Effectiveness and safety of tocilizumab in patients with systemic sclerosis: a propensity score matched controlled observational study of the EUSTAR cohort


ABSTRACT

Objectives Tocilizumab showed trends for improving skin fibrosis and prevented progression of lung fibrosis in systemic sclerosis (SSc) in randomised controlled clinical trials. We aimed to assess safety and effectiveness of tocilizumab in a real-life setting using the European Scleroderma Trial and Research (EUSTAR) database.

Methods Patients with SSc fulfilling the American College of Rheumatology (ACR)/EULAR 2013 classification criteria, with baseline and follow-up visits at 12±3 months, receiving tocilizumab or standard of care as the control group, were selected. Propensity score matching was applied. Primary endpoints were the modified Rodnan skin score (mRSS) and FVC at 12±3 months compared between groups. Secondary endpoints were the percentage of progressive/regressive patients for skin and lung at 12±3 months.

Results Ninety-three patients with SSc treated with tocilizumab and 3180 patients with SSc with standard of care fulfilled the inclusion criteria. Comparison between groups did not show significant differences, but favoured tocilizumab across all predefined primary and secondary endpoints: mRSS was lower in the tocilizumab group (difference −1.0, 95% CI −3.7 to 1.8, p=0.48). Similarly, the percentage of progressive/regressive patients for skin and lung at 12±3 months was higher in the tocilizumab group (difference −1.0, 95% CI −3.7 to 1.8, p=0.48). The percentage of progressive/regressive patients for skin and lung at 12±3 months was higher in the tocilizumab group (difference −1.0, 95% CI −3.7 to 1.8, p=0.48).

Conclusion Tocilizumab showed trends for improving skin fibrosis and preventing progression of lung fibrosis in patients with SSc in real-life settings. These results reflect the consistency of direction in all predefined primary and secondary endpoints, but require confirmation in a prospective RCT.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

⇒ Two placebo-controlled randomised controlled clinical trials (RCTs) with tocilizumab have been conducted in systemic sclerosis (SSc). Both RCTs were recruiting a highly enriched population of patients with inflammatory, early, diffuse, skin-progressive SSc. Main messages from these two RCTs were for potential effectiveness in a broader SSc population.

WHAT DOES THIS STUDY ADD?

⇒ No significant effectiveness of tocilizumab was shown in this broader, multicentre, propensity score matched, controlled observational, heterogeneous, non-enriched real-life SSc population from the large European Scleroderma Trial and Research registry.

HOW MIGHT THIS IMPACT ON CLINICAL PRACTICE OR FUTURE DEVELOPMENTS?

⇒ Adds important information from real-life to the existing RCTs with tocilizumab by generating hypothesis for potential effectiveness in a broader SSc population rather than in highly selective RCT.
INTRODUCTION

Systemic sclerosis (SSc) is a rare but potentially lethal autoimmune connective tissue disease characterised by inflammation, fibrosis and microvasculopathy. It is a multi-organ disease involving the skin and various internal organs. Mortality is high, especially if lungs, heart or kidneys are involved. Even though new trials on various disease-modifying drugs have been conducted over the last years, therapy is still mainly based on treatment of organ-specific complications.

Several preclinical and translational studies have shown that interleukin 6 (IL-6) might play an important role in SSc, in particular when inflammation is driving the disease process. IL-6 serum concentrations in patients with diffuse cutaneous (dc) SSc are significantly higher than in healthy individuals. Serum IL-6 levels correlate with disease severity and mortality, and are associated with higher C reactive protein (CRP) levels and platelet counts. Inhibition of IL-6 prevented the development of inflammation-driven dermal fibrosis induced by bleomycin in mice, but did not show effects in the non-inflammatory TSK-1 model.

Tocilizumab (TCZ) is a humanised monoclonal antibody against the IL-6 receptor. Two randomised placebo-controlled clinical trials (RCTs) with tocilizumab have been conducted in SSc. In the phase II faSScinate trial, a trend for improving skin fibrosis over placebo was found. Exploratory analysis revealed a possible stabilisation of FVC. The phase III focusSSced study confirmed the trend on skin fibrosis and additional HRCT quantification, was observed. Both RCTs were recruiting a highly enriched population of patients with inflammatory, early, diffuse, skin-progressive SSc.

