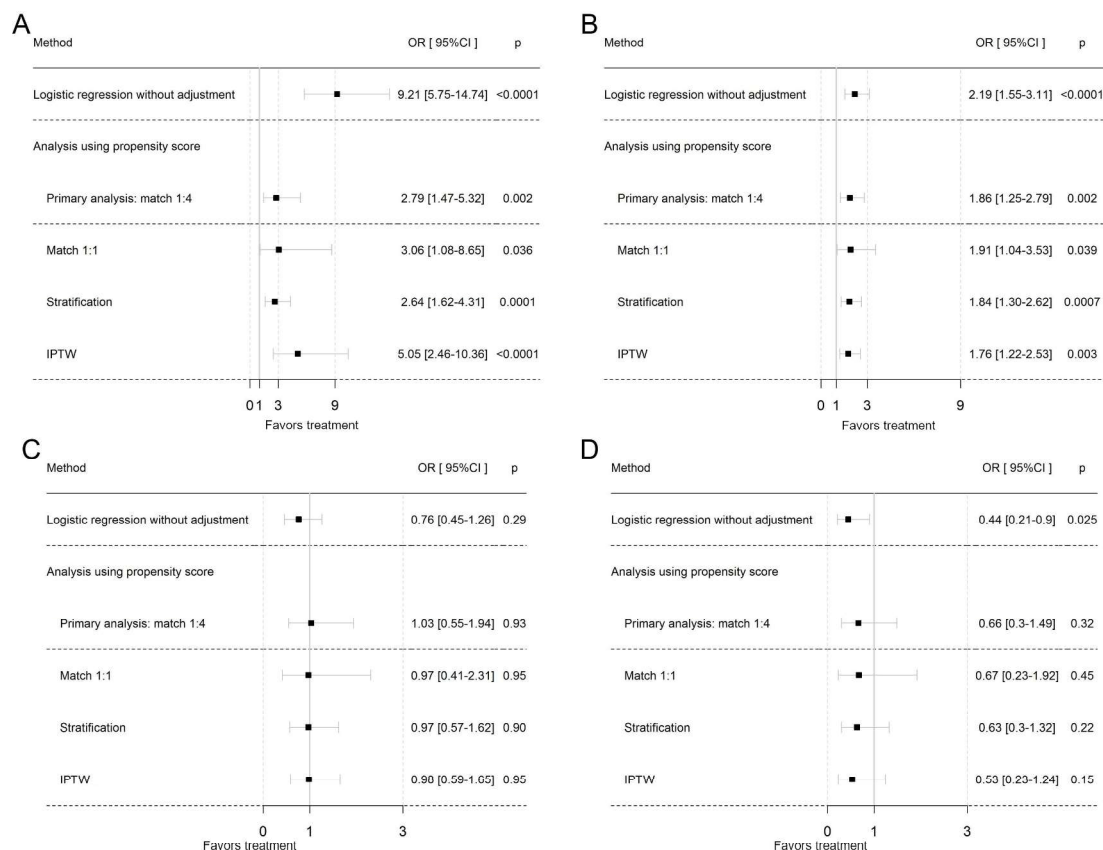
### Efficacy

Among the 14 239 patients who underwent  $\geq 1$  visit, 9575 had  $\geq 1$  follow-up (table 1). Comparison of characteristics between patients with and without follow-up showed minor differences (online supplementary table IV). Matching for skin and lung allowed comparability of cases and controls (figure 1).

### Skin fibrosis

The mRSS of patients treated for skin fibrosis decreased from mean  $\pm$  SD 22.1 ( $\pm 9.3$ ) to 14.1 ( $\pm 8.4$ ) in treated patients ( $n=74$ ) vs 21.1 ( $\pm 10.5$ ) to 16.2 ( $\pm 10.3$ ) ( $p<0.0001$ ) in untreated patients matched according to propensity score ( $n=281$ ) (figure 2A). In patients with a mRSS  $\geq 10$  ( $n=131$ ), the mRSS decreased from 21.2 ( $\pm 8.8$ ) to 13.4 ( $\pm 7.9$ ) vs 20.4 ( $\pm 8.2$ ) to 16.0 ( $\pm 8.2$ ) in controls ( $p<0.0001$ ) (figure 2B).





**Figure 3** Adjusted OR for skin fibrosis improvement and lung fibrosis worsening among propensity score-matched patients treated or untreated with rituximab. The analyses of decrease in the modified Rodnan score of 5 points and 25% and decrease in the FVC of 10% and decrease in the DLCO of 15% were based on propensity score matching with a ratio 1:4. For each complete imputed data set, propensity score was estimated and association between decrease in the modified Rodnan score/ in FVC and in DLCO, respectively, and treatment was evaluated using conditional logistic regression. We used other matching method with ratio 1:1 within a calliper of 0.05 SD of the logistic propensity score, stratification on the quintiles of the propensity score and IPTW. Decrease in the modified Rodnan score of 5 points and 25% in patients with (A) skin indication; (B) modified Rodnan skin score >10 at baseline; (C) decrease in the FVC of 10% in patients with lung indication for the treatment; (D) decrease in the DLCO of 15% in patients with lung indication for the treatment. DLCO, diffusing capacity of lung for carbon monoxide; FVC, forced vital capacity; IPTW, inverse probability of treatment weighting.

