**SUPLEMENTARY MATERIAL**

**Appendix: 2**

**Appendix 1**

**Collaborators of the EUSTAR centres in numerical order (of the centers)**

Serena Guiducci, Department of Medicine, Section of Rheumatology, University of Florence, Italy; Ulrich A. 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**Appendix II**

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

|  |  |  |
| --- | --- | --- |
|  | **Item No** | **Recommendation** |
| **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract |
| **Study design is indicated in the title and in the abstract page 4 (method section).** |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found  **This was done pages 4-5.** |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported  **The scientific background is clearly explained page 6** |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses  **They were stated page 6.** |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper  **They are presented in the method section page 7.** |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection  **They are clearly described in the method section pages 7 and 8.** |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  **This is described in the method section pages 7 and 8.** |
| (*b*)For matched studies, give matching criteria and number of exposed and unexposed  **They are presented page 9 (covariates) and the numbers of exposed/unexposed patients are detailed page 7.** |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable  **They are defined in the method section pages 8-10.** |
| Data sources/ measurement | 8\* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group  **They are defined in the method section pages 8.** |
| Bias | 9 | Describe any efforts to address potential sources of bias  **They are detailed in the statistical analysis pages 9-10.** |
| Study size | 10 | Explain how the study size was arrived at  **This is explained in the method section.** |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why  **This is explained in the statistical analysis page 9.** |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
| **They are detailed in the statistical analysis pages 9-10.** |
| (*b*) Describe any methods used to examine subgroups and interactions  **They were described page 10.** |
| (*c*) Explain how missing data were addressed  **We used imputations to minimize the possible role of missing values. This is explained in the method section pages 8-9.** |
| (*d*) If applicable, explain how loss to follow-up was addressed  **NA** |
| (*e*) Describe any sensitivity analyses  **Sensitivity analyses were described page 10.** |
| **Results** | | |
| Participants | 13\* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed  **This is reported page 11** |
| (b) Give reasons for non-participation at each stage  **They were reported in the results section** |
| (c) Consider use of a flow diagram  **Flow diagram is presented in Appendix Figure 1** |
| Descriptive data | 14\* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  **This is reported page 11, Table I, Table IV, and in Appendix Tables II and III.** |
| (b) Indicate number of participants with missing data for each variable of interest  **This is reported in Appendix Table 1.** |
| (c) Summarise follow-up time (eg, average and total amount)  **This is reported in Table I.** |
| Outcome data | 15\* | Report numbers of outcome events or summary measures over time  **This is reported pages 12-14 (number of events per 100 person-years).** |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included  **This is reported in Figures 1 and 2 and Appendix Figure 2.** |
| (*b*) Report category boundaries when continuous variables were categorized  **This is reported** |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period  **NA** |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses  **They are reported in the results section and in Figure 2, Appendix Figures 3 and 4 and in Appendix Table IV.** |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives  **Key results were summarized in the discussion section** |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias  **Limitations of the study were discussed in the discussion section page 17.** |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence  **This was performed in the discussion section** |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results  **This was discussed in our discussion.** |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based  **The funding source and its role were described page 10.** |

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

**Supplementary TABLE I: Number of missing data for each characteristic of SSc-patients treated with rituximab and untreated SSc-controls from EUSTAR database**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Total N=9829 | Non treated n=9575 | Treated n=254 |
| Sex | 0 (0%) | 0 (0%) | 0 (0%) |
| Age | 0 (0%) | 0 (0%) | 0 (0%) |
| ANA | 256 (2.6%) | 247 (2.6%) | 9 (3.5%) |
| Anti-Scl70 | 614 (6.2%) | 604 (6.3%) | 10 (3.9%) |
| ACA | 634 (6.5%) | 624 (6.5%) | 10 (3.9%) |
| RNA pol III antibodies | 6800 (69.2%) | 6790 (70.9%) | 10 (3.9%) |
| Cutaneous form | 96 (1%) | 86 (0.9%) | 10 (3.9%) |
| Disease duration (years) | 1144 (11.6%) | 1144 (11.9%) | 0 (0%) |
| Previous IS or biologics | 0 (0%) | 0 (0%) | 0 (0%) |
| Modified Rodnan skin score | 991 (10.1%) | 958 (10%) | 33 (13%) |
| FVC | 5142 (52.3%) | 5105 (53.3%) | 37 (14.6%) |
| DLCO | 2922 (29.7%) | 2887 (30.2%) | 35 (13.8%) |
| Prednisone | 4608 (46.9%) | 4608 (48.1%) | 0 (0%) |
| Lung fibrosis | 5944 (60.5%) | 5944 (62.1%) | 0 (0%) |
| Follow-up (months) | 7 (0.1%) | 0 (0%) | 7 (2.8%) |

SSc: systemic sclerosis. Values are median [interquartile range] or mean ± SD or numbers (%) of observations. ANA: antinuclear antibodies; ACA: anticentromeres; RNA pol III: RNA polymerases III antibodies; lung fibrosis was diagnosed on HRCT (high-resolution computed tomography); CT: computed tomography, FVC: forced vital capacity; DLCO: diffusing capacity of lung for carbon monoxide. Previous IS (immunosuppressive drugs) include Methotrexate, Mycophenolate Mofetil, Azathioprin and Cyclophosphamide, whereas biologics include anti-TNF alpha, Tocilizumab and Abatacept.

