Conclusion: Although the treatment was safe, short-term treatment with anti-TNFα therapy does not appear to provide clinically meaningful improvements in OA symptoms in patients with established radiographic knee OA. Analyses of structural endpoints will be reported when results are available.

REFERENCES:

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ANTIHISTAMINE USE AND STRUCTURAL PROGRESSION OF KNEE OA: A POST-HOC ANALYSIS OF TWO PHASE III CLINICAL TRIALS

A. R. Bihlet1, C. P. Miller1, I. Byrjalsen1, J. R. Andersen2, M. Karsdal2, M. C. Baker3, T. R. Rao3. 1NBCD A/S, Herlev, Herlev, Denmark; 2Nordic Bioscience A/S, Herlev, Herlev, Denmark; 3Mobility Bio Inc., Palo Alto, Palo Alto, CA, United States of America; 4Stanford, Division of Immunology and Rheumatology, Stanford, United States of America

Background: Prior studies indicate that mast cells are involved in chronic inflammation and that their activity in the synovium may contribute to structural progression of osteoarthritis (OA), however the exact role of mast cells in OA remains unclear. Antihistamines act by blocking histamine receptors, and further are found to have anti-inflammatory effects by stabilizing mast cell membranes. Current reports describing antihistamine use in OA patients suggest that antihistamines may reduce development of OA and lead to reduced risk of structural progression.

Objectives: We aimed to investigate whether antihistamine use during a two-year trial period was associated with differences in structural progression of OA, as compared with non-use.

Methods: This is a post-hoc analysis of two large phase III trials investigating oral salmon calcitonin in knee OA (NCT00486434 and NCT00704847). The primary outcome measure was structural progression defined as the change in minimum joint-space width measured by use of x-ray imaging from baseline to Year Two. In these trials, participants reported use of antihistamines, defined as medication coded with the ATC code R06A. In our study, we evaluated differences between groups of participants who reported use of antihistamines, versus those who did not, over the 2-year study period. Secondly, the duration of antihistamine use divided into categories of either non-use, 1-49, 50-299 or >300 days of use was investigated to evaluate exposure-response relationships. The effect of use of antihistamines was evaluated using ANCOVA analysis adjusting for age, sex, BMI, and baseline JSW.

Results: Of a total study population of 2,206 participants, 1,485 completed the trial. Of these, 1,327 were non-users of antihistamines (mean age 64.4 years, 64.1% female, mean BMI 29.0 kg/m²) and 158 reported use of antihistamines of any duration during the trial (mean age 64.5 years, 75.2% female, mean BMI 28.1 kg/m²). Seventy-four participants reported use of antihistamines of a duration between 1-49 days, 21 participants between 50-299 days, and 63 reported use of 300 days or more. As illustrated in Figure 1A, the mean JSW change from baseline in the group of non-users was -0.32 mm (95% CI: -0.36 to -0.29), versus -0.19 mm (95%CI: -0.29 to -0.08, p=0.02 for difference) in the group of patients reporting antihistamine use of any duration. A trend towards an association between duration of antihistamine use and reductions in narrowing of JSW was observed (p for trend: 0.02, Figure 1B).

Conclusion: Use of antihistamines was associated with reduced structural progression in knee OA. Further research evaluating the role of antihistamines in OA is needed to further characterize this observation.