Rituximab-treated patients had a higher probability of improvement in dermal fibrosis as compared with propensity score matched-controls (22.7 vs 14.03 events per 100 person-years; OR: 2.79 [1.47–5.32];  $p=0.002$ ). This was confirmed in sensitivity analyses (figure 3A).

Same results were observed for patients with a mRSS  $\geq 10$  (OR: 1.86 [1.25–2.79];  $p=0.002$ ) (figure 3B) as well as in subgroup analyses (diffuse and early forms; online supplementary figure 2A,B).

### Lung fibrosis

In lung treated patients ( $n=146$ ), FVC remained stable during the follow-up (76.3 ( $\pm 19.3$ ) to 77.7 ( $\pm 20.2$ )), similarly to controls (79.1 ( $\pm 20.6$ ) to 80.7 ( $\pm 21.1$ )) ( $n=497$ ) (figure 2C). DLCO also remained stable both in treated patients (54.4 [ $\pm 18.8$ ] to 55.5 [ $\pm 19.5$ ]) and in controls (55.6 [ $\pm 18.7$ ] to 54.7 [ $\pm 20.2$ ]) (figure 2D). Extent of fibrosis remained stable (20.0 [ $\pm 2.1$ ] to 20.0 [ $\pm 2.5$ ]) ( $n$  available=60). Treated patients did not have significantly different rates of decrease in FVC >10% (6.5 vs 6.6 events per 100 person-years; OR: 1.03 [0.55–1.94];  $p=0.93$ ) nor in DLCO decrease (figure 3C,D), which was confirmed in all secondary analyses (online supplementary figure 2 C, D and 3). In univariate cox models, lung function had a trend to improve

**Table 2** Factors associated with lung improvement in patients treated with rituximab

	Univariate model		Multivariate model	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex	0.84 (0.34 to 2.06)	0.71		
Age >55 years	0.9 (0.42 to 1.9)	0.78		
ANA	1.07 (0.07 to 16.77)	0.96		
Anti-Scl70	0.84 (0.41 to 1.72)	0.63		
ACA	0.68 (0.18 to 2.64)	0.58		
RNA pol III antibodies	4 (0.45 to 35.38)	0.22		
Diffuse cutaneous form	1.57 (0.78 to 3.18)	0.21		
Disease duration <5 years	2.02 (0.98 to 4.17)	0.058	1.94 (0.94 to 4.03)	0.077
Previous IS or biologics	0.95 (0.47 to 1.93)	0.89		
DLCO <70%	1.68 (0.68 to 4.2)	0.27		
FVC <80%	2.05 (0.96 to 4.38)	0.066	1.96 (0.91 to 4.23)	0.089

Variables identified in univariate analysis with  $p<0.1$  were tested in multivariate analysis adjusted on region. Lung fibrosis improvement was defined by increase in forced vital capacity during the follow-up. Previous IS (immunosuppressive drugs) include methotrexate, mycophenolate mofetil, azathioprine and cyclophosphamide, whereas biologics include anti-TNF alpha, tocilizumab and abatacept. Cut-off values to define DLCO and FVC were defined according to distribution. ACA, anticentromeres; ANA, antinuclear antibodies; DLCO, diffusing capacity of lung for carbon monoxide; FVC, forced vital capacity; RNA pol III, RNA polymerases III antibodies.

**Table 3** Evolution of musculoskeletal involvement during treatment with rituximab

Variables	Baseline	Last follow-up	P value
Tender joints count (/28) (n=85)	7.6±8.6	2.4±4.7	<0.0001
Swollen joints count (/28) (n=81)	3.1±5.2	0.7±2.2	<0.0001
DAS28 ESR (n=25)	5.40 (3.99–6.22)	3.29 (2.02–4.24)	<0.0001
DAS28 CRP (n=29)	4.68 (3.55–5.88)	2.60 (1.59–3.87)	<0.0001
Joint contracture, n (%)	44/84 (52.4%)	37/84 (44%)	0.35
Tendon friction rubs, n (%)	20/76 (26.3%)	8/76 (10.5%)	0.021
Morning stiffness (min) (n=47)	78.9±72.1	32.1±46.3	<0.0001
Visual analogic scale for articular pain (n=33)	70(50–80)	35 (20–52.5)	<0.0001
HAQ-DI (n=12)	1.31 (1.12–1.92)	1.20 (0.45–1.81)	0.10

Values are median (IQR) or mean±SD numbers (%) of observations. P comparing baseline and last follow-up data using Wilcoxon-test or paired t-test for quantitative variables and McNemar or paired  $\chi^2$ -test for proportions, according to distributions.

