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Adaptive immunity (T cells and B cells) in rheumatic diseases / Innate immunity in rheumatic diseases

OP0066 IMPACT OF DIAGNOSIS AND TREATMENT OF TROPHERYMA WHIPPLEI INFECTION IN PATIENTS WITH PRE-EXISTING CHRONIC INFLAMMATORY RHEUMATIC DISEASES: DATA FROM THE NATIONAL TW-IRD REGISTRY

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Background: Tropheryma whipplei (Tw) infection is a rare condition, characterized by inflammatory joint symptoms in more than 75% of the cases, which can lead the physician to diagnose chronic inflammatory rheumatic diseases (IRD) and to initiate DMARDs. DMARDs are often ineffective and may reveal digestive signs, systemic manifestations or involvement of other organs. We hypothesized that treatment of Tw infection has a favorable impact on rheumatologic and extra-rheumatologic manifestations attributed to IRD.
Objectives: To validate this hypothesis, we initiated a registry with the objectives to describe the characteristics of IRD and their treatments, the diagnostic and therapeutic modalities of Tw infections and the impact of the treatment of Tw infection on the evolution of IRD and associated DMARDs.
Methods: We initiated a French National register including adult patients with pre-existing IRD, treated with DMARDs, later diagnosed with Tw infection. Cases were identified through a call for observation via the "Club Rhumatismes et inflammations" website. We collected clinical and biological data about the characteristics of IRD and their treatments, the diagnostic and therapeutic modalities of Tw infections, and the impact of the treatment of Tw infection on the evolution of IRD and associated DMARDs.
Results: Seventy-three IRD patients were included. Mean age at diagnosis was 49 years (SD +/- 10.9), with 78% of men, median IRD duration was 79 months (IQR 36; 140), including rheumatoid arthritis (31 cases), spondyloarthritis (14 cases), psoriatic arthritis (6 cases) and other IRDs (22 cases). All IRD patients were treated with DMARDs, with no therapeutic response in 51% of the cases, worsening of rheumatologic symptoms in 34% of the cases, and occurrence of extra-articular manifestations in 27% of the cases. Screening for Tw infection mainly involved saliva and stool PCR, while diagnostic modalities involved organ specific PCR and biopsies, in particular duodenal biopsies (PCR positive in 87% of cases and histology in only 38% of cases). At the time of Tw infection diagnosis, mean age was 58 years (SD +/- 10.1), all patients had joint involvement, 33% axial involvement, 11% entheseal involvement, 84% extra-articular manifestations, 93% elevated CRP, 86% hypoalbuminemia and 67% anemia. Tw infection treatment modalities (median follow-up of 22 months) mainly involved a combination of doxycycline (95%) and hydroxychloroquine (96%), with complete recovery in 79% of the cases and Tw-related deaths in 2 cases. At the same time, Tw infection treatment was associated with IRD remission in 93% of cases, with a median time to remission of 2 months (IQR 1; 4.25), leading to DMARD withdrawal in 94% of cases and corticosteroid therapy withdrawal in 65% of cases.
Conclusion: A Tw infection should be considered in IRD patients with peripheral joint involvement and inadequate response to DMARDs, particularly in the presence of extra-articular manifestations, elevated CRP and hypoalbuminemia. In such patients, positive results of screening and diagnostic tests for Tw infection may lead to the initiation of Tw infection treatment which is associated with complete recovery of Tw infection and rapid remission of the IRD, allowing DMARD and corticosteroid therapy withdrawal in most the cases.
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Disclosure of Interests: None declared.
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OP0067 MORE THAN SIX-FOLD INCREASED MORTALITY RISK IN PATIENTS WITH INCIDENT RHEUMATOID ARTHRITIS AND DEPRESSION IN A LARGE COHORT WITH 10-YEAR FOLLOW-UP

