LONGITUDINAL TRENDS IN MULTIMORBIDITY IN SYSTEMIC SCLEROSIS: RESULTS FROM AN INCIDENT POPULATION-BASED COHORT (1980-2018)

Keywords: Comorbidities, Systemic sclerosis, Epidemiology

A. Makol1, A. Karn1, S. Achenbach2, A. M. Hinze1, C. S. Crowson2.

1Mayo Clinic, Division of Rheumatology, Rochester, United States of America
2Mayo Clinic, Department of Quantitative Health Sciences, Rochester, United States of America

Background: Systemic sclerosis (SSc) is a chronic inflammatory autoimmune disease characterized by vascular dysfunction and widespread internal organ fibrosis. Multimorbidity (MM), defined as the co-occurrence of two or more chronic conditions, can impact life expectancy, increase risk of hospitalizations, healthcare resource utilization and reduce quality of life. The accrual of MM in SSc and its determinants are not well studied.

Objectives: To assess the longitudinal trends of MM (i.e., the presence of ≥2 morbidities) in an incident population-based cohort of patients with SSc vs. age- and sex-matched non-SSc comparators, and identify drivers of these trends.

Methods: A population-based cohort of incident physician diagnosed SSc patients between Jan 1, 1980, to Dec 31, 2018, was identified and compared to a 2:1 cohort of age- and sex-matched non-SSc comparators from the same population. Patients were followed until death, migration from the geographic area or Dec 31, 2021. Data on 21 morbidities identified by the US Department of Health and Human Services (DHHS) and 13 morbidities included in the Charlson Comorbidity Index (CCI) were retrieved. Cumulative incidence of MM (MM2+) or substantial MM (MM5+; ≥5 morbidities) adjusting for the competing risk of death was estimated. Cox models adjusted for age, sex, index year and morbidity count at index date were used to compare cases and comparators. Sensitivity tests using a mixed-effects model of event type before index date were excluded from respective analyses.

Results: 85 patients with SSc were compared to 170 age- and sex-matched non-SSc comparators (mean age 55.4 ± 9.1% female, 90% white/non-Hispanic). At incidence/index date, a significantly higher prevalence of chronic obstructive pulmonary disease (COPD) (14% vs 4%, p=0.004), arthritis (33% vs 22%, p=0.054), peripheral vascular disease (40% vs 22%, p=0.001) and liver disease (5% vs 1%, p=0.04) were noted in patients with SSc. During a mean length of follow-up of 12.4 y (SD 9.8) for SSc & 15.5 y (SD 9.8) for comparators, the development of DHHS morbidities of heart failure (HR (2.90; 95% confidence interval [CI] 1.46-5.74), cardiac arrhythmia (hazard ratio [HR] 1.60; 95% CI 1.03-2.49), stroke (HR 2.08; 95% CI 1.04-4.16), chronic kidney disease (HR 1.86; 95% CI 1.09-3.18), and COPD (HR 2.02; 95% CI 1.09-3.80) were higher in SSc vs. non-SSc comparators. While osteoporosis (HR 2.03; 95% CI 1.18-3.51) was also higher in SSc patients, it did not reach statistical significance when adjusted for baseline morbidity count at index date. Similarly, CCI morbidities of HF (HR 2.26; 95% CI 1.51-5.42), peripheral vascular disease (HR 11.32; 95% CI 6.59-19.44), cerebrovascular disease (HR 2.43; 95% CI 1.26-4.72), chronic pulmonary disease (HR 3.82; 95% CI 2.18-6.69), myocardial infarction/severe renal disease (HR 2.32; 95% CI 1.30-4.16), and any liver disease (HR 3.02; 95% CI 1.36-6.92) were also significantly higher in SSc when compared to non-SSc comparators. The cumulative incidence of DHHS MM2+ during follow-up did not differ, but the development of DHHS MM5+ was significantly higher in SSc patients vs. comparators at 10 (44% vs 32%), 15 (52% vs 45%) and 20 (64% vs 58%) years of follow up (HR 1.58, 95% CI 1.09-2.31). The development of CCI-MM2+ (HR 4.56; 95% CI 3.00-6.93) was significantly higher among SSc patients but CCI-MM5+ was not statistically significant after adjusting for morbidity count at index (HR 1.65; 95% CI 0.80-3.43).

Conclusion: Multimorbidity is significantly more prevalent in patients with SSc and adds a substantial healthcare burden on these patients. Patients with SSc have a 1.5-3 fold higher risk of developing multiple cardiopulmonary morbidities. Patients who meet risk of developing peripheral vascular disease during longitudinal follow up than age- and sex-matched individuals without SSc. Multimorbidity assessment must be prioritized early in the disease course to reduce healthcare utilization and optimize long-term outcomes in this population.