DAS, disease activity score; HAQ, Health Assessment Questionnaire.

in early disease and in patients with FVC <80%, which was not confirmed in multivariate analysis (table 2).

In secondary analyses, the concomitant use of mycophenolate to rituximab (n=37 with lung indication) showed a trend for better outcomes (delta FVC with controls: 5.22 [0.83–9.62]; p=0.019 vs delta FVC: 3 [0.66–5.35]; p=0.012 in patients receiving rituximab alone). Furthermore, 9/31 (29%) had an increase >10% in FVC. The difference with patients treated by rituximab alone was not statistically significant (delta: 2.98 [–2.12 to 8.09]; p=0.25). No adjusted analysis could be performed due to the small sample size. DLCO did not change significantly in this subgroup.

There was no difference for skin and lung outcomes according to rheumatoid factor, anti-CCP antibodies or smoking status (online supplementary table V).

### Musculoskeletal involvement

All articular parameters, but two (joint contractures and HAQ-DI) significantly decreased with rituximab (table 3). No controlled analysis could be performed because of a high proportion of missing data (eg, 81% for tender and swollen joint counts in control group).

### Inflammation and cotreatments

CRP levels decreased during the treatment from 11.5 (±1.0) to 6.7 (±0.7) mg/L (p<0.0001). About one quarter of the patients treated with steroids at baseline could stop steroids and steroids dosage decreased from 9.5 (±0.5) mg/day to 7.0 (±0.3) mg/day (p<0.0001) in the 130 remaining patients. Patients treated with rituximab were more likely to decrease or stop steroids in controlled analyses (25.3 vs 18.0 events per 100 person-years; OR: 2.34 [1.56–3.53], p<0.0001) (online supplementary figure 3B).

### Dose-effect

Rituximab regimens were variable according to centres: for each infusion: dose of 1000 mg for 203 patients, 500 mg for 27 375 mg/m<sup>2</sup> for four patients. We observed a dose-effect with a better effect on skin involvement for a total dosage higher than 4000 mg (online supplementary table VI).

## DISCUSSION

In a large cohort of carefully matched patients treated with rituximab for skin, or lung involvement, rituximab was associated with a good safety profile. The outcomes showed a high efficacy on skin fibrosis, but not on lung. Patients treated with rituximab were 2-fold more likely to stop or decrease steroids.

Following previous promising studies suggesting an amelioration of lung involvement, the raw analyses after propensity score matching clearly show no difference between treated and not treated patients and overall a large proportion of non-progressive patients.<sup>7 10 12 14–16 19</sup> Therefore, the results should be interpreted as the lack of effects of rituximab in this sample of patients with SSc. Nevertheless, one may advocate that the lung trajectory of rituximab-treated patients may differ from the one of untreated patients. Indeed, if the treating physician decided to offer rituximab therapy, then it is most of the time because of lung activity and severity, which are identified as poor predictive factors. These biases (selection biases, persistence of confounders despite the matching) are limitations to our study inherent to its observational design.<sup>30</sup> Therefore, the potential stabilisation of ILD following rituximab therapy has to be addressed in the future but only a randomised trial will provide robust answer.

Some previous small uncontrolled or unadjusted series have suggested some efficacy of rituximab on cutaneous involvement in SSc.<sup>5–13 19 29</sup> However, evaluation of drug efficacy in SSc might be difficult because of spontaneous improvement in skin fibrosis during the first years, highlighting the need of control group. In our study, patients treated with rituximab were twofold more likely to improve skin fibrosis in all matched analyses, sensitivity analyses and subgroup approaches. The mRSS is a validated surrogate marker<sup>31–34</sup> frequently used as an outcome measure in clinical trials.<sup>36</sup> Indeed, worsening in mRSS is associated with higher mortality, and worsening of internal organ involvement.<sup>32 37 38</sup> Conversely, improvement of the skin score is predictive of favourable outcomes, including better survival.<sup>38</sup> Therefore, improvement in mRSS observed in rituximab-treated patients might indicate a better prognosis for these patients. Consistently, CRP levels, a marker of disease activity and severity,<sup>39</sup> decreased following rituximab treatment.