Thus, while these data are promising and have resulted in the approval of tocilizumab for SSc-associated interstitial lung disease (SSc-ILD) by the FDA, little is known about the effects of tocilizumab in a broader SSc population. Data from large ‘real-life’ registries could better determine the effects of tocilizumab on a more heterogeneous, non-enriched population. The aim of the present study was to estimate the treatment effect and safety of tocilizumab in patients with SSc, as compared with patients not treated with tocilizumab in a large real-life observational cohort study using the European Scleroderma Trials and Research (EUSTAR) database.

MATERIAL AND METHODS

Study design

This study was designed as a multicentre, propensity score matched no-treatment controlled observational study. Data for tocilizumab-treated patients were requested from the EUSTAR network using a case report form (CRF) designed by the lead investigators. The treating physicians made the treatment decision according to their local practice and routine. Requested data included demographics, clinical characteristics, treatment details and adverse events (see online supplemental file for CRF). Queries were sent to centres for missing data and data clarification. The matched control group was formed from patients prospectively registered in the EUSTAR database, not treated with tocilizumab. Database extraction was done on 30 October 2017.

The local ethic committees of the participating centres approved the data collection. All patients signed informed consent forms when required by the local ethics committees. This study was conducted in accordance with the guidelines for good clinical practice and the principles of the Declaration of Helsinki and registered at www.drks.de under DRKS00015537, including a predefined detailed statistical analysis plan (provided in online supplemental file).

Inclusion criteria and selection of control patients

Inclusion criteria for the treatment group were definite SSc according to the American College of Rheumatology (ACR)/EULAR 2013 criteria, treatment with tocilizumab and age ≥17 years. For analysis of primary and secondary outcomes, only patients with at least three applications of tocilizumab and follow-up at 12±3 months were included. Safety data were analysed for all patients. Additional/different inclusion criteria for the control group were absence of tocilizumab therapy, disease duration <35 years to meet the tocilizumab group and date of observations after 1 January 2010 (start of the online EUSTAR database). If multiple visits existed for one control patient, we used the most recent one, and this approach was revisited in the sensitivity analysis.

Primary and secondary outcomes

The primary outcomes were the difference at 12±3 months of follow-up between the tocilizumab and the control group in the modified Rodnan skin score (mRSS) for skin fibrosis and the FVC for pulmonary function compared. Both outcomes were addressed separately, but a single matched set of patient treated-control pairs was used for analysis.

Secondary outcomes were the percentage of progressive patients for skin fibrosis (increase in mRSS of 5 points and 25%), lung fibrosis (decrease in either FVC ≥10% or FVC ≥5% and diffusing capacity of the lung for carbon monoxide DLCO ≥15%), and the percentage of regressive patients for skin and for lung (decrease in mRSS of 5 points and 25% or increase in either FVC ≥10% or FVC ≥5% and DLCO ≥15%). Presence of
ILD was defined as evidence for ILD on HRCT or X-ray as judged by the local investigator. Safety measures were assessed as percentage of patients suffering from adverse events.

**Subgroup analysis**

Predefined subgroup analyses included mRSS ≥10 versus mRSS <10 at baseline and dcSSc versus limited cutaneous SSc (lcSSc) (for the outcome mRSS) and FVC ≥80% versus FVC <80% at baseline and FVC <80% and X-ray or high-resolution CT (HRCT) positive versus FVC ≥80% and X-ray or HRCT negative (for the outcome FVC).

Exploratory subgroup analysis included disease duration ≤3 years versus disease duration >3 years and C reactive protein (CRP) ≤5 mg/L versus CRP >5 mg/L and HRCT and/or X-ray positive versus HRCT and/or X-ray negative.

Subgroup analyses were preceded by a test for interaction. Subgroup results were only reported if there was evidence for differential treatment effect between subgroups (if p<0.05).

**Propensity score matching**

Based on expert opinion and considering the published literature, the following variables were identified as confounders in an interdisciplinary team discussion (SJ, OD, SK, UH, KS): age at diagnosis, gender, disease subtype (diffuse or limited), baseline mRSS, FVC, DLCO, co-therapy with immunosuppressive disease-modifying antirheumatic drugs (either one of prednisone >10 mg/day, methotrexate, azathioprine or mycophenolate mofetil), rituximab within 6 months before baseline, disease duration in years, and year of treatment.

