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POS0006
IDENTIFICATION OF FIBROTIC AND FIBROLYTIC ENDOGENOUS IN RHEUMATIC DISEASE COHORTS
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Background: Ankylosing spondylitis (AS), psoriatic arthritis (PsA) and systemic lupus erythematosus (SLE) are distinct diseases with common molecular features such as an imbalance in fibrosis and fibrolysis in connective and calcified tissues. Type III, IV and VI collagens are abundant in connective tissue, and type I, II and X of the skeletal tissue. Blood biomarkers are available to measure fibrosis (C1M, C2M, C3M, C4M, C6M, C10C) and fibrolysis (C1M, C2M, C3M, C4M) (4% of healthy, 21% of AS, 31% of PsA, 4% of SLE pts). C4 had high biomarker levels (4% of healthy, 21% of AS, 31% of PsA, 9% of SLE pts).

Objective: To profile AS, PsA and SLE healthy, 67% of AS, 48% of PsA, 46% of SLE pts). C3 was described by median biomarker levels (8% of healthy, 67% of AS, 48% of PsA, 46% of SLE pts). C4 had high biomarker levels (4% of healthy, 21% of AS, 31% of PsA, 9% of SLE pts).

Conclusion: Fibrosis and fibrolysis blood biomarkers were significantly elevated in AS, PsA and SLE pts. Subsets of pts from each indication were found in clusters with either low (C1/2), median (C3) or high (C4) levels of fibrosis/fibrolysis biomarkers. These findings may provide a first step towards precision medicine for guiding the use of anti-inflammatory vs. anti-fibrotic treatments in pts with rheumatological disorders.

Fig. Radar plot showing medians of standardized biomarker levels by cluster.

Table. Patient group description and fibrosis/fibrolysis biomarkers levels (ng/ml) in healthy and AS, PsA or SLE pts.


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POS0007
HLA-DQ2 IS ASSOCIATED WITH ANTI-DRUG ANTI-BODY FORMATION TO INFlixIMAB ACROSS IMMUNE-MEDIATED INFLAMMATORY DISEASES
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fibrolysis (C1M, C2M, C3M, C4M, C6M, C10C) and fibrosis (PRO-C1, PRO-C2, PRO-C3, PRO-C4, PRO-C6) of these collagens.
Background: Immunogenicity is a leading cause of treatment failure to TNF inhibitors, and also affects drug safety. Variations in HLA class II genes have been suggested to predispose to anti-drug antibody formation (ADA), but characterization of biologically relevant HLA haplotypes, based on high-resolution genotyping, is lacking.

Objectives: To assess associations between HLA loci and formation of ADA to infliximab across different immune mediated inflammatory diseases.

Methods: Patients with immune mediated inflammatory diseases on infliximab therapy (N=612; 181 spondyloarthritis, 120 rheumatoid arthritis, 72 psoriatic arthritis, 114 ulcerative colitis, 80 Crohn’s disease and 45 psoriasis) participating in the Norwegian Drug Monitoring (NOR-DRUM) trials (1, 2) were included in the present analyses. Neutralising ADA were assessed with an automated fluorescence assay at each infusion. Next generation sequencing-based HLA typing was performed. Associations with ADA formation were assessed at locus, allele, haplotype and amino acid level. Peptide binding predictions for infliximab were performed.

Results: ADA were detected in 147 patients (24%). Significant associations were shown between ADA and several HLA loci, whereas conditional analyses indicated HLA–DQB1 (p=1.4x10^-6) as the primary risk locus. Highest risk of ADA formation was seen for patients carrying at least one of the HLA–DQ2 haplotypes; DQB1*02:01–DQA1*05:01 and DQB1*02:02–DQA1*02:01 (OR 3.18, 95% CI 2.15 to 4.69, p=5.9x10^-9) (Figure 1). These findings were consistent across diagnoses (Table 1), and remained significant when adjusting for other possible predictors of ADA. Computational predictions indicated that both these HLA–DQ2 haplotypes could strongly bind two peptide motifs (INTVESEDI and VYACE-VTHQ) in the infliximab heavy and light chain.