One may also highlight the different trajectory between skin and lung outcomes in our sample. It must be pointed out that this has already been observed and by example the recent tocilizumab trial showed some benefit on lung whereas skin was less influenced.<sup>40</sup> This highlights the difficulties to design clinical trials in SSc regarding both the choice of the primary outcome measure and also the patients selection criteria.<sup>41</sup> A clue for the future to get a better impact on SSc outcomes might be combination therapy which seems to be more effective on lung involvement in our study and has shown clear benefit for treatment with rituximab in other diseases.<sup>42</sup>

Surprisingly, few patients have been previously treated with cyclophosphamide.<sup>43</sup> This choice of using first rituximab might be driven by the need of concomitant treatment for musculoskeletal involvement in almost half of the cohort (online supplementary figure 1). Furthermore, common use of rituximab in other diseases like RA but also connective tissue diseases and vasculitis has given rheumatologists confidence in the management and in the safety of rituximab. Finally, the use of cyclophosphamide and mycophenolate mofetil could be limited by safety data.<sup>44</sup>

Interestingly, rituximab use doubled the probability of discontinuing or decreasing steroids. This is of major importance, since steroids cumulative dose increases the risk of subclinical/clinical atherosclerosis<sup>45</sup> and SRC<sup>46</sup> in SSc.

In our study, safety profile of rituximab was acceptable with in particular no progressive multifocal leukoencephalopathy or related-death. Furthermore, despite the use of intravenous steroids, only two SRCs were reported.

The main strengths of our study are (1) large sample size, (2) availability of well-matched controls, (3) standardised collection of data according to a questionnaire and (4) broad spectrum of patients included corresponding to 'real-life' patients and allowing subgroup analyses (diffuse forms, early SSc). Using extensive matching methods, we accounted for many potential cofounders of the associations between rituximab use and outcomes. We also performed several sensitivity and subgroups analyses, which were highly consistent.

Our study has limitations: first, rituximab regimens were variable according to centres. We analysed effect of the dose received and observed a dose-effect for a dosage higher than 4000 mg for skin involvement, suggesting that a dosage of 1000 mg should be used for the first infusions. This is an open label study, which can bias study results towards beneficial effect for the test medication (if the examiner anticipates beneficial effect of the treatment) in an outcome measure that is less objective (ie, mRSS) than FVC, which is more objective and less dependent on the examiner's bias. There are also limitations inherent to the observational design of this study. However, the importance of disease registries, like EUSTAR, in rare diseases was recently highlighted, as they allowed collecting detailed case studies with standardised information and improving understanding of SSc and its treatment.<sup>47</sup> Furthermore, the study reflects clinical practice in this orphaned heterogeneous disease. The duration of exposure to rituximab was relatively short (2 years), which limited precision for safety analyses. We could also not assess safety in control group (no data available) or outcomes that occurred after withdrawal of rituximab. Finally, despite highly matched cohorts across a wide range of characteristics, we cannot rule out residual confounders.

#### Author affiliations

- <sup>1</sup>Rheumatology A Department, Paris Descartes University, Cochin Hospital, Paris, France
- <sup>2</sup>Unit of Clinical Research, Paris Seine Saint Denis University, Bobigny, France
- <sup>3</sup>Center of Experimental Rheumatology, Zurich, Switzerland
- <sup>4</sup>Rheumatology and Internal Medicine, Ghent University Hospital, Ghent, Belgium
- <sup>5</sup>Unit for Molecular Immunology and Inflammation, VIB Inflammation Research Center (IRC), Ghent, Belgium
- <sup>6</sup>Department of Internal Medicine, University of Florence, Firenze, Italy
- <sup>7</sup>Rheumatology, Hospital Peset, Valencia, Spain
- <sup>8</sup>Rheumatology Department, Bordeaux University Hospital, Bordeaux, France
- <sup>9</sup>B. Shine Department of Rheumatology, Rambam Health Care Campus and Technion, Haifa, Israel
- <sup>10</sup>Interdisciplinary Department of Medicine-Rheumatology Unit, Policlinico, University of Bari, Bari, Italy
- <sup>11</sup>Clinic of Nephrology, Internal and Occupational Diseases, First Moscow State Medical University, Moscow, Russian Federation
- <sup>12</sup>Internal Medicine, CHU south hospital, RENNES, France
- <sup>13</sup>Rheumatology, Charit University Hospital, Berlin, Germany
- <sup>14</sup>Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, Barcelona, Spain
- <sup>15</sup>Rheumatology and Clinical Immunology Service, Spedali Civili di Brescia, Brescia, Italy
- <sup>16</sup>Rheumatology Department, Second University of Naples, Naples, Italy
- <sup>17</sup>Laboratory of Tissue Homeostasis and Disease, Skeletal Biology and Engineering Research Center, Department of Development and Regeneration, KU Leuven, Leuven, Belgium
- <sup>18</sup>Univ. Lille, Inserm, CHU Lille, U995 - LIRIC - Lille Inflammation Research International Center, Service de Médecine Interne, Hôpital Claude Huriez, Centre de Référence pour la Sclérodémie Systémique, FHU IMMInENT, F-59000, Lille, France
- <sup>19</sup>Division of Rheumatology Department of Medicine III, Technical University of Dresden, Dresden, Germany
- <sup>20</sup>Institute of Rheumatology, Russian Academy of Medical Science, Moscow, Russian Federation