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Background: The occurrence of depression is increased in patients with rheumatoid arthritis (RA) compared with the background population. (1) Recently, we described that in RA the most frequent indication for filling antidepressant prescriptions is depression and the frequency of filling coincides with the occurrence of depression reported in the scientific literature. (2) In patients with stroke, depression defined as filling of antidepressants or a diagnosis with depression is associated with increased mortality risk and the risk is similar for both definitions of depression. (3)
Objectives: We used the first filling of antidepressants as proxy for depression with the objective to describe the mortality risk associated with depression in patients with incident RA.
Methods: We included patients diagnosed with incident RA (index date) from the nationwide DANBIO register (4) from January 1, 2008 to September 30, 2018. Participants were identified by unique personal registration numbers. Included patients were without a recorded filling of methotrexate (Anatomic Therapeutic Chemical code L01BA01) and antidepressants (N06A) in the Danish National Prescription Register or recorded hospital contacts with RA and depression (International Classification of Diseases (version 10) codes M05, M06, F32) in the Danish National Patient Register, three years prior to the index date. From the index date, we defined depression as first filling of antidepressants and collected death dates from the Danish Civil Registration System. The participants were followed until December 31, 2018 and all-cause mortality estimated in two dynamic risk periods: the period from the index date until first filling of antidepressants (if it occurred) and the period after filling of antidepressants. We calculated hazard rate ratios (HRR) by modelling filling of antidepressants as time-varying exposure for total follow-up and adjusted for potential confounders defined *a priori*: age, sex, comorbidity, cohabitation, employment status, highest attained education, and income. Cumulative mortality was described by Kaplan-Meier curves. Results were reported with 95% confidence intervals (CI).
Results: Among 11,071 RA patients followed for 56,993 person-years, 1,095 (10%) filled prescriptions for antidepressants. The median age at diagnosis was 61 years, 66% were female, and 64% diagnosed with seropositive RA. Adjusted HRR was highest in the age group <55 years but also increased between 55-70 years, >70 years, among females and males, and in patients diagnosed with seropositive and seronegative RA (Table 1). The cumulative mortality is seen in Figure 1.

Table 1.

Strata		HRR (95% CI)	
		Crude	Adjusted
Age, years	<55	8.40 (4.20-16.80)	6.66 (2.80-15.85)
	55-70	3.27 (2.35-4.54)	3.30 (2.27-4.80)
	>70	2.97 (2.36-3.75)	2.94 (2.26-3.83)
Sex	Female	3.72 (2.95-4.70)	2.91 (2.22-3.81)
	Male	3.10 (2.32-4.15)	3.70 (2.66-5.14)
RA diagnosis	Seropostive (M05)	3.73 (2.99-4.65)	3.45 (2.66-4.47)
	Seronegative (M06)	2.85 (2.07-3.91)	3.08 (2.17-4.37)

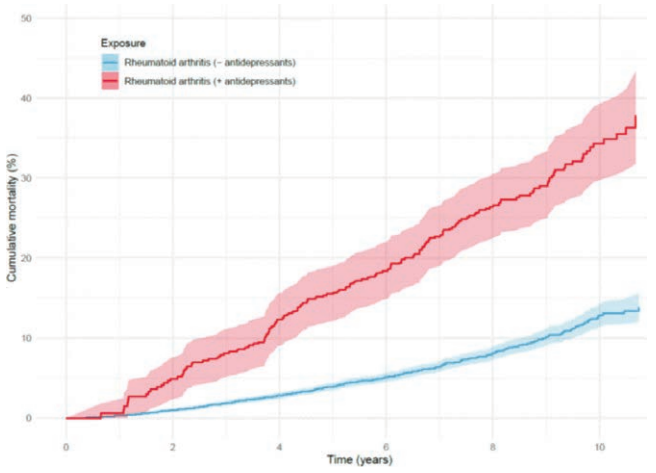

Figure 1.

Conclusion: Depression, defined as first filling of antidepressants, was associated with more than six-fold increased mortality risk in patients with incident RA.

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OP0068

DISTINCT STROMAL AND IMMUNE CELL INTERACTIONS SHAPE THE PATHOGENESIS OF RHEUMATOID AND PSORIATIC ARTHRITIS

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Background: Rheumatoid (RA) and psoriatic arthritis (PsA) are common autoimmune and autoinflammatory diseases of unknown aetiology characterised by complex synovial pathology with a detrimental effect on the patient's quality of life. Significant differences in pathophysiology may explain distinct clinical manifestations and account for differential responses to specific therapeutics. Recent implementation of single cell transcriptomic analysis of sorted synovial cells has revealed the diverse cellular landscape of the RA synovial stromal and immune cell compartments, however, a complete analysis of immune and stromal cells in tandem, for RA and PsA patient synovial tissue has not been performed.

Objectives: To combine novel scRNA transcriptomic approaches and *ex vivo* assays in order to: identify differences in the cellular landscape of RA and PsA synovial tissue inflammation and immune – stromal cell interactions that drive pathology in RA and PsA.

Methods: Single cell transcriptomic profiling of 178,000 synovial tissue cells from 5 PsA and 4 RA patients, importantly, without prior sorting of immune and stromal cells. This approach enabled the generation of a unique cell atlas of intact synovial tissue identifying immune and stromal cell interactions. State of the art data integration and annotation techniques identified and characterised 18 stromal and 14 immune cell clusters. Bioinformatic examination of cell-cell communication via construction of receptor-ligand interaction networks with further *in vitro* validation of stromal and immune cell crosstalk through flow cytometric analysis, multiplex ELISA and mitochondrial and single cell metabolic profiling by multiphoton and florescent lifetime imaging microscopy, seahorse.

