Objectives: To study early ADAs formation according to clinical response to an adalimumab therapy in RA patients and the relationship between ADAs and circulating B cell subsets.
Methods: 28 RA patients and 13 healthy controls were included. Patients all presented inadequately controlled RA under conventional treatment, were naive of biotherapies, and started an adalimumab treatment at baseline (M0). Responder status was determined according to the DAS28CRP score (<or>3.2) at 3 (M3) and 6 months (M6). ADAs plasma concentration >10pg/mL at M3 defined the immunized patient group. Circulating B cell subsets were quantified by flow cytometry at M0 and M3.
Results: 11 (42.3%) patients were immunized at M3. Among them, 4 (36.4%) were responders at M6 and 7 (63.6%) were non-responders. Presence and concentration of ADAs at M3 was associated to non-responder status at M6 (p=0.043; p=0.042). Immunized patients had lower transitional B cells count at M0 compared to non-immunized patients (p=0.031).
Conclusion: A high but classical proportion of RA patients developed ADAs after only 3 months of adalimumab treatment. This immunization was associated to non-responder status at M6 and to a low blood transitional B cells count at baseline. Our results suggest transitional B cells implication in
RA activity and biotherapy resistance due to immunization. Low concentrations of transitional B cells could be an early biomarker of immunization process against adalimumab.
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Table. Patients characteristics at baseline

Characteristics	All RA patients (n=28)	M6 responders (n=16)	M6 non-responders (n=10)
Age (years)	60.5 [47-78]	65.5 [47-76]	54 [47-78]
Sex ratio M/F (% of F)	0.4 (71,4%)	0.5 (68.8%)	0.3 (80.0%)
Disease duration, (years)	5.6 [0.7-43.0]	6.8 [1.0-43.0]	2.9 [0.7-31.0]
Oral steroid use, (%)	18 (64,3%)	9 (56.2%)	8 (80.0%)
Oral steroids, dose (mg/day)	5.0 [2.0-15]	5.0 [4.0-12.5]	8.5 [2.5-15.0]
Methotrexate use, (%)	24 (50.9%)	14 (87.5%)	8 (80.0%)
Methotrexate, dose (mg/week)	20 [10-25]	20 [10-25]	15 [10-20]*
Leflunomide use, (%)	3 (10.7)	1 (6.3%)	2 (20.0%)
Leflunomide, dose (mg/day)	20 [20-20]	20 [20-20]	20 [20-20]
CRP, (mg/dL)	5.5 [1.0-57.0]	6.6 [1.0-46.8]	3.6 [1.0-57.0]
DAS28CRP score	4.3 [3.3-5.7]	4.1 [3.3-5.2]	4.5 [3.4-5.7]
RF positive, (%)	20 (71.4%)	12 (75.0%)	6 (60.0%)
RF, (U/mL)	116 [19-640]	88 [21-640]	181 [19-336]
ACPA positive, (%)	25 (89.3%)	15 (93.8%)	8 (80.0%)
ACPA, (U/mL)	340 [11-340]	340 [14-340]	340 [11-340]

Values are medians with ranges and frequencies with percentages. *p=0.050.

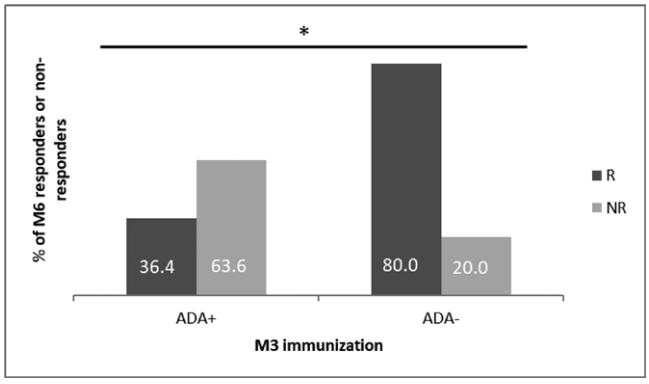

Figure 1. Graph 1 Immunization against treatment at 3 months and clinical response at 6 months in RA patients (n=26). Presence of ADAs at 3 months is associated to non-responder status at 6 months. Fisher exact test.R, responders at 6 months; NR, non-responders at 6 months; ADA+, immunized patients at 3 months; ADA-, non-immunized patients at 3 months.

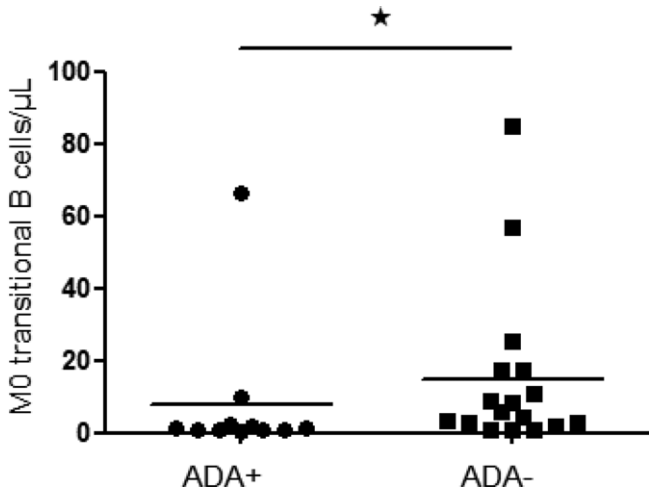

Figure 2. Graph 2 Absolute number of transitional B cells at baseline in RA patients (n=28) according to immunized status at 3 months. Immunized patients at 3 months had lower transitional B cells at baseline than non-immunized patients. ADA+, immunized patients at 3 months; ADA-, non-immunized patients at 3 months. Data represent the mean; *p<0.05 by Mann-Whitney U test.