- <sup>21</sup>Internal Medicine, Rheumatology, Immunology and Nephrology, Asklepios Clinic Altona, Hamburg, Germany
- <sup>22</sup>Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
- <sup>23</sup>Department of Internal Medicine III, University of Erlangen, Erlangen, Germany
- <sup>24</sup>Department of Dermatology, University of Cologne, Cologne, Germany
- <sup>25</sup>Department of Rheumatology, Rikshospitalet University Hospital, Oslo, Norway
- <sup>26</sup>Clinical Medicine and Therapy, Sapienza University of Rome, Rome, Italy
- <sup>27</sup>Rutgers-Robert Wood Johnson Medical School Scleroderma Program, New Brunswick, New Jersey, USA
- <sup>28</sup>Dipartimento di Medicina, Ospedale San Gerardo, Monza, Italy
- <sup>29</sup>Rheumatology 2 Department, Universitatea de Medicina si Farmacie Gr T Popa Iasi Facultatea de Medicina, Iasi, Romania
- <sup>30</sup>Center for Sclerotic Systemic -Dipartimento di Medicina Clinica, Università LaSapienza, Rome, Italy
- <sup>31</sup>Internal Medicine and Rheumatology Department, Cantacuzino Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
- <sup>32</sup>Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan
- <sup>33</sup>University Medical Center Comprehensive Pulmonary Hypertension Center (UMC-CPHC); Tulane University Lung Center Tulane, New Orleans Scleroderma and Sarcoidosis Patient Care and Research Center New Orleans, New Orleans, Louisiana, USA
- <sup>34</sup>Division of Immunology and Allergy, HCUGE, Geneva, Switzerland
- <sup>35</sup>Department of Rheumatology, Lund University, Lund, Sweden
- <sup>36</sup>University Hospital of Copenhagen, Department of Dermatology, Hospital Bispebjerg, Copenhagen, Denmark
- <sup>37</sup>Department of Rheumatology, University of Marmara, Istanbul, Turkey
- <sup>38</sup>Clinica Reumatologie, Cluj-Napoca, Romania
- <sup>39</sup>Rheumatology Unit, University of Verona, Verona, Italy
- <sup>40</sup>URC CRC, Hôpital Avicenne, Bobigny, France
- <sup>41</sup>Rheumatology A Department, Cochin Hospital, APHP, Paris Descartes University, Paris, France