The propensity score was the estimated probability of a patient in the EUSTAR database to receive tocilizumab. To estimate the propensity score, a logistic regression model was fitted to the confounders. We used a nearest neighbour 1:1 propensity score matching (PSM) algorithm. Balancing of baseline characteristics before and after matching was assessed with descriptive statistics, the standardised mean difference (SMD) and exploratory p values. If the SMD was smaller than 0.1, the distribution of confounders was assumed to be balanced.

**Handling of missing values**

The procedure for handling of missing values of potential control patients and treated patients varied. The following variables were used in the multiple imputation model as predictor variables: age in years (numeric), gender (binary), subtype (binary), prednisone (binary), methotrexate (binary), azathioprine (binary), mycophenolate mofetil (binary), rituximab (biologic) within 6 months before baseline (binary), disease duration in years (numeric), year of treatment (numeric) as well as baseline and follow-up of mRSS, FVC and DLCO (numeric). Age, disease duration in years, baseline and follow-up mRSS, FVC and DLCO were imputed using predictive mean matching. Subtype, prednisone, methotrexate, azathioprine, mycophenolate mofetil and rituximab (biologic) within 6 months before baseline were imputed via logistic regression and co-therapy was passively imputed. Missing data in the primary outcomes (mRSS and FVC) in potential control patients led to listwise exclusion of these patients, whereas none of the patients in the TCZ group were excluded due to missing parameters in the primary outcomes. Covariates with a percentage of missing values of more than 50% were a priori defined to be excluded from the analysis. For the remaining variables, missingness patterns were assessed. As we assumed that data were missing completely at random or missing at random, multiple imputation using chained equations (MICE) was used for confounders and outcomes at baseline as well as follow-up. The number of multiply imputed data sets was set to 60 (m=60).

**Statistical analysis**

Descriptive statistics included mean and SD or median and IQR for continuous variables, and number and percentage of total for categorical variables.

The primary outcomes, mRSS and FVC, were compared with linear mixed-effects models to account for the correlation between the matched samples. The results from multiply imputed data sets were combined using Rubin’s rule. We used a generalised linear mixed model with binomial family with a random intercept accounting for pair membership of matched treated and control patients.

Binary secondary outcomes were compared with ORs and 95% CIs between treatment groups; again, these were corrected for correlation in matched pairs due to matching. Between-group differences for continuous outcomes were estimated and reported with 95% CIs. The effect measures for the binary outcomes are marginal ORs. The significance level for confirmatory p values was set to 0.05.

A sensitivity analysis was conducted to address preprocessing decisions (selection of most recent vs random observation for control patients with multiple suitable time intervals), as well as matching algorithm (nearest neighbour vs exact matching) and robustness of the results. For further details and specifications, see the statistical analysis plan (online supplemental file).

All data analyses were conducted using R, V.4.1.2 for Windows and the packages tableone, mice, MatchIt, reshape2, dplyr, mitools, lsmeans, VIM, cobalt, ggplot2, lmer and glmer. Results of the study were reported according to the STROBE guidelines.

**RESULTS**

**Baseline characteristics of tocilizumab and control patients**

Data from 109 patients with SSc treated with tocilizumab were collected from 25 EUSTAR centres. Of these 109 patients, 12 were excluded for the effectiveness analysis due to missing follow-up at 12±3 months and 4 due to absence of at least three tocilizumab applications. Route of administration was intravenous in 65 (69.9%),
subcutaneous in 13 (14.0%) and no information available in 15 (16.1%).

From the EUSTAR database, 3180/10,426 patients were fulfilling the inclusion criteria for the control group. There were 14.0% missing data in baseline mRSS and 40.9% at follow-up. For FVC, the corresponding percentages were 25.8% at baseline and 45.2% at follow-up. Through application of MICE and PSM on these patients, 60 imputed sets of 93 matched sets of treated and control patients were generated (figure 1).