**Supplementary TABLE II: Other characteristics of SSc-patients treated with rituximab.**

|  |  |
| --- | --- |
|  | N=254 |
| Rheumatoid factor | 48/233 (21%) |
| Anti-CCP antibodies | 22/210 (10.7%) |
| Other antibodies | 36/244 (14.7%) |
| Overlap syndrome | 62/243 (25.5%) |
| Overlap with rheumatoid arthritis | 23/243 (9.5%) |
| Overlap with myositis | 19/243 (7.8%) |
| Overlap with Sjögren syndrome | 16/243 (6.6%) |
| Digital ulcers | 51/245 (20.8%) |
| Upper gastrointestinal symptoms | 144/239 (60.2%) |
| Lower gastrointestinal symptoms | 52/240 (21.7%) |

SSc: systemic sclerosis. Values are median ± interquartile range or numbers (%) of observations/number of available data. Other antibodies include anti-SSA (n=14), anti-RNP (n=9), anti-PM-Scl (n=9), anti-SSB (n=5), anti-fibrillarine (n=3), anti-Sm (n=2), anti-ds DNA (n=2), anti-mitochondrial antibodies (n=1), anti-SRP (n=1) and anticardiolipin antibodies (n=1). Other overlapping diseases were as follow: antisynthetases syndrome (n=1), primary biliary cirrhosis (n=1), vasculitis (n=5), mixed connective tissue disease (n=3) and systemic lupus erythematosus (n=5).

**Supplementary TABLE III: Side effects during treatment with rituximab**

|  |
| --- |
| Minor side effects \* 43 (17%)   * Infections 27 (10.6%) * Upper respiratory tract 7 (2.8%) * Lower respiratory tract 9 (3.5%) * Cutaneous 7 (2.8%) * Urinary 1 (0.4%) * Gastrointestinal 1 (0.4%) * Osteomyelitis 2 (0.8%) * Hypogammaglobulinemia 23 (9.1%) * Cardiovascular 8 (3.1%) * Arrhythmia 3 (1.2%) * Arterial hypertension 2 (0.8%) * Retrosternal pain\*\* 1 (0.4%) * Atherosclerosis 1 (0.4%)   (stenosis of the carotid artery)   * Congestive diastolic dysfunction 1 (0.4%) * Cutaneous eruption 5 (2.0%) * Dyspnea 1 (0.4%) * Itching 2 (0.8%) * Transient leukopenia 4 (1.6%) * Anemia 2 (0.8%) * Vasculitic skin lesions 1 (0.4%) * Fasciculation 1 (0.4%) * Asthenia 1 (0.4%) * Articular pain 1 (0.4%) |
| Severe side effects\* 36 (14.2%)   * Severe infections\*\*\* 16 (3.5%) * Respiratory 6 (2.4%) * Cutaneous 6 (2.4%) * Gastrointestinal 2 (0.8%) * Osteoarticular 2 (0.8%) * Respiratory 5 (2.0%) * Dyspnea 3 (1.2%) * PAH 1 (0.4%) * Respiratory insufficiency 1 (0.4%)   Context of lung cancer   * Cancer 5 (2.0%) * Lung carcinoma 2 (0.8%) * Rectal carcinoma 1 (0.4%) * Leiomyosarcoma 1 (0.4%) * Pancreas carcinoma 1 (0.4%) * Cardiovascular 4 (1.6%) * Angina Pectoris 1 (0.4%) * Palpitations/ atrial tachycardia 1 (0.4%) * Heart failure 1 (0.4%) * Diastolic dysfunction/congestive 1 (0.4%)   disease   * Scleroderma renal crisis 2 (0.8%) * Anaphylactic reactions 2 (0.8%) * Depression/suicide attempt 1 (0.4%) * Agranulocytosis 1 (0.4%) * Serum sickness 1 (0.4%) |

Values are number of patients (%); \*some patients had several side effects; \*\* retrosternal pain was probably caused by known pleuropericarditis; \*\*\*severe infection required hospitalization. PAH: pulmonary arterial hypertension