**Collaborators** EUSTAR coworkers, Serena Guiducci; Ulrich A. Walker; Diego Kyburz; Giovanni Lapadula; Britta Maurer; Suzana Jordan; Rucsandra Dobrota; Radim Becvar; Stanislaw Sierakowski; Otylia Kowal Bielecka; Alberto Sulli; Maurizio Cutolo; Giovanna Cuomo; Ileana Nicoara; André Kahan; Panayiotis G. Vlachoyiannopoulos; Carlo Maurizio Montecucco; Roberto Caporali; Jiri Stork; Murat Inanc; Patricia E. Carreira; Srdan Novak; László Cziráj; Cecilia Varju; Eugene J. Kucharz; Anna Kotulska; Magdalena Kopec-Medrek; Malgorzata Widuchowska; Franco Cozzi; Blaz Rozman; Carmel Mallia; Bernard Coleiro; Armando Gabrielli; Dominique Farge; Chen Wu; Zora Marjanovic; Helene Faivre; Darin Hij; Roza Dhamadi; Frank Wollheim; Agneta Scheja; Dirk M Wuttge; Kristofer Andréasson; Duska Martinovic; Alexandra Balbir-Gurman; F. Trotta; Andrea Lo Monaco; Raffaele Pellerito; Ospedale Mauriziano; Paola Caramaschi; Jadranka Morovic-Vergles; Carol Black; Christopher Denton; Nemanja Damjanovic; Jörg Henes; Vera Ortiz Santamaria; Stefan Inmann; Dorota Krasowska; Matthias; Paul Hasler; Harald Burkhardt; Andrea Himsel; Gianluigi Bajocchi; José Antonio Pereira Da Silva; Maria João Salvador; Bojana Stamenkovic; Aleksandra Stankovic; Carlo Francesco Selmi; Maria De Santis; Mohammed Tikly; Lev N. Denisov; Ariane Herrick; Ulf Müller-Ladner; Marc Frerix; Ingo Tarner; Raffaella Scorza; Francesco Puppo; Merete Engelhart; Gitte Strauss; Henrik Nielsen; Kirsten Damgaard; Gabriela Szűcs; Antonio Zea Mendoza; Carlos de la Puente; Sifuentes Giraldo WA; Øyvind Midtvedt; Silje Reiser; Thorhild Garen; David Launay; Guido Valesini; Ruxandra Maria Ionescu; Laura Groseanu; Daniela Opris; Roxana Sfrent Cornateanu; Razvan Ionitescu; Ana Maria Gherge; Alina Soare; Marilena Gorga; Mihai Bojinca; Mihaela Milicescu; Cord Sunderkötter; Annegret Kuhn; Nora Sandorfi; Georg Schett; Christian Beyer; Pierluigi Meroni; Francesca Ingegnoli; Luc Mouthon; Filip De Keyser; Karin Melsens; Francesco P. Cantatore; Line Iversen; Carlos Alberto von Mühlen; Jussara Marilu Bohn; Lilian Scussel Lonzetti; Kilian Eyerich; Rüdiger Hein; Elisabeth Knott; Piotr Wiland; Magdalena Szmyrka-Kaczmarek; Renata Sokolik; Ewa Morgiel; Marta Madej; Frédéric A. Houssiau; Brigitte Krummel-Lorenz; Petra Saar; Martin Aringer; Claudia Günther; Rene Westhovens; Jan Lenaerts; Branimir Anic; Marko Baresic; Miroslav Mayer; Maria Üprus; Kati Otsa; Brigitte Granel; Carolina de Souza Müller; Sebastião C. Radominski; Valderilio F. Azevedo; Sergio Jimenez; Joanna Busquets; Svetlana Agachi; Liliana Groppa; Lealea Chiaburu; Eugen Russo; Sergei Popa; Thierry Zenone; Margarita Pilecky; Alessandro Mathieu; Alessandra Vacca; Percival D. Sampaio-Barros; Natalino H. Yoshinari; Roberta G. Marangoni; Patricia Martin; Luiza Fuocco; Simon Stebbings; John Highton; Peter Chapman; John O'Donnell; Lisa Stamp; Alan Doube; Kamal Solanki; Douglas Veale; Marie O'Rourke; Esthela Loyo; Mengtao Li; Walid Ahmed Abdel Atty Mohamed; Antonio Amoroso; Antonietta Gigante; Fahrettin Oksel; Figen Yargucu; Cristina-Mihaela Tanaseanu; Monica Popescu; Alina Dumitrascu; Isabela Tiglea; Rosario Foti; Rodica Chiriac; Daniel Furst; Peter Villiger; Sabine Adler; Jacob van Laar; Cristiane Kayser; Nihal Fathi; Manal Hassanien; Paloma García de la Peña Lefebvre; Silvia Rodriguez Rubio; Marta Valero Exposito; Emmanuel Chatelus; Jean Sibilla; Jacques Eric Gottenberg; Hélène Chiffot; Ira Litinsky; Paul Emery; Maya Buch; Francesco Del Gaudio; Algirdas Venalis; Irena Butrimiene; Paulius Venalis; Rita Rugiene; Diana Karpec; Joseph A. Lasky; Vanesa Cosentino; Eduardo Kerzberg; Fabiana Montoya;



Washington Bianchi; Sueli Carneiro; Giselle Baptista Marette; Dante Valdetaro Bianchi; Massimiliano Limonta; Antonio Luca Brucato; Elide Lupi; Itzhak Rosner; Michael Rozenbaum; Gleb Slobodin; Nina Boulman; Doron Rimar; Maura Couto; Sarah Kahl; Fei Chen; Deborah McCloskey; Halina Malveaux; François Spertini; Camillo Ribí; Guillaume Buss; Thierry Martin; Aurélien Guffroy; Vincent Poindron; Fatima Chotchaeva; Nikolay A. Mukhin; Sergey Moiseev.

**Contributors** ME, MB and YA formulated the study hypotheses and contributed to its design, literature search, composition of the tables and figures and redaction of the first draft and subsequent iterations of the manuscript. ME, MB, CB-Q and YA: analysis and interpretation of data. ME and MB performed the statistical analyses. OD, VS, MM-C, JJAS, M-ET, YB-M, FI, PIN, AL, ES, IC, PA, SV, EDL, EH, AE, LA, MK, FJL-L, JHWD, NH, A-MH-V, VR, VMH, MRP, CA, ER, CM, MK, LAS, CC, RH, SU, SY, SR, CC and YA conceived and launched the EUSTAR database, collected data in their respective countries and offered critical comments regarding the manuscript. All authors have finally approved the submitted version to be published.