Table 1. HLA–DQ2 carrier frequencies according to the different disease phenotypes and for all diagnosis combined

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>HLA–DQ2 carrier frequency among patients with ADA formation</th>
<th>HLA–DQ2 carrier frequency among patients without ADA formation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA (N=120)</td>
<td>0.316</td>
<td>0.134</td>
<td>0.02</td>
</tr>
<tr>
<td>PsA (N=72)</td>
<td>0.55</td>
<td>0.231</td>
<td>0.01</td>
</tr>
<tr>
<td>SPA (N=181)</td>
<td>0.364</td>
<td>0.182</td>
<td>0.02</td>
</tr>
<tr>
<td>UC (N=114)</td>
<td>0.556</td>
<td>0.264</td>
<td>0.006</td>
</tr>
<tr>
<td>CD (N=80)</td>
<td>0.429</td>
<td>0.303</td>
<td>0.33</td>
</tr>
<tr>
<td>Py (N=45)</td>
<td>0.867</td>
<td>0.267</td>
<td>0.0004</td>
</tr>
<tr>
<td>All disease</td>
<td>0.469</td>
<td>0.217</td>
<td>5.9x10^-9</td>
</tr>
</tbody>
</table>

Conclusion: The risk of ADA to infliximab was three-fold higher in patients carrying the HLA–DQ2 risk haplotypes across diseases. A biological role for the HLA–DQ2 molecules encoded by the two different HLA–DQ2 risk haplotypes in the formation of ADA was further supported by peptide binding predictions. These novel findings provide promise for future incorporation of HLA–DQ2 testing to facilitate personalised treatment decisions.

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Disclosure of Interests: The authors declare that they have no conflict of interest.

Figure: Kaplan–Meier survival curves of time to ADA formation (years) for the significant HLA–DQB1*02/DQA1*05 haplotypes and HLA–DQ2

The utility of trans-bronchial lung biopsies to guide the treatment in patients with rheumatic inflammatory diseases: a retrospective cross-sectional study

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Background: Rheumatic inflammatory disease associated interstitial lung disease (R-ILD) is associated with significant mortality and morbidity. On a patient level, imaging which is a cornerstone in diagnosing R-ILD may not be sufficient to determine the underlying cause of the imaging pathology or the degree of reversibility. Furthermore the prevalence of co-morbidity and differential diagnoses such as infections or malignancy needs to be taken into account when determining the therapeutic strategy. The role of transbronchial lung biopsies (TBB) in the diagnostic workup of R-ILD is unclear and TBB is not generally recommended.

Objectives: The study objective was to examine the utility of TBB to guide treatment in a population of patients with R-ILD referred for bronchoscopy.

Methods: All patients from the Department of Rheumatology, Rigshospitalet, Copenhagen, Denmark referred for a TBB on the suspicion of R-ILD, from 2002 to 2016 were identified.

Patient demographics as well as smoking status, previous lung disease, pulmonary function test, CT-diagnosis, imaging results and immunomodulatory therapy pre- and post-bronchoscopy were obtained.

Histology findings were used to dichotomize patients into a high inflammatory or a low inflammatory group. The high inflammatory group primarily consisted of non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP), lymphocytic infiltrating pneumonia (LIP) and granulomatous inflammation whereas the low inflammatory group primarily consisted of histological findings of usual interstitial pneumonitis (UIP) and biopsies describing fibrosis and/or sparse unspecific inflammation. Therapeutic consequence was defined as intensification of therapy. Differences in treatment intensification were calculated using a binomial logistic regression model adjusted for age, gender, smoking status, previous lung disease, diffusion capacity, rheumatologic diagnosis, c-reactive protein level prior to TBB. Covariates with P>0.1 were excluded by a stepwise ‘backwards’ elimination.

Results: 96 patients had TBB performed. Biopsies from 55 patients were categorized as high-inflammatory and 41 as low-inflammatory, respectively. In the high-inflammatory group thirty-eight (69%) had their therapy intensified compared to 6 (14%) in the low-inflammatory group (P<0.001). TBB inflammation type was the only covariate that was significantly associated with treatment intensification.

No procedure related complications were registered.

Conclusion: TBB findings can guide treatment strategy in R-ILD patients with suspected activity in the pulmonary disease. TBB appears safe and could be considered as part of the diagnostic workup in patients with inflammatory diseases where clinical features, bloodsamples, imaging and/or pulmonary function test do not provide sufficient information to guide the therapeutic strategy.

REFERENCES:

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