Results: Following quality control and data integration the PsA and RA cellular landscape was generated and nine mega clusters indicative of fibroblasts, endothelial cells, pericytes, macrophages, dendritic cells (DC), B cells, plasma cells, T cells and NKT consisting of several sub clusters were identified. Distinct points of transcriptomic deviation and convergence between RA and PsA were identified for each of the major cell types of the joint. Specifically, cell cycle and trajectory analysis revealed that only a fraction of synovial T cells are actively proliferating. Additionally, the differential usage of immunoglobulin light chains by memory and plasma cells indicates that plasma cells are potentially not derived from the local memory B cell pool of the synovial tissue. Importantly, we report distinct fibroblast and endothelial cell transcriptomes indicating differentially abundant subpopulations in RA and PsA characterised by distinct transcription factor usage and signalling pathway enrichment. Specifically transcriptomic imputation analysis revealed abundance of invasive FAPα^{+}THY1^{+} regulated by transcription factor TEAD1 in RA compared to PsA synovial tissue. In order to identify potential cell-cell communication driving inflammation in RA and PsA, novel receptor–ligand interaction networks were generated and downstream of the receptor, target characterisation was performed. Herein we identify RA-specific synovial T cell-derived TGF-β and macrophage IL-1β synergy in driving the transcriptional profile of FAPα^{+}THY1^{+} invasive synovial-fibroblasts, expanded in RA compared to PsA synovial tissue biopsies (Figure 1). Ex vivo treatment of RA patient synovial fibroblasts identified TGF-b and IL-1b synergy are a major driver of IL-6 production, fibroblast activation and adhesion molecule expression. Interestingly, the aforementioned proinflammatory changes of RA patient synovial fibroblasts were coupled with significant alterations in mitochondrial eccentricity and size and a marked metabolic adaptation towards a strongly glycolytic profile (Figure 1).

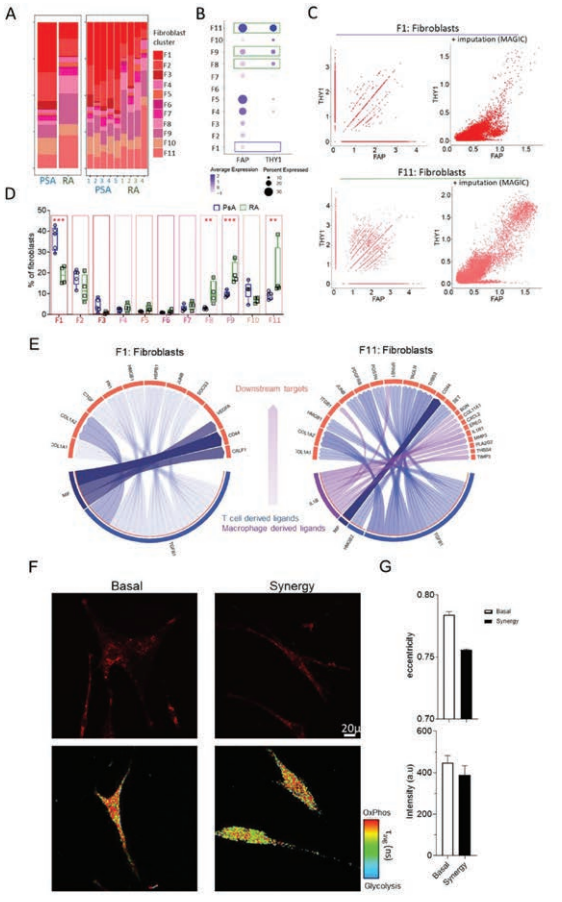

Figure: Immune-stromal cell crosstalk as a driver of synovial inflammation.
A. Abundance of fibroblast clusters in RA and PsA patient synovial biopsies. B. Expression and percentage of positive cells per fibroblast cluster for FAP and THY1. C. Scatterplots for showing the relation between THY1 and FAP expressing cells before and after data imputation for RA and PsA fibroblast cluster 1 and fibroblast cluster 11. Fibroblast clusters with significantly different abundances between RA and PsA are indicated by green (higher in RA) and blue (higher in PsA) boxes. D. Frequency of fibroblast clusters in PsA and RA patient synovial biopsies (n=4-5), data are presented as Box and whiskers plots (min to max), symbols represent individual samples. E. Circo plot depicting the top ligand and downstream target interaction for enriched in PsA synovial fibroblast cluster F1 and enriched in RA, invasive synovial fibroblast cluster F11. F. Representative images of RA patient synovial fibroblasts mitochondrial and metabolic analysis. G. Synovial fibroblast eccentricity and staining intensity under basal conditions or following treatment with TGF-b and IL-1B.

Figure 1.