Novel etiopathogenic aspects in SLE and Sjögren’s syndrome

OPO231

MASS CYTOMETRY DATA RECLASSIFY SYSTEMIC AUTOIMMUNE DISEASE PATIENTS IN PHENOTYPICALLY DISTINCTIVE GROUPS

1GENYO, Centre for Genomics and Oncological Research Pfizer/University of Granada/Andalusian Regional Government, PTS, Genomic Medicine, Granada, Spain; 2VIB Center for Inflammation Research, Data Mining and Modeling for Biomedicine, Department of Applied Mathematics, Computer Science and Statistics, Ghent University, Ghent, Belgium; 3Mammonides Institute for Research in Biomedicine of Cordoba (IMIBIC), Reina Sofia University Hospital/University of Cordoba, Cordoba, Spain; 4Servicio de Medicina Interna. Unidad de Enfermedades Autoinmunes Sistémicas, Departamento de Medicina, Universidad de Granada. Hospital Universitario San Cecilio, P.T.S. Granada, Granada, Spain; 5Servicio de Reumatología, Hospital Universitario San Cecilio, P.T.S. Granada, Granada, Spain; 6Biobanco del Sistema Sanitario Público de Andalucía, Andalusian Public Health System Biobank, Granada, Spain

Background: Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSC), Sjögren’s syndrome (SJS), mixed connective tissue disease (MCTD), primary antiphospholipid syndrome (PAPS) and undifferentiated connective tissue disease (UCTD) are classified as systemic autoimmune diseases (SADs). They are diagnosed based on different clinical and laboratory criteria. Due to their high internal heterogeneity and overlapping symptoms, SADs are difficult to diagnose. Therefore, molecular and cellular-based studies need to be undertaken to precisely classify the patients. Mass cytometry is a single-cell proteomics technology that measures approximately 50 markers per cell, thus it is a suitable tool to perform deep-phenotyping studies in SADs.

Objectives: Explore differences and similarities between SADs and build reclassification framework using high-dimensional cytometry data.

Methods: The whole blood samples collected from 129 individuals, including patients and controls were stained with a 39-plex antibody panel and acquired...
in 9 batches on a CyTOF (HELIOS) instrument. Data were cleaned, and nor-
malized for batch effects using semi-automated cytof analysis pipeline. Cell
frequencies and median signal intensities (MSI) for each population were
extracted using FlowSOM for mononuclear cells (PBMC) and Phenograph
for granulocytes. Secretion of 44 cytokines and chemokines were analyzed using
a multiplexed luminex assay. Diseases were compared by Kruskal-Wallis anal-
ysis and hierarchical clustering and reclassification was done using unsuper-
vised k-means clustering. Cytokine analysis across clusters was performed using
Kruskal-Wallis test.

Results: Differently expressed features were observed between patient groups,
regarding frequency of classical monocytes, B and T cells subpopulations,
mature and immature granulocytes and intensities of CD38, HLA-DR and CD95
across various populations. However, none of them were disease specific.
K-means clustering identified four patient clusters, which were composed by a
mixture of different diagnosis. Cluster C1 was characterized by increased levels
of circulating cells from PBMC compartment, and lower activation of different
populations of the T cell compartment. It presented lower frequency in multiple
granulocyte populations and the highest expression of CD95 and CD38. This
cluster was also associated with antimalarial and steroid treatment. Clusters C1
and C2 were exactly opposite to each other, cluster C3 was characterized by
intermediate features between C1 and C2 and cluster C4 could be considered
as undifferentiated, mixed group. Higher production of TNFα, IL-10 and IP-10
were found in patients from C1 compared to C2, suggesting more active pheno-
type in C1 and physiological one in C2. The cytokine levels were independent
of the treatment.

Conclusion: We constructed a patient reclassification framework using
cell frequencies and expression levels of functional markers. To our know-
ledge this is the first time when 7 different SADs were compared using
mass cytometry. In agreement with other reports we did not detect any
disease-specific cellular markers. Distribution of diagnosis across different
clusters confirms diseases heterogeneity. Patients can be classified into
phenotypically similar groups, that could potentially benefit from the same
line of treatment.