**Supplementary TABLE IV: Characteristics of SSc-patients with and without follow-up in EUSTAR database**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Not followed n=4664 | Followed n=9575 | p |
| Sex (Female) | 3961 (84.9%) | 8256 (86.2%) | 0.040 |
| Age, Mean ± SD | 55.9 ± 14.5 | 54.5 ± 13.8 | <0.0001 |
| Diffuse cutaneous form | 1394 (30.6%) | 2866 (30.2%) | 0.63 |
| Disease duration (years),  Median (Q1-Q3) | 5.7 [2.1-12] | 5.2 [2-11.1] | 0.0002 |
| ANA | 4088 (92.4%) | 8813 (94.5%) | <0.0001 |
| Anti-Scl70 | 1315 (31.3%) | 2994 (33.4%) | 0.021 |
| ACA | 1539 (36.6%) | 3410 (38.1%) | 0.10 |
| RNA pol III antibodies | 145 (5.2%) | 145 (5.2%) | 0.31 |
| Modified Rodnan skin score, Median (Q1-Q3) | 6 [2-13] | 7 [3-13] | <0.0001 |
| Lung fibrosis | 748 (44.2%) | 1505 (41.4%) | 0.062 |
| FVC, Mean ± SD | 92.6 ± 21.8 | 95.2 ± 21.4 | <0.0001 |
| DLCO, Mean ± SD | 69.9 ± 31 | 70.7 ± 23 | <0.0001 |
| Tender joints count, Median (Q1-Q3) | 0 [0-0] | 0 [0-0] | 0.25 |
| Swollen joints count, Median (Q1-Q3) | 0 [0-0] | 0 [0-0] | 0.22 |
| CRP, Median (Q1-Q3) | 2.7 [1-6.2] | 2.4 [1-6] | 0.20 |
| Previous IS or biologics | 840 (18%) | 1698 (17.7%) | 0.70 |
| Prednisone (mg/d ), Median (Q1-Q3) | 0 [0-5] | 0 [0-5] | 0.49 |

SSc: systemic sclerosis. Values are median [interquartile range] or mean ± SD or numbers (%) of observations. ANA: antinuclear antibodies; ACA: anticentromeres; RNA pol III: RNA polymerases III antibodies; lung fibrosis was diagnosed on high-resolution computed tomography; CT: computed tomography, FVC: forced vital capacity; DLCO: diffusing capacity of lung for carbon monoxide. Previous IS (immunosuppressive drugs) include Methotrexate, Mycophenolate Mofetil, Azathioprin and Cyclophosphamide, whereas biologics include anti-TNF alpha, Tocilizumab and Abatacept.

**Supplementary TABLE V: Effect of rheumatoid factor, anti-CCP positivity and smoking status on skin and lung in the rituximab-treated patients**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Rodnan | | FVC | | DLCO | |
|  | OR  [95CI%] | p | OR  [95CI%] | p | OR  [95CI%] | p |
| AntiCCP (22/210) | 0.96 [0.07-12.94] | 0.98 | 3.16 [0.85-11.76] | 0.089 | 1.45 [0.16-13.13] | 0.74 |
| RF (48/233) | 0.69 [0.13-3.64] | 0.66 | 1.93 [0.63-5.86] | 0.25 | 1.04 [0.2-5.44] | 0.97 |
| Smoking (past or current) (86/226) | 1.18 [0.48-2.87] | 0.72 | 1.25 [0.44-3.61] | 0.68 | 2.39 [0.51-11.14] | 0.27 |
| Current smoker  (27/226) | 0.67 [0.23-1.99] | 0.48 | 1.33 [0.36-4.91] | 0.67 | 0.68 [0.07-6.71] | 0.74 |

 FVC: forced vital capacity; DLCO: diffusing capacity of lung for carbon monoxide. RF: rheumatoid factor; number are cases/number of data available.

**Supplementary TABLE VI: Effect of rituximab on skin involvement according to cumulative dosage**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Cumulative dosage | | | |
|  | ≤ 4000 | | > 4000 | |
|  | OR [IC95%] | p | OR [IC95%] | p |
| Modified Rodnan skin score | 1.74 [0.78-3.9] | 0.18 | 6.12 [1.83-20.46] | 0.003 |

Results of matching with a ratio 1:4 are presented.

**LEGEND OF SUPPLEMENTARY FIGURES**

**Supplementary Figure 1: flow-chart for patients treated with rituximab and controls from EUSTAR database.**

MS: musculoskeletal. 12 other indication: 4 vasculitis, 1 malt NH lymphoma, 1 cardiac involvement + mantle cell lymphoma, 1 upper gastrointestinal involvement, 1 cardiac involvement, 4 data not provided.

**Supplementary Figure 2: Ajusted OR for skin fibrosis improvement and lung fibrosis worsening among propensity score-matched patients treated or untreated with rituximab in subgroup analyses**.

The analyses of decrease in the modified Rodnan score of 5 points and 25% and decrease in the FVC of 10% 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 treatment was evaluated using conditional logistic regression. We used other matching method with ratio 1:1 within a caliper of 0.05 standard deviation of the logistic propensity score, stratification on the quintiles of the propensity score, and inverse probability of treatment weighting (IPTW). Decrease in the modified Rodnan score of 5 points and 25% in patients with (A) early disease (disease duration ≤ 5 years) (B) diffuse cutaneous form (C) Decrease in the FVC of 10% in patients with early disease (disease duration ≤ 5 years) and in patients with diffuse cutaneous form (D).

**Supplementary Figure 3: Ajusted OR for decrease in FVC and decrease in steroids use among propensity score-matched patients treated or untreated with rituximab**

The analyses of decrease in the FVC (A) and stopping or tapering steroids (B) 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 FVC/ stopping or tapering steroids respectively was evaluated using conditional logistic regression. We used other matching method with ratio 1:1 within a caliper of 0.05 standard deviation of the logistic propensity score, stratification on the quintiles of the propensity score, and inverse probability of treatment weighting (IPTW).