Disclosure of Interests: None declared
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AB0035 **TWO DIFFERENT ABNORMAL BEHAVIORS IN CD4+T LYMPHOCYTES IN FIBROMYALGIA PATIENTS AND FIBROMYALGIA ASSOCIATED TO SJÖGREN'S SYNDROME**

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Background: Primary fibromyalgia syndrome is a prevalent rheumatic condition characterized by widespread pain and whose etiopathogenesis is not well understood. Fibromyalgia can also be secondary to other rheumatic diseases like Sjogren's syndrome; however, its relation to this disease is unknown. It has been suggested that the immune system is involved in their pathogenesis. The role of activation stages and cytokines profiles of CD4+T lymphocytes in fibromyalgia or fibromyalgia secondary to Sjogren´s syndrome are completely unclear and could play a key role in the pathophysiology of these diseases.
Objectives: The objective of this study is to investigate the counts and distribution of the CD4+T lymphocyte activation subsets and their pattern of cytokine production in women with primary fibromyalgia, fibromyalgia secondary to Sjogren´s, Sjogren´s syndrome and healthy controls (HC). The counts and distribution of naïve (T_N), central memory (T_{CM}), effector memory (T_{EM}) and effector (T_E) CD4+T lymphocyte subsets were analyzed in these diseases. Furthermore, we investigated their pattern of IL-4, IL-10, IL-17A, IFNγ, and TNFα production.
Methods: Counts and distribution of CD4+T subsets (T_N, T_{CM}, T_{EM}, $T_{E)}$ and their cytokine producing capacity were measured using multiparametric flow cytometry in peripheral blood mononuclear cells (PBMC) from 20 primary fibromyalgia, 15 fibromyalgia associated to Sjögren and 15 primary Sjögren patients and 15 female controls. Fibromyalgia and/or Sjögren's syndrome were diagnosed based on ACR criteria. CD4+T cell activation stages were analyzed by the expression of the CD3, CD4, CD45RA, CD27 and CCR7 antigens. Cytokine CD4+T producing cells subsets were assayed stimulating PBMC during 6 hours, fixed, permeabilized and simultaneously stained with IL-4, IL-10, IL-17A, IFNγ, and TNFα intracellular cytokines.
Results: Fibromyalgia patients showed a significant increase in the CD4+T, T_N and T_{CM} cells counts with compared to fibromyalgia secondary to Sjogren, Sjogren´s syndrome and HC. The counts of IL-17A, IL-4 and IFNγ producing

CD4+T cells were increased in fibromyalgia patients with respect to HC. However, only IL17A and IFNγ, but not IL-4 producing CD4+T lymphocytes were increased with respect fibromyalgia secondary to Sjogren. These alterations were due to an increment of T_{EM} IL-17A, T_{CM} and T_{EM} IL-4 and T_N T_{CM} and T_{EM} IFNγ producing CD4+T cell subsets in fibromyalgia patients. Furthermore, IFNγ producing CD4+T cells were decreased in fibromyalgia secondary to Sjogren´s with respect to fibromyalgia patients and HC. Counts of T_N TNFα producing CD4+ T cells were increased in fibromyalgia with respect fibromyalgia secondary to Sjogren. IL-10 producing CD4+T cells were normal in fibromyalgia but decreased in fibromyalgia secondary to Sjogren.

Conclusion: Fibromyalgia patients show an abnormal circulating activation stages of CD4+T cells, as well as, express unusual elevated counts of CD4+T cells producing IL-17A, IL-4 and IFNγ. These alterations could differentiate two different pathologic and inflammatory behaviors of the T cell compartment between fibromyalgia and fibromyalgia secondary to Sjogren patients.

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AB0036 CHILDREN WITH EXTENDED OLIGOARTICULAR AND POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS HAVE A CYTOKINE PATTERN FAVOURING B CELL ACTIVATION IN CIRCULATION

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Background: Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. The majority of polyarticular JIA (pJIA) and a large fraction of extended oligoarticular JIA (oJIA) patients fulfil classification criteria for rheumatoid arthritis (RA) in adulthood. B-cells play several important roles in RA pathogenesis, but it is still unclear if the pattern of B-cell involvement in pJIA and extended oJIA follows what has been described for adults with RA.

Objectives: The main goal of this study was to determine the concentration of cytokines potentially relevant for B-cell activation in serum from children with pJIA and extended oJIA when compared to children with persistent oJIA, adult JIA, early and established RA.

