LONGITUDINAL PRE-DISEASE TO DISEASE SERUM SAMPLES IDENTIFY BIOMARKERS THAT ARE UPREGULATED PRIOR TO THE DIAGNOSIS OF RHEUMATOID ARTHRITIS

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Background: Rheumatoid Arthritis (RA) patients have autoantibodies reactive against several citrullinated peptides that develop 10-15 years before the clinical onset of disease. However, there is a more limited understanding of serological biomarkers of disease progression, specifically those that are upregulated in patients 6-18 months before the clinical diagnosis of RA.

Objectives: Identification of biomarkers that could classify patients 6-18 months before the clinical diagnosis of RA.

Methods: We identified 500 subjects with RA, 500 with Reactive Arthritis (ReA) (based on ICDC9-CM code) as well as 250 age, gender and time-matched healthy control subjects from the Defense Medical Surveillance System (DMSS). For each subject, up to four serum samples were obtained from the Department of Defense (DoD) serum repository, 3 pre-disease diagnosis points and one immediately prior to or around disease diagnosis. A discovery subset of these serum samples was assessed for soluble PD-1 (sPD-1), as well as 497 protein analytes measured by SomaLogic SOMAscan proteomic platform.

Results: Serum levels of sPD-1 increased over time from pre-diagnosis to RA but trended to decrease over time in ReA subjects and healthy controls. A composite score of 24 SOMAscan analytes associated with recently diagnosed RA increased in serum 6-8 months before RA diagnosis and, to a lesser extent, before ReA diagnosis. IFN-inducible chemokines (CXCL9 (MIG), CXCL10 (IP-10), CXCL11 (I-TAC) and CXCL14 (BLC)) increased over time preceding RA but not ReA diagnosis. Acute phase proteins (CRP, SAA, haptoglobin) and MMP-3 increased before diagnosis in serum samples from both RA and ReA patients. These proteins represented potential new biomarkers of early RA.

Conclusion: Samples from the US DoD serum repository have identified novel biomarkers (sPD-1 and IFN-inducible chemokines) of early RA that are elevated within 8 months of disease diagnosis. These protein analyses may afford the opportunity to develop novel biomarker(s) for diagnosis and disease progression to early RA. An understanding of the role of these proteins could provide increased insight into RA pathogenesis prior to disease diagnosis.


Disclosure of Interests: The treat-to-target (T2T) strategy has been established as a key concept in the management of patients with rheumatoid arthritis (RA) aiming to achieve remission or at least low disease activity [1]. However, it might be more important for patients to set individual treatment goals which are related to their specific life context. For this reason, Ferreira at al [2] recently proposed a dual T2T strategy including both biological remission and individual patient reported symptom remission. It is currently unclear how achieving biological remission and individual patient treatment goals overlap and whether patients who reach the T2T target also reach their individual treatment goals.

Objectives: To explore if achieving T2T biological remission and individual patient treatment goals overlap in RA patients with initially low, moderate, or high disease activity (LDA, MDA, HDA).

Methods: We recruited a consecutive convenience sample of patients with RA diagnosed according to ACR/EULAR criteria and with LDA, MDA, or HDA into this observational longitudinal study. Disease activity was measured with the Clinical Disease Activity Index (CDAI) and the individual patient goals were assessed with the Goal Attainment Scale (GAS) at baseline and after three to five months. The number and proportion of patients who reached the T2T target, but not their individual goals and vice versa were calculated.

Results: We enrolled 162 patients in the study (131 [80.9%] women, median age 59.0, IQR= 49-71). 101 patients (62%) had a follow up visit with no missing data after three to five months. Of these, 48 (47.6%) patients had LDA, 43 (42.6%) had MDA, and 10 (9.9%) had HDA at baseline. 62 patients (61.4%) reached remission (14.7%) or stayed in LDA, 43 (42.6%) had MDA, and 10 (9.9%) had HDA at baseline. Of these proteins could provide increased insight into RA pathogenesis prior to disease diagnosis.
had to be supplemented by the individual patient reported treatment goals.

REFERENCES


Table 1. Comparison of achieved T2T and individual patient goals

<table>
<thead>
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<th>T2T achieved, n (%)</th>
<th>Yes</th>
<th>No</th>
<th>Overall</th>
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</thead>
<tbody>
<tr>
<td>Patient goal(s) achieved, n (%)</td>
<td>44</td>
<td>22</td>
<td>66 (65.3)</td>
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<tr>
<td>(43.6)</td>
<td>(21.8)</td>
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<td>18</td>
<td>17</td>
<td>35 (34.7)</td>
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<td>(17.8)</td>
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<tr>
<td>Overall</td>
<td>62</td>
<td>39</td>
<td>101</td>
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<tr>
<td>(61.4)</td>
<td>(38.6)</td>
<td>(100.0)</td>
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Disclosure of Interests: Claudia Oppenauer: None declared, Martina Durechova: None declared, Martin Zauner: None declared, Martin Posch: None declared, Susanne Urach: None declared, Klaus Machold: Grant/research support from: AbbVie, Bristol-Myers Squibb, and MSD, Consultant for: AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Medac, Merck, MSD, Pfizer Inc, Roche, and UCB, Speakers bureau: AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Medac, Merck, MSD, Pfizer Inc, Roche, and UCB, Ricardo Ferreira: None declared, Tanja Stamm: Grant/research support from: HTS.