Baseline demographics and clinical characteristics of the tocilizumab group and the control group before and after multiple imputation and propensity score matching can be found in table 1. As expected, the proportion of patients with the diffuse subtype, the prevalence of increased inflammation markers (CRP/erythrocyte sedimentation rate above normal limits) and patients with arthritis, and overlap to rheumatoid arthritis (online supplemental table S1) was high, reflecting the typical real-life indications for tocilizumab at time of the study. Indeed, the majority of physicians selected tocilizumab as a treatment because of SSc-associated arthritis (table 2). After multiple imputation and propensity score matching, the pooled SMD of baseline covariates between the two groups was <0.1 for all matching variables. Therefore, baseline covariates were considered balanced and further adjustment was not needed (online supplemental table S2). In addition, online supplemental table S4 shows baseline characteristics with SMD and p values for a randomly drawn data set after multiple imputation.

No covariates had a percentage of missing values >50%; therefore, no covariate needed to be excluded.

**Effects of tocilizumab on skin and lung fibrosis**

Follow-up mRSS as a measure of skin fibrosis after 12±3 months of therapy was lower in the tocilizumab group (mean estimate of 11.2, 95% CI 9.1 to 13.3) compared with the control group (12.2, 9.7 to 14.6, p=0.48). This effect was stable regardless of the pre-processing decisions and the matching algorithm (see sensitivity analyses).

Similar to skin fibrosis, we could consistently see a tendency towards a benefit of tocilizumab therapy for lung fibrosis as measured by FVC per cent predicted, which did not reach statistical significance. FVC at follow-up was 88.7 (83.7 to 93.7)% predicted in the tocilizumab group versus 87.2 (80.8 to 93.6)% predicted in the control group (p=0.70). Results from the pre-defined main analysis of primary outcomes are shown in table 3 and figure 2. Accordingly, the mean estimated difference (with 95% CI) between groups for skin fibrosis measured by mRSS was lower in TCZ −1.0 (−3.7 to 1.8) and higher in TCZ for lung fibrosis measured by FVC (% predicted) 1.5 (−6.1 to 9.1).

**Secondary outcomes**

The percentage of progressive patients for skin fibrosis as well as for lung fibrosis (online supplemental table S3) was lower under tocilizumab therapy as compared with the control group without reaching statistical significance. The OR for mRSS was 0.7 (0.1 to 4.8, p=0.74) and 0.8 (0.3 to 2.2, p=0.63) for progression of ILD as measured by decline in FVC.

No significant effectiveness of tocilizumab could be shown for percentage of regressive patients under therapy, with an OR of 1.1 (0.4 to 2.7, p=0.86) for regression of...
mRSS and 1.5 (0.6 to 3.8, p=0.41) for increase of FVC (table 4).

Interaction tests for differential treatment effects between the subgroups showed no evidence for subgroup effects (online supplemental table S5), suggesting that either the results are not different or the sample size is too small for patients with mRSS \( \geq 10 \) versus mRSS <10, dcSSc versus lcSSc (for the outcome mRSS) as well as FVC \( \geq 80\% \) versus FVC <80\% and FVC \( \geq 80\% \) and X-ray or HRCT positive versus FVC <80\% and X-ray or HRCT negative (for the outcome FVC).

**Sensitivity analysis**

The sensitivity analysis addressed multiple observations in patients with more than one suitable time interval as well as different matching algorithms. The sensitivity...
Superinfection of digital ulcers was reported in >50,000/µL. Twenty-six events resulted in discontinuation of tocilizumab.

The resulting progression of FVC was comparable with that seen in idiopathic pulmonary fibrosis and allowed demonstrating the strong difference of FVC in the tocilizumab group compared with placebo with a stabilised FVC. This strong difference of FVC would be more difficult to be shown with less enriched patient populations and slower progression of FVC in the placebo/control group such as in the Senscis trial or in the present study.