Methods: Serum samples were collected from children with extended oJIA (n=8), persistent oJIA (n=6), pJIA (n=6), adult JIA (n=8), untreated early RA (<1 year of disease duration, n=12), established RA patients treated with synthetic disease-modifying anti-rheumatic drugs (DMARDs) (n=10) and two groups of age- and sex-matched healthy donors (children, n=6 and adults, n=10). A proliferation-inducing ligand (APRIL), B-cell activating factor (BAFF), interleukin (IL)-6 and IL-21 serum levels were measured by enzyme-linked immunosorbent assay (ELISA).

Results: Children with extended oJIA, early and established RA patients had significantly higher BAFF serum levels when compared to controls, but no significant differences were observed in children with persistent oJIA, pJIA and adult JIA when compared to all groups included. APRIL serum levels were significantly increased in early and established RA patients when compared to both controls and children with persistent oJIA. No significant differences were found in APRIL concentrations between children with JIA, adult JIA and controls. IL-6 serum levels were significantly increased in children with extended oJIA, pJIA, early and established RA when compared to controls, but no significant differences were found in children with persistent oJIA and adult JIA patients. IL-21 serum levels were significantly increased in early RA when compared to controls, but no significant differences were observed between any of the other groups included.

Conclusion: The similarity in B-cell cytokine pattern found between extended oJIA, pJIA, early and established RA patients, contrarily to what was observed in persistent oJIA, suggests an early B-cell involvement in the pathogenesis of extended oJIA and pJIA as described for RA.

Disclosure of Interests: None declared

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AB0037 EXPRESSION OF NEGATIVE CHECKPOINT MOLECULES BTLA AND HVEM IS DYSREGULATED IN AUTOIMMUNE DISEASES

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Background: Immune checkpoint blockade with agents targeting CTLA4 and PD-1/PD-L1 alone or in combination has demonstrated exceptional efficacy in multiple cancer types by "unleashing" the cytotoxic action of quiescent, tumor-infiltrating T cells. However, the therapeutic action of these immunotherapies goes hand in hand with the loss of immune tolerance and appearance of immune-related adverse events such as colitis, arthralgia and inflammatory arthritis in responsive patients. Therefore, immune checkpoint molecules have been proposed as targets for the treatment of autoimmune diseases.

Objectives: Herein, we interrogate the potential of BTLA/HVEM axis as a target for restoring immune homeostasis in rheumatoid arthritis (RA), Systemic Lupus Erythematosus (SLE) and Sjogren's Syndrome (SjS) by examining their expression patterns in autoimmune disease tissues.

Methods: Message and protein expression of BTLA and HVEM were examined in RA and SLE synovial tissues, SLE cutaneous lesions, SjS salivary glands and peripheral blood samples of autoimmune disease by RNA sequencing and flow cytometry.

Results: Tissue dysregulation of the BTLA-HVEM axis was observed: Increased BTLA RNA level in RA synovium, SLE-affected skin, and SjS salivary gland samples, whereas HVEM level was affected only in the RA synovium when compared to unaffected tissues. Detailed immunophenotyping of B, T, and myeloid cell populations in RA, SLE, SjS and healthy control PBMCs revealed differential modulation of the BTLA+ or HVEM+ immune cell subsets in a disease-context dependent manner. SjS patients showed an overall decrease in memory B cells and most of the BTLA+ B cell subsets while a decrease in HVEM+ B cells was observed only in SLE PBMC samples and not RA and SLE samples. Immunophenotyping with a T cell panel exhibited decreased BTLA and HVEM expression on T cell subsets in SjS and SLE but not in RA patients. In addition, protein levels of HVEM were differentially decreased in SLE myeloid cell subsets. Finally, we demonstrate tissue-specific surface expression patterns of BTLA in RA and SLE samples: higher surface BTLA levels on RA and SLE PBMC B cells than matched tissue-derived B cells.

Conclusion: Our results demonstrate a dysregulation of the BTLA/HVEM axis in either lesional tissue or peripheral blood in an autoimmune disease context-dependent manner. These results also indicate the potential of targeting BTLA-HVEM axis for the treatment of multiple autoimmune diseases.

Disclosure of Interests: Sunil Nagpal Shareholder of: Janssen Pharmaceuticals, Employee of: Janssen Pharmaceuticals, Suzanne Cole Shareholder of: Janssen Research & Development employee, Employee of: Janssen Research & Development employee, Achilleas Floudas: None declared, Mihir Wechalekar Grant/research support from: Grant from Janssen Research & Development, Qingxuan Song Shareholder of: Employee of Janssen Research, Employee of: Employee of Janssen Research, Tom Gordon: None declared, Roberto Caricchio Grant/research support from: Financial grant from Janssen Research & Development, Douglas Veale: None declared, Ursula Fearon: None declared, Navin Rao Shareholder of: Janssen Pharmaceuticals, Employee of: Janssen Pharmaceuticals, Ling-Yang Hao Shareholder of: Employee of Janssen Research, Employee of: Employee of Janssen Research

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AB0038 IMMUNE PHENOTYPING OF ERDHEIM-CHESTER DISEASE THROUGH MASS CYTOMETRY

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