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SAT0632

NEUTROPHIL ACTIVATION IDENTIFIES PATIENTS WITH ACTIVE POLYARTICULAR GOUT – A NOVEL BIOMARKER?

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Background: Neutrophils are key immune cells participating in host defense through several mechanisms, including the formation of neutrophil extracellular traps (NETs). Although beneficial from a host-pathogen perspective, excessive neutrophil activation has been linked to inflammation and autoimmunity, including systemic lupus erythematosus (SLE) and gout.(1) In gout models, uric acid crystals induce NETosis. Though NETs are known to induce marked inflammation through TLR9- and cGAS-dependent pathways, as well as partake in induction of tissue damage and thrombotic events, the role of NETs in human gout has not been carefully investigated.

Objectives: Our objective is to investigate evidence of systemic neutrophil activation, and the clinical utility of neutrophil-derived biomarkers in gout. We hypothesize that uric acid crystals will activate neutrophils to undergo NET formation, with these processes contributing to immune cell activation, and local joint destruction.

Methods: Plasma samples from 75 gout patients participating in the ‘Reade gout cohort Amsterdam’ were compared with 30 healthy controls (HC). Levels of NETs, and NET-derived markers (cell-free DNA and peroxidase activity) were analyzed using a MPO-DNA ELISA, as well as fluorometry.(2) Levels of calprotectin (S100A8/A9) were analyzed by ELISA, Mitochondrial (mt, COXII), as well as genomic (n, RPLP0) DNA levels were analyzed by qPCR. All of the analyzed markers were compared between gout patients and healthy individuals, and related to markers of inflammation and disease activity.

Results: Levels of NETs, as well as other neutrophil biomarkers, were significantly increased in gout patients as compared to healthy subjects (p<0.01, Figure 1A). In contrast to SLE, gout patients did not have elevated levels of circulating mtDNA (p=0.96), but only nDNA (p=0.006). No associations were found between markers of cell death (cDNA and NETs) and disease activity. Peroxidase activity correlated with disease activity (RAPID score: r=0.43, p=0.01, RAPID function: r=0.54, p=0.001) and inflammation markers (CRP: r=0.40, p=0.001, and ESR: r=0.43, p=0.001). Involution of ankle and wrist resulted in significant higher peroxidase levels compared to mono-articular disease (p=0.01, and p=0.03, respectively), suggesting peroxidase activity being a marker of polyarticular gout (Figure 1B). Calprotectin (S100A8/A9) correlated with the inflammation markers CRP and ESR (r=0.30, p=0.01, and r=0.30, p=0.001, respectively) and morning stiffness, especially in patients with chronic polyarticular gout (r=0.61, p=0.001).

Conclusion: To our knowledge, this is the first report demonstrating presence of NETs in the peripheral blood of gout patients. Although markedly elevated, levels of NETs did not associate with markers of disease activity or inflammation, possibly due to the lack of inflammatory mitochondrial DNA within the NETs. Even so, our data demonstrate an important role of neutrophils in gout pathogenesis, with neutrophil activation markers associating with characteristics of active, and more pronounced polyarticular disease.

REFERENCES


Disclosure of Interests: Daisy Vedder Speakers bureau: Novartis, Martijn Gerritsn Grant/research support from: Grunenthal has sponsored the Reade Cohort, Michael Nurmohamed Grant/research support from: AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, MSD, Mundipharma, Pfizer, Roche, Sanofi and UCB, Consultant for: AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Mannari, MSD, Mundipharma, Pfizer, Roche, Sanofi and UCB, Speakers bureau: AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Mannari, MSD, Mundipharma, Pfizer, Roche, Sanofi and UCB, Ronald van Vollenhoven: None declared, Christian Lood: None declared.


SA0633

PREGNANCY SUCCESS RATE AND RESPONSE TO HEPARINS AND/OR ASPIRIN DIFFERS IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS ACCORDING TO THE GAPSS SCORE

Massimmo Radin1, Irene Cecchi2, Karen Schreiber3, Savino Sciascia1, Dario Roccatello1, 1University of Turin, Turin, Italy; 2Copenhagen Lupus and Vasculitis Clinic, Copenhagen, Denmark

Background: Current standard of care (SoC) in pregnancy for patients with Systemic lupus erythematosus (SLE) and/or aPL positivity includes treatment with low dose aspirin (75–100mg/day) and low molecular heparin or unfractionated heparin. However, up to 30% of women continue to have pregnancy complications despite SoC. Therefore, identifying patients that are at greater risk to develop pregnancy complications despite the SoC and might benefit from additional therapeutic approaches, is still an unmet clinical need. Recently, our group conceived and validated the global antiphospholipid syndrome score (GAPSS) [1], as a risk score for predicting aPL-related clinical manifestations (thrombotic and/or pregnancy morbidity).

Objectives: We aimed to investigate response to SoC in women with SLE and/or aPL positivity when stratifying their risk according to GAPSS Score.

Methods: 143 women ever pregnant treated with SoC therapy with SLE and/or aPL positivity were included. Data on cardiovascular risk factors and aPL positivity were retrospectively collected. The individual GAPSS was calculated for each patient by calculating the sum of each risk factor score, as follows: 3 for hyperlipidaemia, 1 for arterial hypertension, 5 for antiphospholipid IgG/IgM, 4 for anti-β2glycoprotein I IgG/IgM, 3 for anti-phosphatidylserine/prothrombin antibodies IgG/IgM and 4 for lupus anticoagulant. The patients GAPSS was then grouped according to the patients’ GAPSS into low risk (<6), medium risk (6-11) and high risk (≥12).