Patient goal(s) achieved, n (%) Yes No Overall

T2T achieved, n (%) Yes 44 22 66 (65.3) (%) (43.6) (21.8) No 18 17 35 (34.7) (17.8) (16.8) Overall 62 39 101 (61.4) (38.6) (100.0)

BACKGROUND

Tenderness, swelling and loss of motility of the joints are the main determinants of the disability function (DF) of Rheumatoid Arthritis (RA) patients (RApts)1. The evaluation of DF is performed by Patient Reported Outcomes (PROs), like Health Assessment Questionnaire (HAQ)2. The lack of objective evaluation of DF is one of the most important "unmet needs" in RA. The Hand Test System (HTS) is an engineered glove, nowadays applied for neuroscience studies to evaluate hands motility with interesting perspectives of use in other clinical research fields3,4.

OBJECTIVES

To quantify the DF of RApts by the analysis of speed and right execution of fingers opposition movement in both hands, evaluated by HTS. To verify the correspondence with the HAQ.

METHODS

In this pilot study 14 consecutives RApts (3 males, 11 females, mean age 61 ± 11,5 years, mean duration of disease 11,21 ± 5,07 years), classified according to 2010 ACR/EULAR criteria5, and 13 healthy controls (HC, 7 males, 6 females, mean age 50 ± 15 years) were enrolled from the RC clinic. After consent, all participants undergone HTS test that recognizes the touches between the finger tips during the opposition movements of the hands in standard sequences of movements, after dressed in a glove. A multiple finger evaluation (MFE) and a single finger evaluation (SFE) were performed using a dedicated software that provided the touches between the finger tips during the opposition movement in both hands, evaluated by HTS.

RESULTS

In RApts seemed to perform slightly better than a clinically active finger (AF) but significantly worse than average HC finger (ANOVA, p < 0.001).

CONCLUSION

HTS is a new easy and totally safe tool that seems to quantify in an objective manner the hand DF in RApts. The significant correlation found with HAQ underlines the value and veracity of self-assessment tools in clinical practice. Further studies are ongoing with larger number of RApts to validate its application to monitor the improvement or the worsening of RA in order to optimize pharmacological treatments. The study is now extended in other Rheumatoid and Musculoskeletal Diseases.

REFERENCE


Disclosure of Interests: None declared


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NOVEL SUBCLASS OF INTRAVASCULAR NON-CLASSICAL SYNOVIAL MONOCYTES ARE CRITICAL FOR RHEUMATOID ARTHRITIS

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BACKGROUND

There are at least three populations of circulating monocytes: classical, intermediate and non-classical. We demonstrated that circulating non-classical monocytes are required for the effector phase of arthritis and spontaneous models of arthritis in mice. While the vast majority of studies on monocytes have focused those in circulation, very little is known about the monocytes in the synovium.

OBJECTIVES

The aim of this study was to examine the heterogeneity of tissue monocytes with those circulation and determine their involvement in inflammation.

METHODS

Female 8-10-week-old NR4A1 -/-, CX3CR1 ERCre.zsGFP, and C57Bl/6 mice were used in all studies. CX3CR1IRG4GFP mice were utilized for cell tracking studies and joint shielded bone marrow chimeras via administration of tamoxifen (tam). Intravascular monocytes were identified using fluorescent anti CD45 antibody before perfusion. STIA was induced via I.V. KBxN sera. Monocyte populations were quantified by flow cytometry and FACScan sorted for RNA-sequencing (RNA seq). Nonclassical tissue monocytes were identified CD45+CD11b+Ly6G-TIM4-CD64-Ly6clo and subdivided into intravascular (CD45-labeled, CD43+), trans-vascular (CD45-labeled CD43-) and extravascular (no CD45-label). Human synovial was obtained from ultrasound guided synovial biopsies and CD45+ cells were FACSorted for single cell RNA seq.

RESULTS

NR4A1 -/- mice exhibit a 95% reduction in circulating Ly6c- monocytes but retain Ly6c+ cells in the joint and develop STIA. The transcriptional profiling of bulk populations of Ly6c+ cells in the synovium are distinct from those circulating in the blood. We then identified three populations of Ly6c+ monocytes in the joint; extra-vascular, trans-vascular, and intra-vascular cells using 18 color flow cytometry. Lineage tracing studies reveal that the origin of extra-vascular and trans-vascular synovial monocytes are from the embryo while the intravascular monocytes are derived post-natally. The intravascular monocytes are depleted with clodronate loaded liposomes while the extravascular and trans-vascular remain unaffected. Moreover, the intravascular monocytes rapidly expand during the first 1hour of STIA, increasing by 30x in population size. RA patients also display similar populations of non-classical monocytes using single cell RNA seq.

CONCLUSION

We have identified and described three previously uncharacterized populations of non-classical monocytes cells in the joint, an intravascular adherent, a trans-vascular population and an extra-vascular