**Funding** EUSTAR database is supported by the World Scleroderma Foundation.

**Competing interests** OD has consultancy relationship with Actelion, Bayer, BiogenIdec, Boehringer Ingelheim, ChemomAb, espeRare foundation, Genentech/Roche, GSK, Inventiva, Italfarmaco, Lilly, medac, MedImmune, Mitsubishi Tanabe Pharma, Pharmacyclis, Novartis, Pfizer, Sanofi, Sinova and UCB in the area of potential treatments of scleroderma and its complications. OD has received research funding from Actelion, Bayer, Boehringer Ingelheim, Mitsubishi Tanabe Pharma and Roche in the area of potential treatments of scleroderma and its complications. In addition, OD has a patent mir-29 for the treatment of systemic sclerosis licensed. M-ET has received consulting fees, speaking fees or honoraria from Abbvie, BMS, Lilly, Medac, MSD, Pfizer, Roche and UCB. PA has received travel expenses from Roche (<2500€). SV received speaking fees by Pfizer, Abbvie, Bristol-Myers Squibb, consultant fee from Thermofischer and Boehringer-Ingelheim Italia and Educational support from Pfizer, Roche, BMS. EH has received speaker fees and/or honoraria for consultations from Roche, less than 10 000€. NH received lecture fees from Actelion Pharmaceuticals, Pfizer, Roche and grant support from Actelion and Bayer Pharmaceuticals. CM has/had consultancy relationship and/or has received honoraria from Actelion, Abbvie, Roche and Geneva Romfarm in the area of systemic sclerosis and its complications. CC has received travel grants from Roche. YA has/had consultancy relationship and/or has received grants from Actelion, Bayer, BMS, Boehringer-Ingelheim, Inventiva, Roche, Sanofi-Aventis in the area of systemic sclerosis.

**Patient consent for publication** Obtained.

**Ethics approval** Each participating centre obtained approval of the local ethics committee and all registered patients granted their informed consent.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional unpublished data from the study are available.

## REFERENCES

- Varga J, Trojanowska M, Kuwana M. Pathogenesis of systemic sclerosis: recent insights of molecular and cellular mechanisms and therapeutic opportunities. *J Scleroderma Relat Disord* 2017;2:137–52.
- Elhai M, Meune C, Avouac J, et al. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. *Rheumatol Oxf Engl* 2012;51:1017–26.
- Elhai M, Meune C, Boubaya M, et al. Mapping and predicting mortality from systemic sclerosis. *Ann Rheum Dis* 2017;76:1897–905.
- Volkman ER, Tashkin DP. Treatment of systemic Sclerosis-related interstitial lung disease: a review of existing and emerging therapies. *Annals ATS* 2016;13:2045–56.
- Thiebaud M, Launay D, Rivière S, et al. Efficacy and safety of rituximab in systemic sclerosis: French retrospective study and literature review. *Autoimmunity Reviews* 2018;17:582–7.
- Vilela VS, Marette GB, Gama LM da S, et al. Rituximab for the therapy of systemic sclerosis: a series of 10 cases in a single center. *Rev Bras Reumatol* 2016;56:458–63.
- 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;44:428–36.
- Smith V, Van Praet JT, Vandooren B, et al. Rituximab in diffuse cutaneous systemic sclerosis: an open-label clinical and histopathological study. *Ann Rheum Dis* 2010;69:193–7.
- Bosello S, De Santis M, Lama G, et al. B cell depletion in diffuse progressive systemic sclerosis: safety, skin score modification and IL-6 modulation in an up to thirty-six months follow-up open-label trial. *Arthritis Res Ther* 2010;12.
- Daoussis D, Tsamandas AC, Liossis S-NC, et al. B-cell depletion therapy in patients with diffuse systemic sclerosis associates with a significant decrease in PDGFR expression and activation in spindle-like cells in the skin. *Arthritis Res Ther* 2012;14.
- Smith V, Piette Y, van Praet JT, et al. Two-year results of an open pilot study of a 2-treatment course with rituximab in patients with early systemic sclerosis with diffuse skin involvement. *J Rheumatol* 2013;40:52–7.
- 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;43:257–8.
- Smith V, Pizzorni C, Riccieri V, et al. Stabilization of microcirculation in patients with early systemic sclerosis with diffuse skin involvement following rituximab treatment: an open-label study. *J Rheumatol* 2016;43:995–6.
- Daoussis D, Liossis S-NC, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatol Oxf Engl* 2010;49:271–80.
- 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;46:625–31.
- Lafyatis R, Kissin E, York M, et al. B cell depletion with rituximab in patients with diffuse cutaneous systemic sclerosis. *Arthritis Rheum* 2009;60:578–83.
- Giuggioli D, Lometti F, Colaci M, et al. Rituximab in the treatment of patients with systemic sclerosis. our experience and review of the literature. *Autoimmun Rev* 2015;14:1072–8.
- Melsen 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;73:119–25.
- 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. *Rheumatol Oxf Engl* 2018;57:2106–13.
- Jordan S, Distler JHW, 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;74:1188–94.
- van den Hoogen F, Khanna D, Fransen J, et al. Classification criteria for systemic sclerosis: an American College of rheumatology/European League against rheumatism collaborative initiative. *Ann Rheum Dis* 2013;2013:1747–55.
- Meier FMP, Frommer KW, Disner R, et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR scleroderma trials and research Group database. *Ann Rheum Dis* 2012;71:1355–60.
- Elhai M, Avouac J, Kahan A, et al. Systemic sclerosis at the crossroad of polyautoimmunity. *Autoimmun Rev* 2013;12:1052–7.
- Boletto G, Avouac J, Wipff J, et al. Predictors of hypogammaglobulinemia during rituximab maintenance therapy in rheumatoid arthritis: a 12-year longitudinal Multi-Center Study. *Semin Arthritis Rheum*. [Epub ahead of print: 21 Feb 2018].
- Maurer B, Graf N, Michel BA, et al. Prediction of worsening of skin fibrosis in patients with diffuse cutaneous systemic sclerosis using the EUSTAR database. *Ann Rheum Dis* 2015;74:1124–31.
- Le Gouellec N, Duhamel A, Perez T, et al. Predictors of lung function test severity and outcome in systemic sclerosis-associated interstitial lung disease. *Plos One* 2017;12.
- White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30:377–99.
- Mitra R, Reiter JP. A comparison of two methods of estimating propensity scores after multiple imputation. *Stat Methods Med Res* 2016;25:188–204.
- Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar Behav Res* 2011;46:399–424.
- Wang MTM, Bolland MJ, Grey A. Reporting of limitations of observational research. *JAMA Intern Med* 2015;175:1571–2.
- Moazedi-Fuerst FC, Kielhauser SM, Hermann J, et al. Decrease in autoantibody titres during long-term treatment of scleroderma with rituximab: a promising surveillance marker of therapy? *Scand J Rheumatol* 2015;44:519–20.
- Steen VD, Medsger TA. Improvement in skin thickening in systemic sclerosis associated with improved survival. *Arthritis Rheum* 2001;44:2828–35.
- Kumánovics G, Péntek M, Bae S, et al. Assessment of skin involvement in systemic sclerosis. *Rheumatol Oxf Engl* 2017;56(suppl\_5):v53–66.
- Hachulla E, Carpentier P, Gressin V, et al. Risk factors for death and the 3-year survival of patients with systemic sclerosis: the French ItinerAIR-Scleroderme study. *Rheumatol Oxf Engl* 2009;48:304–8.
- Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR scleroderma trials and research (EUSTAR) database. *Ann Rheum Dis* 2010;69:1809–15.
- Khanna D, Furst DE, Clements PJ, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. *J Scleroderma Relat Disord* 2017;2:11–18.
- Dobrota R, Maurer B, Graf N, et al. Prediction of improvement in skin fibrosis in diffuse cutaneous systemic sclerosis: a EUSTAR analysis. *Ann Rheum Dis* 2016;75:1743–8.
- Steen VD, Medsger TA, Rodnan GP. D-penicillamine therapy in progressive systemic sclerosis (scleroderma): a retrospective analysis. *Ann Intern Med* 1982;97:652–9.
- Muangchant C, Pope JE. The significance of interleukin-6 and C-reactive protein in systemic sclerosis: a systematic literature review. *Clin Exp Rheumatol* 2013;31:122–34.

