WHAT SEROLOGIC PROFILING PROVIDES OPTIMAL ENTRY CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS CLINICAL TRIALS?

Ewa Olech1, Eduard van Rijen1, Alexander Kant1, Ali Ashrafzadeh1, Joan T Merrill2

1IQVIA, Durham, United States of America; 2Oklahoma Medical Research Foundation, Oklahoma City, United States of America

Disclosure of Interests: Theresa Kissel: None declared, Karin van Schie: None declared, Hans Ulrich Scherer Grant/research support from: Sanofi, BMS, Heidi Kokkonen: None declared, Lise Hafkenscheid: None declared, Anders Lundquist: None declared, Theresa Kissel: None declared, Karin van Schie: None declared

Conclusion: Our analysis revealed that ACPA IgG molecules can harbor V-domain glycans already relatively long time before disease onset. An increase in ACPA-V-domain glycosylation, presumed due to the generation of ne novo N-glycosylation sites or the expansion of N-glycosylation site-bearing clones was associated with an increase in ACPA levels. These results suggest that ACPA-expressing B cells gain a selective advantage through the generation V-domain N-glycosylation in parallel with rising ACPA-levels in serum in the phase prior to the development of arthritis.

REFERENCES:
[1] https://doi.org/10.1038/nrrheum.2011.204
[6] https://doi.org/10.1371/journal.pone.0200280

Table 1. Impact of serologic features on markers of active SLE

<table>
<thead>
<tr>
<th>Subset</th>
<th>N</th>
<th>Mean/Median C3/C4</th>
<th>p value</th>
<th>Mean/Median C3/C4</th>
<th>p value</th>
<th>% with Low C3/C4</th>
<th>p value</th>
<th>% DNA</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>ALL</td>
<td>1019</td>
<td>1056</td>
<td>186</td>
<td>39.2%</td>
<td>35.8%</td>
<td>0.001</td>
<td>43.6%</td>
<td>0.001</td>
</tr>
<tr>
<td>N=1019</td>
<td>ENA+</td>
<td>670</td>
<td>990</td>
<td>162</td>
<td>42.1%</td>
<td>0.001</td>
<td>43.6%</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ENA-</td>
<td>349</td>
<td>1130</td>
<td>210</td>
<td>23.8%</td>
<td>30.7%</td>
<td>0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>DNA+</td>
<td>399</td>
<td>890</td>
<td>130</td>
<td>63.9%</td>
<td>0.001</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>DNA-</td>
<td>620</td>
<td>1130</td>
<td>210</td>
<td>22.9%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ENA+ DNA-</td>
<td>378</td>
<td>1117</td>
<td>198</td>
<td>25.9%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ENA- DNA-</td>
<td>242</td>
<td>1211</td>
<td>0.001</td>
<td>18.2%</td>
<td>0.001</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Screen N=783</td>
<td>ALL</td>
<td>783</td>
<td>***</td>
<td>***</td>
<td>32.1%</td>
<td>24.9%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ANA neg</td>
<td>190</td>
<td>1230</td>
<td>&lt;0.001</td>
<td>15.3%</td>
<td>0.073</td>
<td>7.4%</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ANA=1:80</td>
<td>74</td>
<td>1130</td>
<td>228</td>
<td>25.7%</td>
<td>comp</td>
<td>17.6%</td>
<td>comp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ANA=1:160</td>
<td>104</td>
<td>1110</td>
<td>210</td>
<td>25.0%</td>
<td>ns</td>
<td>19.2%</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ANA=1:320</td>
<td>97</td>
<td>1110</td>
<td>190</td>
<td>29.9%</td>
<td>ns</td>
<td>22.7%</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ANA=1:640</td>
<td>104</td>
<td>960</td>
<td>152</td>
<td>47.1%</td>
<td>#0.006</td>
<td>34.6%</td>
<td>#0.019</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ANA=1:1280</td>
<td>88</td>
<td>904</td>
<td>160</td>
<td>45.4%</td>
<td>#0.015</td>
<td>35.2%</td>
<td>#0.019</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ANA=1:2560</td>
<td>52</td>
<td>920</td>
<td>160</td>
<td>48.1%</td>
<td>#0.016</td>
<td>44.2%</td>
<td>#0.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ANA=1:5120</td>
<td>74</td>
<td>959</td>
<td>135</td>
<td>45.9%</td>
<td>#0.016</td>
<td>48.6%</td>
<td>#0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ANA - ENA -</td>
<td>61</td>
<td>1122</td>
<td>203</td>
<td>21.3%</td>
<td>ns</td>
<td>13.1%</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ANA - DNA -</td>
<td>129</td>
<td>1254</td>
<td>0.007</td>
<td>12.4%</td>
<td>4%</td>
<td>#0.001</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ANA &lt;1:80 or DNA+</td>
<td>607</td>
<td>1020</td>
<td>**</td>
<td>37.7%</td>
<td>#0.012</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DNA+ or ENA+ or DNA=1:640</td>
<td>318</td>
<td>940</td>
<td>0.001</td>
<td>46.5%</td>
<td>-</td>
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</tbody>
</table>