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INDUCTION OF REGULATORY T CELLS AND EFFICACY OF LOW DOSE INTERLEUKIN-2 IN SYSTEMIC SCLEROSIS: INTERVENTIONAL OPEN-LABEL PHASE 1–PHASE 2A STUDY

Keywords: Adaptive immunity, Investor initiated trial, Systemic sclerosis

F. Barde1, R. Lorenzon2,3, S. Riviere1, P. Caccoub2,4, M. Rosenzweig2,3, C. Cacciatori1, A. Dagueneul-Nguyen1, O. Fain1,2, D. Klatzmann2,3, A. Mekikian1,2,1Hospital Saint-Antoine Ap-Hp, Internal Medicine, Paris, France
2Sorbonne University, Faculté de Médecine, Paris, France
3University Hospitals Pitié Salpêtrière - Charles Foix, Clinical Investigation Center for Biotherapies and Inflammation-Immunopathology-Biotherapy Department, Paris, France
4University Hospitals Pitié Salpêtrière - Charles Foix, Department of Internal Medicine and Clinical Immunology, Paris, France
5Hospital Saint-Antoine Ap-Hp, Pharmacy, Paris, France

Background: Systemic sclerosis (SSc) is a chronic autoimmune disease, with impaired immune response, increased fibrosis, and endothelial dysfunction. (1,2) Regulatory T cells (Tregs), which are essential to prevent autoimmunity, showed a decreased frequency and impaired function during SSc. (3,4) Low-dose interleukin-2 (id-IL2) can expand and activate Tregs, but there are no data in SSc.

Objectives: To assess the in vivo biological efficacy of id-IL2 on Tregs and its safety in patients with SSc.

Methods: We performed an interventional prospective, open-label phase I-IIa study in nine patients with SSc without severe organ involvement (eight patients with limited cutaneous subtype). This trial is a part of the TRANSREG study. All patients received 1 Million International Units (MIU)/day of IL2 for five days, followed by fortnightly injections for 6 months. The primary endpoint was the change in the relative Tregs blood concentration identified as CD25hiCD127loFoxP3+ cells frequencies on day 8 among TCD4+ cells compared with baseline. Laboratory and clinical evaluations (modified Rodnan skin score (mRSS), Global Global Impression (CGI) activity and severity scale) were performed between day 8 and month 18.

Results: At day 8, the primary endpoint was reached with a 1.8 ± 0.5 fold increase of Tregs levels among TCD4+ lymphocytes (p=0.008). Changes in concentration of effector T cells (Tefs) and BCD19+ cells were not statistically significant at day 8 and during maintenance period until month 6. Patients' clinical assessments were stable throughout the follow-up with no modification on mRSS CGI activity and severity scale. Ld-IL2 was well tolerated, and no serious adverse events occurred.

Conclusion: Ld-IL2 at a dosage of 1 MIU/day for five consecutive days selectively activates and expands Tregs in SSc. Safety data were very encouraging. Phase II efficacy trials are needed to validate therapeutic potential of id-IL2.

REFERENCES:

Table: Lymphocyte subpopulations analysis

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 8</th>
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<tbody>
<tr>
<td>Treg cells/µL/mm³</td>
<td>84.8 ± 36.7</td>
<td>121 ± 7.4*</td>
</tr>
<tr>
<td>% Among CD4°</td>
<td>10.7 ± 8.9*</td>
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<tr>
<td>Lymphocytes/µL/mm³</td>
<td>1307 ± 458</td>
<td>1819 ± 14*</td>
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<tr>
<td>Treg cells/CD4°</td>
<td>4.6 ± 12</td>
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<td>% Among CD4°</td>
<td>8.1 ± 1.9*</td>
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<tr>
<td>CD3+ T cells/µL/mm³</td>
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<td>1463 ± 407*</td>
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<tr>
<td>CD4° T cells/µL/mm³</td>
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<td>1108 ± 369*</td>
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<td>CD8° T cells/µL/mm³</td>
<td>281 ± 156</td>
<td>358 ± 150</td>
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<tr>
<td>CD57° T cells/µL/mm³</td>
<td>159 ± 89</td>
<td>140 ± 71</td>
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<tr>
<td>CD19° B cells/µL/mm³</td>
<td>4.6 ± 1.52</td>
<td></td>
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<tr>
<td>CD3+CD56° NK cells/µL/mm³</td>
<td>84.8 ± 36.7</td>
<td>178 ± 66.5***</td>
</tr>
</tbody>
</table>

Data are represented as mean ± sd. Changes between baseline and day 8 were analyzed using by ANOVA for ranked data considering factor time °p<0.05; **p<0.01; ***p<0.001.