Results: The analysis included 143 patients (mean age 30.8 ±6.4) with SLE (122; 85.3%) and/or aPL positivity, for a total of 352 pregnancies.

<table>
<thead>
<tr>
<th>GAPSS Score</th>
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<th>n=66</th>
<th>n=34</th>
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<tr>
<td>GAPSS &lt; 6</td>
<td>30.7 (±5.9)</td>
<td>30.6 (±6.2)</td>
<td>34 (±11.1)</td>
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Demographics

Age, mean (±S.D.)

Diagnosis

SAT0633

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Diagnosis
Overall, we observed a live birth rate of 70.5%, with a total of live birth of 248 out of the 352 pregnancies. Forty-five patients (31%) experienced at least one event of PM, defined as early or late. When considering patients who ever experienced PM while treated with SoC, all patients in the high risk group (GAPSS >12) experienced PM, while patients in the medium group (GAPSS 6-11) had a significant higher rate of PM when compared to the low risk (GAPPS <6) group [29 (43.9%) patients vs. 11 (15.3%), respectively; p<0.001]. When analysing the number of pregnancies in the three groups, patients in the high risk group had significantly lower live birth rates, when compared to the other groups [11 (40.7%) live births vs. 100 (62.1%) and 137 (82.5%), respectively; p<0.05]. Furthermore, patients with medium risk group also had significantly lower live birth rates, when compared to the low risk group (p<0.001). Figure 1 resumes the results of PM and live births divided in the three groups.

Conclusion: GAPSS might be a valuable tool for identifying patients with a higher likelihood of response to SoC.

REFERENCES


CO-MORBIDITIES ASSOCIATED WITH DISCORDANCE BETWEEN STRUCTURAL SEVERITY AND PAIN IN OSTEOARTHRITIS: IMPLICATIONS FOR CLINICAL TRIAL DESIGN IN OA – A POST-HOC ANALYSIS OF DATA FROM TWO RANDOMIZED CONTROLLED TRIALS

Jonathan Jetsmark Bjerre-Bastos1, Inger Byrjalsen1, Morten Asser Karsdal2, Jeppe Ragnar Andersen1, Asger Bihler1, 1Nordic Bioscience, Clinical Development, Herlev, Denmark, 2Nordic Bioscience, Herlev, Denmark

Background: Development of new disease-modifying drugs in OA (DMOADs) is complicated by heterogeneous study populations and insensitive endpoints of structural change and symptoms, and discordance between structural disease severity and reported symptoms. In such trials, counterintuitively, mild structural disease may be associated with severe symptoms and vice versa. Research to uncover factors disturbing the perceived severity of symptoms is needed to better characterize the clinical relevance of structural improvement, if any, in DMOAD trials. Anxiety and depressive (AD) disorders are known to affect pain sensitivity and perception, and as common co-morbidities of OA, these conditions may partly explain the observed discordance between structure and symptoms. If established, exclusion of patients with AD in DMOAD trials could potentially improve the understanding of structural benefit in a clinical context.

Objectives: The main objective of this analysis was to investigate the impact of AD on the association between structural features of OA and patient-reported pain.

Methods: Baseline data from two phase 3 trials investigating oral salmon calcitonin in OA, NCT00486344 and NCT00704847 (total N=2206), was analyzed in a post-hoc cross-sectional analysis. Patients with self-reported current or previous depression, anxiety or post-traumatic stress syndrome (PTSD) were selected and compared to a control group, matched by sex, age, BMI and JSW. Spearman’s correlation coefficient between JSW and WOMAC pain was calculated for both groups. Multiple regression analyses of both groups with WOMAC pain as the outcome variable, and age, sex, body mass index (BMI) and baseline JSW or KL-grade as explanatory variables were performed.

Results: In the AD group, 149 patients had AD in medical history of which 123 reported the condition as ongoing at baseline. The study groups of AD and matched controls (MC) were comparable in terms of age, sex, BMI, JSW, KL-grade and WOMAC pain. Associations between pain and JSW in the AD group, no significant correlation between JSW and WOMAC Pain score was found, while BMI was found to be weakly associated with WOMAC pain (R= 0.19, p=0.02) in the multiple regression analysis. In the MC group, a statistically significant (p<0.004), correlation (R= -0.24) was found between JSW and pain indicating that lower JSW was associated with higher pain, with JSW accounting for approximately 6% of the total natural variation behind reported pain. In addition, a positive significant association between male sex and WOMAC pain (R=0.18, p=0.04) was found. The univariate linear relationship between JSW and pain is illustrated in Figure 1, and multivariate analyses are shown in Table 1.

Table 1. Associations between WOMAC pain JSW (in red) and other baseline covariates

<table>
<thead>
<tr>
<th></th>
<th>Anx/Depr. group</th>
<th>Control group</th>
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<tbody>
<tr>
<td></td>
<td>rpartial P-value</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>0.04</td>
<td>0.60</td>
</tr>
<tr>
<td>BMI</td>
<td>0.18</td>
<td>0.03</td>
</tr>
<tr>
<td>Male Sex</td>
<td>0.10</td>
<td>0.21</td>
</tr>
<tr>
<td>JSW</td>
<td>0.03</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Associations between pain and KL-Grade In the model evaluating associations between KL-grade and symptoms, there was no correlation between KL-grade and symptoms in the AD group. Similar to the findings relating to JSW, in the MC group, a weak (R=0.16), borderline