Results: Of 1019 patients who qualified for the studies (baseline population), 399 (39.2%) were positive for DNA and 670 (65.8%) had anti-Extractable Nuclear Antibodies (ENA). Patients with positive DNA or ENA (even in absence of DNA) had lower complement levels and were more likely to have low C3/C4. (Table 1)

In patients at screening, higher titers of ANA were associated with lower comple-
ment levels and were more likely to have low C3/C4. (Table 1)

Conclusion: The following entry criteria may help increase the likelihood that trial subjects have active SLE: ANA=1:640, or DNA, or ENA, or low C3 or C4. To the extent that a modest loss of recruitment increases the probability of entering inappropriate patients, typically ANA≥1:80 and/or positive anti-double stranded DNA (DNA) are required screening elements, but lately other autoantibody vari-
ables have been utilized.

Objectives: To examine serologic features that promote entry of active SLE patients into trials while supporting reasonable recruitment rates.

Methods: Serologic features of 1411 individual subjects who had full laboratory data at screening (N=783) and/or baseline (N=1019) in 4 phase 2 multicenter SLE trials were examined. Complement levels, percent of patients with low C3 or C4, and elevated DNA were used as markers of active disease. Serological profiles consistent with active SLE were tested on screened population for effects on potential screen failure rates.

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Serologic profiles consistent with active SLE were tested on screened population for effects on potential screen failure rates.
Exagen, Bristol Myers Squibb, Medimmune/Astra Zeneca, Lilly, Immpharma, Amgen, Janssen, Sanofi, Neovacs, Anthera, Speakers bureau: UCB, GSX, EMD Serono, Bristol Myers Squibb, Medimmune/Patra Zeneca, Janssen


SATURDAY, 15 JUNE 2019

Lessons learned from checkpoint inhibitors

**OP0335**  
A PROSPECTIVE CLINICAL AND MRI STUDY OF IMMUNE CHECKPOINT INHIBITOR (ICI)-INDUCED MUSCULOSKELETAL MANIFESTATIONS MYO-FASCIITIS AND NOT SYNOVITIS IS THE PROMINENT IMAGING FINDING

Dimitrios Daoussis1, Alexandra Filippopoulou1, Pantelis Kranios2, Spyridoula Theodoraki3, Rafaela Angriadi3, Thomas Makatsoris3, Angelos Koutras3, Akaterini Solomou4, Haralampos Kalofonos5, Stamatis-Nick Lioussis21. Patras University Hospital, University of Patras Medical School, Rheumatology, Patras, Greece; 2Patras University Hospital, University of Patras Medical School, Radiology, Patras, Greece; 3Patras University Hospital, University of Patras Medical School, Oncology, Patras, Greece

**Background:** Immune checkpoint inhibitors (ICI) were a breakthrough in cancer therapeutics. These agents target certain “brakes” of the immune system aiming at activating T cells to fight cancer. Taking into account their mechanism of action it is no surprise that they have been associated with immune related adverse events

**Objectives:** To assess the prevalence, clinical and imaging characteristics of ICI-induced musculoskeletal manifestations in a prospective manner

**Methods:** This is a prospective, clinical and MRI study conducted from Jan 2016 to Oct 2018. All patients treated with ICI who developed musculoskeletal manifestations were referred to the Rheumatology Department and subjected to a full clinical assessment and laboratory workup. An MRI of the involved area(s) was performed within one week of the initial clinical evaluation. In 2 patients MRI was not performed due to claustrophobia (n=1) and presence of non compatible metal implant (n=1).

**Results:** During the study period a total of 130 patients were treated with ICI. Of those, 10 (7.7%) developed ICI-induced musculoskeletal manifestations. They suffered from lung (n=4), bladder (n=3), renal cancer (n=2) or melanoma (n=1) and received treatment with nivolumab (n=7), pembrolizumab (n=1), durvalumab (n=1) and atezolizumab (n=1). They were mostly male (n=8) with a mean ± SEM age of 66.7 ± 2.6 years. The median (range) time from ICI treatment since development of symptoms was 2.5 (1-22) months. Autoantibodies (RF/ACPA/ANA) were negative in all patients and only 3/10 had a mild/moderate increase of inflammatory markers at disease onset. Three different patterns of musculoskeletal manifestations were found: i) Prominent joint involvement (n=3). Areas involved were the small joints of the hands (n=2) and knee/ankle (n=1). The MRI of the latter patient depicted not only synovitis but also myositis of the muscles surrounding the involved joints, ii) Prominent “periarticular” involvement (n=4). These patients had diffuse swelling of the hands (n=4) feet (n=3) or knees (n=1). Joints retained a good and relatively painless range of motion. MRI depicted mild synovitis with more prominent myositis and/or fasciitis in the surrounding tissues in all cases, iii) Myo-fasciitis (n=3). In all 3 such cases the involved area was the knee. Clinically, these patients presented with pain in the knee and either no objective signs of arthritis (n=2) or swelling with non inflammatory synovial fluid. MRI depicted myo-fasciitis of the surrounding muscles in all cases; a partial tear of the quadriceps tendon was also found in the patient with knee swelling. Overall, symptoms were mild/moderate and responded well to treatment (low dose steroids in 6 and NSAIDs/analogesics in 4) with no need for ICI discontinuation.

