Interferon-associated cytokine and chemokine expression in patients with serologically active clinically quiescent systemic lupus erythematosus

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Disclosures
• None

Background - Interferon-α (IFN-α)
• Proinflammatory molecule produced by plasmacytoid dendritic cells (pDCs), driven by autoantibodies
• Elevated in SLE
• Thought to play prominent role in SLE pathogenesis
  o Disrupts peripheral immune tolerance
  o Upregulates Blys/BAFF
  o Upregulates other proinflammatory molecules

Background - SACQ
• Serologically active clinically quiescent (“SACQ”)
  o Persistent serologic activity
  o Anti-dsDNA
  o Hypocomplemetemia
  o No evidence of clinical activity

Background - SACQ
• To date we have
  o Described the SACQ period and its patients
  o Determined flare cannot be predicted by fluctuations in anti-dsDNA and/or complement levels during a SACQ period
  o Determined that anti-dsDNA and anti-chromatin antibody isotypes do not differ in patients who remain SACQ versus those who flare

Background
• The mechanism by which SACQ patients remain clinically quiescent despite evidence of persistent production of autoantibodies is unknown

Hypothesis
• IFN-associated cyto/chemokines will differ in SACQ patients compared to serologically and clinically active (SACA) and serologically and clinically quiescent (SQCQ) patients

Methods - setting
• Prospective longitudinal cohort study
• SLE patients followed at the University of Toronto Lupus Clinic
• Clinical and laboratory variables collected according to a standard protocol 2-6 months intervals

Methods - patient selection
• SACQ / SQCQ
  • At least 2 years
  • May be taking antimalarials
  • Cannot be taking any corticosteroid or immunosuppressive medication

• SACA
  • Disease activity requiring corticosteroids or immunosuppressives

Methods - Study Protocol
History, physical exam, lab, protocol completion (SLEDAI-2K)

Anti-dsDNA (Farr)
C3/C4 (nephelometry)

6Ckine, BCA-1, CTACK, EGF, ENA-78, Estaxin, Estaxin-2, Estaxin-3, FGF-2, Flt-3L, Fractalkine, G-CSF, GM-CSF, GRO-I, I309, IFNα2, IFNγ, IL-1α, IL-1β, IL-10, IL-12 (p40 and p70), IL-15, IL-16, IL-17, IL-20, IL-21, IL-23, IL-28a, IL-33, IP-10, ILF, MCP-1, MCP-2, MCP-3, MCP-4, MDC, MMP-1, MMP-10, MMP-12, POGE, POGF-AB/BB, RANTES, TF-1, IL-10, IP-10, MCP-1, RANTES, TRAIL

IFN-α, IFN-γ, IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12 (p40 and p70), IL-17, IL-21, IL-23, IP-10, MCP-1, RANTES, TRAIL

IFN-α concentration in SACQ/SQCQ vs SACA patients

* Significant with less conservative Bonferroni correction applied
Demographics

<table>
<thead>
<tr>
<th></th>
<th>SACQ (n=25)</th>
<th>SQCQ (n=28)</th>
<th>SACA (n=48)</th>
<th>p (SACQ vs SACA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% female)</td>
<td>88</td>
<td>96.43</td>
<td>87.5</td>
<td>1.00</td>
</tr>
<tr>
<td>Age at study date</td>
<td>43.4 ± 13.8</td>
<td>55.3 ± 12.4</td>
<td>29.4 ± 9.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Disease duration at study date</td>
<td>18.5 ± 12.1</td>
<td>24.2 ± 11.1</td>
<td>7.4 ± 7.3</td>
<td>0.0002</td>
</tr>
<tr>
<td>Adjusted mean SLEDAI</td>
<td>3.8 ± 1.6</td>
<td>1.9 ± 1.3</td>
<td>12.8 ± 8.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SLEDAI-2K 1st clinic visit</td>
<td>11.2 ± 10.3</td>
<td>6.6 ± 5.5</td>
<td>12.4 ± 8.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Clinical manifestations did not differ between groups

Autoantibody profile

<table>
<thead>
<tr>
<th></th>
<th>SACQ (n=25) (%)</th>
<th>SQCQ (n=28) (%)</th>
<th>SACA (n=48) (%)</th>
<th>p (SACQ vs SACA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>100</td>
<td>92.9</td>
<td>97.8 (n=45)</td>
<td>1.00 (Fisher's)</td>
</tr>
<tr>
<td>dsDNA (Farr)</td>
<td>92</td>
<td>67.9</td>
<td>93.8</td>
<td>0.78</td>
</tr>
<tr>
<td>Sm</td>
<td>24</td>
<td>35.7</td>
<td>38.6 (n=44)</td>
<td>0.215</td>
</tr>
<tr>
<td>La</td>
<td>48</td>
<td>32.1</td>
<td>15.9 (n=44)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ro</td>
<td>84</td>
<td>53.6</td>
<td>50 (n=44)</td>
<td>0.005</td>
</tr>
<tr>
<td>RNP</td>
<td>40</td>
<td>28.6</td>
<td>68.2 (n=44)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Variables associated with SACQ status - multivariate analysis

<table>
<thead>
<tr>
<th></th>
<th>SACQ (vs. SACA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Ro antibody positivity* ¶</td>
<td>OR 20 [2.38,166.67]</td>
</tr>
<tr>
<td>Disease duration ↑</td>
<td>OR 1.12 [1.03, 1.23]</td>
</tr>
<tr>
<td>MCP-1 ↑</td>
<td>OR 0.43 [0.23, 0.81]</td>
</tr>
<tr>
<td>IL-10 ↑</td>
<td>OR 0.14 [0.02, 0.96]</td>
</tr>
</tbody>
</table>

* Also predictive vs SQCQ: OR 4.55[1.23,16.67]
¶ Remained predictive when SACA patients with disease duration < 6 years were excluded

Summary

- IFN-associated cytokine/chemokine profiles differed between SACQ and SACA, but not SACQ and SQCQ, patients
- Decreased levels of MCP-1 and IL-10 were associated with SACQ status
- SACQ status was also associated with
  - Increased disease duration
  - Anti-Ro antibody positivity

Conclusions

- Despite serologic activity, SACQ cytokine signature mirrors that of SQCQ patients
- A lack of proinflammatory factors was associated with SACQ status
- The difference between SACQ and SACA
  - Is not attributable to a lack of autoantibody production
  - Cannot be exclusively attributable to differences in disease duration
- The mechanism for these differences remains to be elucidated

Thank you!