Considering safety, our study did not reveal significant new potential threats of tocilizumab. The profile of adverse events was similar to that of other studies investigating safety parameters in patients with tocilizumab. There was a predominance of infections among the SAEs (5/17) and well-known laboratory abnormalities such as thrombocytopenia or elevated transaminases among the AEs (49/90). However, while previous studies suggested that serious infections might be higher in patients with SSc treated with tocilizumab than in patients with rheumatoid arthritis, our study could not confirm this. Of particular interest are infections of digital ulcers, but with only four infections associated with digital ulcers (two considered serious) observed in 93.8 patient years, with only four infections associated with digital ulcers (two considered serious) observed in 93.8 patient years, although sample sizes might have been too small to detect differences in subgroups. However, a remarkable finding of this study was the consistent, although not significant, point estimates in favour of tocilizumab across all predefined primary and secondary endpoints. Furthermore, additional sensitivity analyses were consistent. The data used in this study were from a large registry including a general population of patients with SSc. Although the estimated effects of tocilizumab were not significant, the results of the study may be seen as hypothesis generating for a potential effectiveness of tocilizumab in broader patient populations than studied in the highly selected and enriched RCT populations. The hypothesis that tocilizumab might also be effective in broader patient populations needs now to be tested in further large prospective RCTs.


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**DISCUSSION**

Our multicentre, propensity score matched, controlled observational study in the EUSTAR database did not show significant effectiveness of tocilizumab on skin and lung fibrosis. Subgroup analysis did not show evidence for differences in effectiveness across subpopulations, although sample sizes might have been too small to detect differences in subgroups. However, a remarkable finding of this study was the consistent, although not significant, point estimates in favour of tocilizumab across all predefined primary and secondary endpoints. Furthermore, additional sensitivity analyses were consistent. The data used in this study were from a large registry including a general population of patients with SSc. Although the estimated effects of tocilizumab were not significant, the results of the study may be seen as hypothesis generating for a potential effectiveness of tocilizumab in broader patient populations than studied in the highly selected and enriched RCT populations. The hypothesis that tocilizumab might also be effective in broader patient populations needs now to be tested in further large prospective RCTs.

Our study has to be interpreted in light of the results from the two RCTs conducted in SSc with a high evidence level. In both RCTs, there was a consistent trend for the primary endpoint mRSS favouring tocilizumab. Considering that in these RCTs, the study population was strongly enriched for mRSS dynamics, the current confirmation of these results in a much less selected observational real-life cohort is encouraging. Regarding lung fibrosis, both RCTs showed strong effects of tocilizumab on FVC as a secondary or exploratory endpoint. An important result of both trials was the successful enrichment for a strong decline of FVC in the placebo groups using a combination of inclusion criteria such as early dcSSc, increased inflammatory markers and recent progression of skin fibrosis. The resulting progression of FVC was comparable with that seen in idiopathic pulmonary fibrosis and allowed demonstrating the strong difference of FVC in the tocilizumab group compared with placebo with a stabilised FVC. This strong difference of FVC would be more difficult to be shown with less enriched patient populations and slower progression of FVC in the placebo/control group such as in the Senscis trial or in the present study.

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Our study has limitations. Despite the relatively large number of patients in the EUSTAR database, there were much less patients available who received treatment with tocilizumab. Therefore, uncertainty increased and the power of the study was not high enough to allow definite conclusions. In general, a higher number of patients is needed to show a treatment effect in observational cohorts than in RCTs because there is more heterogeneity. In addition, the leading indication to treat patients with SSc with tocilizumab was presence of arthritis and/or overlap to rheumatoid arthritis at time of the present study and the associated disease characteristics with, for example, longer disease duration further decrease the likelihood that a significant treatment effect can be observed, at least for mRSS. After publication of the two tocilizumab RCTs, this practice pattern has likely changed and many more patients with SSc-ILD are treated nowadays with tocilizumab. Despite propensity scoring matching for key parameters, some features associated with disease progression, such as increased inflammatory markers and arthritis, were more common in the tocilizumab patients than in controls. However, this should lead to more progression in the tocilizumab group and supports a potential positive effect of tocilizumab in this study. Due to a small number of patients in the subgroups, it was not possible to include all variables into a single imputation model. Therefore, the subgroup results are biased towards null and should be interpreted with caution. Another potential limitation is that we matched for any immunosuppressive treatment, but not for single immunosuppressive drugs. If the immunosuppressive drugs are having very different effects on outcomes than others, this matching would not have been perfect. However, numbers would have been too small for matching of single immunosuppressive drugs and results would have not been meaningful. Moreover, the absolute numbers of AE observed in this trial should be considered with caution, as they were