- 40 ACR Meet. Efficacy and safety of tocilizumab for the treatment of systemic sclerosis: results from a phase 3 randomized controlled trial. Available: <https://acrabstracts.org/abstract/efficacy-and-safety-of-tocilizumab-for-the-treatment-of-systemic-sclerosis-results-from-a-phase-3-randomized-controlled-trial/> [Accessed 27 Oct 2018].
- 41 Saketkoo LANN. Successful trial design and planning in systemic sclerosis: does it take a village? *J Rheumatol* 2018;45:297–9.
- 42 Oldroyd AGS, Symmons DPM, Sergeant JC, *et al.* Long-term persistence with rituximab in patients with rheumatoid arthritis. *Rheumatol Oxf Engl* 2018;57:1089–96.
- 43 Fernández-Codina A, Walker KM, Pope JE, *et al.* Treatment algorithms for systemic sclerosis according to experts. *Arthritis Rheumatol Hoboken NJ* 2018;70:1820–8.
- 44 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;4:708–19.
- 45 Vettori S, Maresca L, Cuomo G, *et al.* Clinical and subclinical atherosclerosis in systemic sclerosis: consequences of previous corticosteroid treatment. *Scand J Rheumatol* 2010;39:485–9.
- 46 Guillevin L, Bézézné A, Seror R, *et al.* Scleroderma renal crisis: a retrospective multicentre study on 91 patients and 427 controls. *Rheumatol Oxf Engl* 2012;51:460–7.
- 47 Frieden TR. Evidence for health decision making — beyond randomized, controlled trials. *N Engl J Med* 2017;377:465–75.