**Conclusion:** In our cohort ICI-induced musculoskeletal manifestations were not uncommon and developed in 7.7% of patients. Imaging evidence of myo-fasciitis was found in all patients indicating that the muscle/fascia is more frequently involved than the synovium. Our clinical and imaging data point to the direction that ICI-induced musculoskeletal manifestations mostly involve periarticular structures and associate mainly with myo-fasciitis and not synovium based pathology

**Disclosure of Interests:** None declared


**OP0336**  
COMMONLY USED DRUGS IN RHEUMATOLOGY MAY ALTER ANTI-TUMORAL RESPONSE TO IMMUNE CHECKPOINT INHIBITORS

Marie Kostina, Eleonora Mauri, Thomas Barretche, Léa Rouxel, Caroline Dutiaux, Léa Dousset, Sorilla Prey, Marie Beylot-Barry, Julien Seneschal, Rémi Veillon, Charlotte Vergnenegre, Amaury Daste, Charlotte Domblices, Baptiste Sionneau, Marine Gross-Goupil, Alain Ravaud, Edouard Forcade, Bernard Bannwarth, Marie-Elise Truchetet, Christophe Richez, Nadia Mehsen-Cetre, Thierry Schaeverbeke, on behalf of the FHU ACRONIM. Bordeaux University Hospital, Bordeaux, France

**Background:** Immune checkpoint inhibitors (ICIs) are revolutionizing the treatment of some advanced cancers. Gut microbiota has emerged as an important component of anti-tumoral response and can also be related to the occurrence of immune-related adverse events (irAEs). It has recently been shown that antibiotic treatment given at the initiation of ICI therapy had a dramatic impact on microbiota that compromised the anti-tumoral effect of ICIs (1).

**Objectives:** To evaluate whether co-medications known to have a potential impact on gut microbiota may alter ICI efficacy and/or irAE occurrence when given at ICI onset.

**Methods:** This was a retrospective cohort study including all cancer patients who received ICIs at our institution from May 2015 to September 2017. Co-medications given to the patients within one month before or one month after the first administration of ICI were extracted from medical records on the basis of a predefined list of medications known to impact gut microbiota. The tumour response, occurrence of irAEs and patient outcomes were assessed on a regular basis. Overall survival (OS) has been considered from the start of ICI therapy.

**Results:** 635 patients (70% male, mean age 64.5 years) were included, of whom 293 had melanoma, 150 had advanced non-small cell lung cancer and 83 had renal carcinoma. A previous autoimmune disorder was present in 8% of patients, mainly rheumatic and endocrine diseases. Psychotropic drugs (41.1%), proton pump inhibitors (PPIs) (37.3%), angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs) (32%), glucocorticoids (GC) (24.2%), antibiotics (21.4%), statins (20.8%) and morphine (20.6%) were the most co-prescribed medications. Baseline GC use, when > 10mg of prednisone equivalent, was associated with a significant decrease in OS (median 4.5 months versus 24.3 months; p<0.0001) and a less frequent tumour response (55% versus 73%; p=0.0001). When given after ICI onset for the management of irAEs, GC did not influence ICI efficacy (Figure A). Baseline PPI use also altered both OS (median 10.9 versus 24.3 months; p<0.0001) and tumour response (62% versus 71%; p=0.02) (Figure B). We confirmed the detrimental impact of antibiotics when given at ICI onset, and also found worse outcomes for patients receiving baseline psychotropic drugs (median OS 9.3 versus 19.4 months; p=0.0001). No significant difference was observed with baseline use of NSAIDs, aspirin, statins and ARBs/ACE. Furthermore, co-medication with antibiotics, GC, PPIs, morphine, NSAIDs, aspirin and psychotropic drugs was associated with decreased occurrence of irAEs.

**Conclusion:** As many of these treatments are used by rheumatologists, one should be aware of their potential detrimental effect when used at ICI initiation, that sometimes could have been avoided.

**REFERENCE:**

Disclosure of Interests: None declared