Table 3  Primary outcomes at follow-up (12±3 months)

<table>
<thead>
<tr>
<th></th>
<th>mRSS</th>
<th>FVC (% predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCZ, n=93</td>
<td>Mean estimate (95% CI)</td>
<td>11.2 (9.1 to 13.3)</td>
</tr>
<tr>
<td>Controls</td>
<td>Mean estimate (95% CI)</td>
<td>12.2 (9.7 to 14.6)</td>
</tr>
<tr>
<td>Between-group difference</td>
<td>Mean estimate (95% CI)</td>
<td>-1.0 (-3.7 to 1.8)</td>
</tr>
<tr>
<td>P value</td>
<td>0.48</td>
<td>0.70</td>
</tr>
</tbody>
</table>

These results represent our main analysis with a nearest neighbour matching algorithm and selection of most recent observation in control patients with multiple possible baseline observations.

CI, confidence interval; FVC, forced vital capacity; mRSS, modified Rodnan skin score; TCZ, tocilizumab.

Figure 2  Modified Rodnan skin score (mRSS) and FVC at follow-up (12±3) months. (A) Primary outcome mRSS estimate (95% CI) tocilizumab (TCZ) vs control between-group mean difference p=0.48. (B) Primary outcome FVC% predicted estimate (95% CI) TCZ vs control between-group difference p=0.70.
collected retrospectively, are therefore likely underestimated, and a control group for the AE was missing. Finally, it must be strongly emphasised that observational studies can provide important signals, which may be used for hypothesis generation and might contribute to generalisation of trial results to real-life setting, but are never of high enough evidence to prove drug effectiveness. Still, the current study adds important supportive data for effectiveness of tocilizumab in SSc in real-life setting consistent with data from the two RCTs.

Strengths of the study include the robust, predefined and preregistered study protocol (www.drks.de), with a detailed statistical analysis plan involving expert biostatisticians and applying propensity score matching and using optimised matching procedures, while accounting for missing data with a multiple imputation approach. All major decisions regarding methodological approaches were re-evaluated in sensitivity analyses. The results remained stable indicating that the methodology or assumptions did not affect the results of this study. This study reports the largest number of patients with SSC treated with tocilizumab with similar numbers as in the phase III focuSSced study.19 In addition, data were collected from a real-life setting avoiding over-enrichment as in standard RCTs. Controls were derived from the very large, prospectively collected EUSTAR database.

CONCLUSION

Taken together, in this large, propensity score matched, controlled observational real-life EUSTAR study, we could not show significant effectiveness of tocilizumab for skin and lung fibrosis across all predefined primary and secondary endpoints. However, the consistency of direction of all predefined endpoints generates hypothesis for potential effectiveness in a broader SSC population than the highly selective population included in the RCTs. This hypothesis needs to be confirmed by prospective RCTs with broader patient populations. Safety analysis confirmed previous AE profiles without new signals.

<table>
<thead>
<tr>
<th>Patient n</th>
<th>Age (years)</th>
<th>Report at visit (month)</th>
<th>Event</th>
<th>Discontinuation of tocilizumab</th>
<th>Hospitalisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 5</td>
<td>42</td>
<td>12</td>
<td>Severe thrombocytopenia</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Patient 39</td>
<td>45</td>
<td>6</td>
<td>Toe necrosis and infection</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 39</td>
<td>45</td>
<td>12</td>
<td>Pneumonitis (after stop of TCZ)</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 43</td>
<td>68</td>
<td>6</td>
<td>Atrial flutter</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Patient 49</td>
<td>32</td>
<td>12</td>
<td>Digital ulcer with osteomyelitis</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Patient 50</td>
<td>41</td>
<td>3</td>
<td>Allergic reaction</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Patient 50</td>
<td>41</td>
<td>3</td>
<td>Influenza</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 69</td>
<td>41</td>
<td>3</td>
<td>Renal crisis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 69</td>
<td>41</td>
<td>6</td>
<td>Thrombophlebitis (after stop of TCZ)</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 70</td>
<td>58</td>
<td>6</td>
<td>Acute heart failure</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>Patient 70</td>
<td>58</td>
<td>12</td>
<td>Amputation last phalanx Dig I foot (after stop of TCZ)</td>
<td>–</td>
<td>NA</td>
</tr>
<tr>
<td>Patient 71</td>
<td>76</td>
<td>6</td>
<td>Deep vein thrombosis</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Patient 80</td>
<td>56</td>
<td>0</td>
<td>Severe allergic reaction</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>Patient 83</td>
<td>58</td>
<td>3</td>
<td>Bilateral keratitis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Patient 92</td>
<td>63</td>
<td>3</td>
<td>Pneumonia</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 92</td>
<td>63</td>
<td>12</td>
<td>Pneumonia</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 97</td>
<td>18</td>
<td>12</td>
<td>Sudden cardiac death</td>
<td>–</td>
<td>NA</td>
</tr>
</tbody>
</table>