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OP0232

HIGH PLASMA C4D/C4 IDENTIFIES LUPUS NEPHRITIS PATIENTS WITH DISEASE MEDIATED BY ACTIVATION OF THE CLASSICAL COMPLEMENT PATHWAY


1Annexon Biosciences, Translational Medicine, San Francisco, United States of America; 2Annexon Biosciences, Research, San Francisco, United States of America; 3Annexon Biosciences, Clinical Development, San Francisco, United States of America; 4University of California, Department of Medicine, San Francisco, United States of America

Background: Proliferative lupus nephritis (LN) involves immune complex depo-
sition in the kidney that can severely impact normal renal clearance mechanisms.
Immune complexes can activate C1q and the classical complement cascade, and
along with pathogenic anti-C1q antibodies (PACAs), may amplify inflammation
and disease progression. Martin et al reported that circulating C4d, a marker
of complement activation downstream of the C1 complex, correlated well with
C4d immunohistochemistry score in kidney tissue and could be a sensitive and
specific marker for diagnosing active LN.1

Objectives: To confirm and extend observations by Martin et al, and to extend
a link between C4d, C1q activation, and PACA levels to identify patients most
likely to have the classical complement pathway as a driving component of
disease. Such patients would be potential candidates for anti-C1q therapy,
such as ANX009, to dampen disease activity and slow disease progression
(NCT04535752).

Methods: Plasma samples were collected from a cohort of 40 LN patients
(20 with disease flare and 20 without disease flare) from the California Lupus Epidemiology Study (CLUES), a multi-racial/ethnic cohort of indi-
viduals with physician-confirmed systemic lupus erythematosus, and 20 healthy controls (Table 1). A panel of complement factors, including 15 com-
plement protein and relevant complexes, were measured using an enzyme-
linked immunosorbent assay. Clinical disease activity was measured using
the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and
proteinuria was evaluated by a random spot urine protein to creatinine ratio
(UPCR).

Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Healthy Control(n=20)</th>
<th>LN Without Flare(n=20)</th>
<th>LN With Flare(n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)*</td>
<td>50 (31-60.8)</td>
<td>28.5 (26-34.5)</td>
<td>43.5 (33.5-52)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (90)</td>
<td>17 (85)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Demographics, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>8 (40)</td>
<td>1 (5)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (15)</td>
<td>9 (45)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>African American</td>
<td>5 (25)</td>
<td>3 (15)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Asian</td>
<td>8 (40)</td>
<td>7 (35)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Median UPCR (mg/mg)*</td>
<td>N/A</td>
<td>18 (13.6-5.6)</td>
<td>0.4 (0.2-0.6)</td>
</tr>
<tr>
<td>Median SLEDAI*</td>
<td>N/A</td>
<td>12 (9-16)</td>
<td>2 (2-4)</td>
</tr>
</tbody>
</table>

*Reported as median (IQR). LN, lupus nephritis; N/A, not applicable; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; UPCR, urine protein:creatinine ratio.

Results: We observed evidence of coordinated complement activation in LN patients relative to healthy controls. Specifically, levels of C4d and the C4d/C4 ratio were highly increased in LN patients with flare, while levels of C1q, C1s, and C4 were decreased, consistent with activation of the classical comple-
ment pathway (increased activation and component consumption). The C4d/
C4 ratio also correlated with levels of PACA isotypes 1 and 3 that are known
to activate the classical pathway. Improvements in C4 and C4d/C4 ratio were
associated with improvements in proteinuria and SLEDAI following treatment
for disease flare, indicating their potential value as biomarkers of treatment
response.

Conclusion: A subset of LN patients exhibited high C4d/C4 ratio along with
specific markers of classical pathway activation, indicating that the classical
complement pathway may be a driving component of their disease. Reduc-
tion in this ratio appears to correlate with treatment response, but its levels
are generally not normalized, suggesting an insufficient resolution of com-
plement-mediated inflammation by currently available treatments. Our data
support a clinical hypothesis that a subset of LN patients may benefit from
a precision medicine approach targeting the classical complement pathway
(Figure 1). This hypothesis will be evaluated in a forthcoming clinical trial
testing the subcutaneously administered C1q inhibitor ANX009 in patients
with active LN.

Figure. Unique Precision Medicine Strategy in Lupus Nephritis

REFERENCES:
Deposition in Kidneys and With Treatment Response in Lupus Nephritis.

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