–, Information is not applicable; NA, data are not available; TCZ, tocilizumab.
Author affiliations
1Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
2Department of Rheumatology, Paris Descartes University, Cochin Hospital, APHP, Paris, France
3Department of Biostatistics at Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland
4Department of Experimental and Clinical Medicine, Division of Rheumatology, University of Florence, Florence, Italy
5Rheumatology Unit, DETO, University Hospital Polyclinic of Bari, Bari, Italy
6Department of Precision Medicine, University of Campania ‘Luigi Vanvitelli’, Naples, Italy
7Clinic for Rheumatology and Immunology, Bad Bramstedt, Germany
8Berlin Institute of Health at Charité, Berlin, Germany
9Clinica Rheumatologica, University of Medicine and Pharmacy, Cluj-Napoca, Romania
10Department of Rheumatology, IRCSS Foundation Policlinico San Matteo, Pavia, Italy
11Department of Rheumatology and Clinical Immunology, Spedali Civili di Brescia, Brescia, Italy
12B. Shine Department of Rheumatology, Rambam Health Care Campus and Technion, Haifa, Israel
13University of Cologne, Cologne, Germany
14Department of Rheumatology, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
15Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy
16Department of Internal Medicine and Rheumatology, Cantacuzino Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
17Department of Rheumatology, Hospital Pusat, Valencia, Spain
18Department of Biophysics, Physiology and Pathophysiology, Medical University of Warsaw, Warsaw, Poland
19Department of Connective Tissues Diseases, Institute of Rheumatology, Warsaw, Poland
20Department of Rheumatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
21University Hospital Hamburg-Eppendorf, Division of Rheumatology and Systemic Inflammatory Diseases, Hamburg, Germany
22Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
23Department of Rheumatology, National Reference Center for Systemic Autoimmune Rare Diseases, Hospital Pellegrin, Bordeaux, France
24Rheumatology Section, Department of Medicine, University of Verona, Verona, Italy
25Department of Allergy and Rheumatology, Nippon Medical School, Tokyo, Japan
26Rheumatology Unit, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy
27Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Padova, Padova, Italy
28Referral Centre for Rare Systemic Autoimmune Diseases for North and North-West of France, Department of Internal Medicine, Claude Huriez Hospital, University of Lille, Lille, France
29Department of Internal Medicine, Department of Rheumatology, Ghent University Hospital, Ghent, Belgium
30Unit for Molecular Immunology and Inflammation, VIB Inflammation Research Centre (IRC), Ghent, Belgium
31Centre for Rheumatology, University College London Medical School—Royal Free Campus, London, UK
32Internal Medicine and Rheumatology Department—St. Maria Hospital, Carlo Davila University of Medicine and Pharmacy, Bucharest, Romania
33Krankenhaus St. Josef, Wuppertal-Elberfeld, Germany
34Department of Internal Medicine III, Erlangen University Hospital, Erlangen, Germany
35Istituto di Scienze Cliniche e Molecolari, Università Politecnica delle Marche, Ancona, Italy
36Department of Rheumatology, Rikshospitalet University Hospital Oslo, Oslo, Norway

Collaborators EUSTAR Collaborators: Principal Investigator Affiliation: Ulrich Walker, Basel (Switzerland); Radim Becvar, Prague (Czech Republic); Maurizio Cutolo, Genova (Italy); Patricia E Carreira, Madrid (Spain); László Czirjak, Pecs (Hungary); Michele Iudici, Geneva (Switzerland); Eugene J Kucharz, Katowice (Poland); Bernard Coleiro, Balzan (Malta); Dominique Farge Bancel, Paris (France); Roger Hesselstrand, Lund (Sweden); Mislav Radic, Split (Croatia); Raffaele Pellerito, Torino (Italy); Nemanja Danjanov, Belgrade (Serbia); Jörg Hennes, Tübingen (Germany); Vera Ortiz-Santamaría, Granollers Barcelona (Spain); Stefan Heilmann, Stuttgart (Germany); Paul Hasler, Aarau (Switzerland); Bojana Stamenkovic, Niska Banja (Serbia); Carlo Francesco Selmi, Rozzano, Milano (Italy); Mohammed Ily, Johannesburg (South Africa); Lidia P Ananieva, Moscow (Russia); Ulf Müller-Ladner, Bad Nauheim (Germany); Merete Engelhart, Hellerup (Denmark); Carlos da la Puente, Madrid (Spain); Cord Sundenkötter, Münster (Germany); Francesca Ingegno, Milano (Italy); Luc Mouthon, Paris (France); Francesco Paolo Cantatore, Foggia (Italy); Susanne Ullman, Copenhagen (Denmark); Maria Rosa Pozzi, Monza (Italy); Piet Wiland, Wrocław (Poland); Marie Vanduyne, Brussels (Belgium); Juan Jose Alegre-Sancho, Valencia (Spain); Brigitte Krummel-Lorenz, Frankfurt (Germany); Christine Herrmann, Dresden (Germany); Ellen De Langhe, Leuven (Belgium); Branimir Anc, Zagreb (Croatia); Sule Yavuz, Atatürkzade-Istanbul (Turkey); Carolina de Souza Müller, Curitiba (Brazil); Svetlana Agachi, Chisinau (Republic of Moldova); Thierry Zenone, Valentine (France); Simon Sæbø, Dundee (Scotland); Alessandra Vaccar, Monzeretto (CA) (Italy); Lisa Stamp, Christchurch (New Zealand); Kamal Solanki, Hamilton (New Zealand); Douglas Veale, Dublin (Ireland); Esthela Loyo, Santiago (Dominican Republic); Mengtao Li, Beijing (China); Wald Ahmad Abby Atty Mohamed, Alexandria (Egypt); Edoardo Rosato, Roma (Italy); Cristina-Mihaela Tanaseanu, Bucharest (Romania); Rosario Foti, Catania (Italy); Cordina Ancuta, Iasi (Romania); Britta Maurer, Ber (Switzerland); Paloma Garcia de la Peña Lafont, Madrid (Spain); Jean Sibilia, Strasbourg (France); Ira Littinsky, Tel-Aviv (Israel); Francesco Del Gado, Leeds (UK); Goda Saez-Fernández, Lisboa (Portugal); Lessley Ann Saketko, New Orleans (USA); Eduardo Kerzberg, Buenos Aires, Argentina; Doron Rimar, Haifa (Israel); Camillo Ribi, Lausanne (Switzerland); Vivien M. Hsu, New Brunswick (USA); Thierry Martin, Strasbourg (France); Lorinda S Chung, Stanford (USA); Tim Schmeiser, Wuppertal-Elberfeld (Germany); Dominik Majewski, Poznan (Poland); Vera Bernardino, Lisbon (Portugal); Piercarlo Sarzi Puttini, Milano (Italy).

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ORCID iDs
Fabo Casalapaglia http://orcid.org/0000-0001-7479-4462
Veronica Codullo http://orcid.org/0000-0003-2557-8514
Ivan Castelví http://orcid.org/0000-0002-5410-5807
Vanessa Smith http://orcid.org/0000-0001-6271-7945
Tim Schmeiser http://orcid.org/0000-0001-7342-0020
Anna-Maria Hoffmann-Vold http://orcid.org/0000-0001-6467-7422
Masatika Kuwana http://orcid.org/0000-0001-8352-6136
Oliver Distler http://orcid.org/0000-0002-0546-8310

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