FRI0042 BAFF-R EXPRESSION IN NAÏVE CD5+IGM+ B CELLS IN RHEUMATOID ARTHRITIS PATIENTS REPOPULATING AFTER RITUXIMAB

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Background: Serum levels of B cell activating factor (BAFF) rise following Rituximab (RTX) therapy in patients with Rheumatoid arthritis (RA). CD5+IgM+B cells are present within transitional and naïve B cell subsets and their increased production or accumulation is associated with some autoimmune diseases. Previous studies have shown that BAFF does not enhance their survival compared with CD5- naïve B cells, suggesting that signalling pathways are important in promoting their survival.
Objectives: To determine serum BAFF levels and BAFF-receptor (BAFF-R) expression in CD5+IgM+B cells in healthy controls (HC), RTX-naïve RA patients (pre-RTX), and relapsing at different time points after peripheral B cell repopulation post-RTX treatment, divided into 2 groups: early relapsers (0–3 months post-B cell return) and later relapsers (>4 months post-B cell return).
Methods: Immunophenotyping of peripheral blood mononuclear cells was used to determine %CD5+IgM+B cells and BAFF-R (% and expression, mean fluorescence intensity (MFI)) in 5 HC, 13 pre-RTX and 12 post-RTX RA patients. Results were analyzed with respect to timing of relapse after peripheral B cell return (≥5 B cells/μL) and serum BAFF levels.
Results: %CD5+IgM+B cells, but not absolute numbers, were significantly higher in post-RTX early relapsers compared to HC ($p<0.01$), pre-RTX patients ($p<0.001$) and post-RTX later relapsers ($p<0.01$). There was a strong inverse correlation between %CD5+IgM+B cells and time after B cell return ($r^2=0.88$, $p<0.0001$). BAFF-R+ expression was significantly lower in both post-RTX groups compared to HC and pre-RTX patients; early relapsers showed the lowest % and MFI BAFF-R+ expression, compared with later relapsers ($p<0.01$). BAFF-R+ expression increased with time after B cell return, both % ($r^2=0.47$, $p<0.002$) and MFI ($r^2=0.76$, $p<0.0004$). BAFF levels were significantly higher in both post-RTX groups compared to HC and pre-RTX patients, with the highest BAFF levels in early relapsers ($p<0.05$ compared to later relapsers). There was a significant inverse correlation between BAFF levels and % ($r^2=0.51$, $p<0.01$) and MFI ($r^2=0.4$, $p<0.05$) BAFF-R+ expression.
Conclusions: Early relapsers show increased %CD5+IgM+ naïve B cells, and decreased BAFF-R expression, similar to ontogeny and what is seen in cord blood B cells. Whether the increased numbers of CD5+ naïve cells were contributing to relapse was not determined but they have the capacity to rapidly mature into autoantibody producing plasma cells, independent of the BAFF/BAFFR system. BAFF-R expression was found to increase with time after B cell return, again mirroring ontogeny with a later relapse showing more normalized BAFF/BAFF-R levels, suggesting their mechanism of relapse may follow a more conventional B cell differentiation pathway.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.6604

FRI0043 PEPTIDES HIGHLY SPECIFIC TO THE VARIABLE REGION OF TNF-ALFA-SPECIFIC REFERENCES LICENSED (RL) MONOCLONAL ANTIBODIES (MAB), AS POTENTIAL TOOL TO EFFECTIVELY ASSESS SIMILARITY BETWEEN BIOSIMILARS AND THE CORRESPONDIG RL MAB

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Background: Monoclonal antibodies (mAb) have greatly facilitated the development of highly specific immunotherapy, with a significant improvement of clinical outcome in certain rheumatologic diseases. However, the approaching of many references licensed mAb (RLM) to the end of their licensing period, have stimulated a tremendous interest in the synthesis of a new generation of low-cost mAb referred to as biosimilars (BS) mAb (BSM), because of their similarity to the RLM. An essential requirement imposed by Regulatory Agencies for a mAb to be considered BS is that its variable region (VR) primary sequence must be highly similar to that of RLM. However, epitope recognition and affinity of a mAb very much depends on its VR conformational structure, which may differ even between two mAb bearing highly similar (but not identical) VR. The availability of reagents highly specific to the RLM VR may offer an unique opportunity to define whether a mAb can or cannot be considered BS to a given RLM.
Objectives: To isolate and characterize phage clone-expressing peptide (pc) which are highly specific for the VR of two anti-TNF-α RLP namely mAb Infliximab (Inf) and Golimumab (Gol).
Methods: Cross-inhibition ELISA on recombinant TNF-α (rTNF-α) was performed to define the spatial relationship among the epitopes detected by mAb. mAb-specific phage clones expressing peptide (pc) were obtained by the panning of a phage peptide display library with TNF-a specific mAb. Characterization of pc-specificity and of the spatial relationship between pc- and the TNF-a-binding site on the variable region of mAb was assessed by binding and inhibition assay.
Results: mAb Inf and Gol specifically and dose-dependently cross-inhibited each to the other in the binding to rTNF-a, indicating the recognition by these 2 mAb of the same or two distinct spatially related epitopes on TNF-a. The panning of mAb Inf and Gol with a phage peptide display library resulted in the isolation of one Inf-specific pc (pcInf) and three Gol-specific pc (pcGol1 to 3). Binding assay showed that pcInf and the three pcGol specifically reacted with the corresponding mAb. Furthermore, pcInf and pcGol3 specifically and dose-dependently inhibited the binding of the corresponding mAb to rTNF-α, suggesting the recognition by the pc of the corresponding mAb antigen-combining site. Finally, pcInf and all three pcGol did not react with two additional TNF-a antagonists, suggesting that they are highly specific for mAb Inf and Gol respectively.
Conclusions: The highly specificity of the pc described indicates that they can be eventually employed to predict similarity between a newly synthesized BSM and the claimed RLM, based on the BSM reactivity (or the lack of reactivity) with RLM-specific pc.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.6358

FRI0044 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ARE MORE BENEFICIAL THAN ANTI-TNFα DRUGS ON THE RADIOGRAPHIC DAMAGE IN ARTHRITIS: A STUDY IN ADJUVANT INDUCED ARTHRITIS

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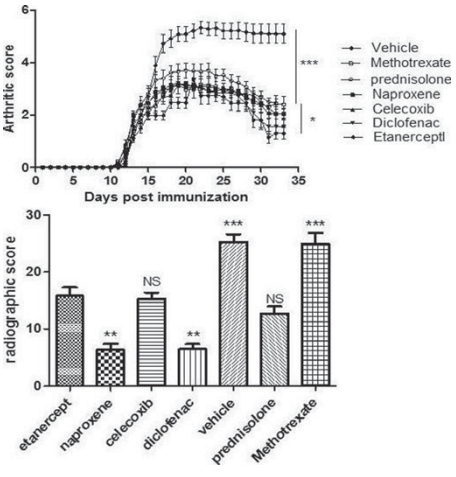
Background: The management of the chronic inflammatory rheumatisms has dramatically evolved in the last decade with a concept of "treat to target". The theory of a window of opportunity with more beneficial effects of an early intensive treatment is supported by several evidences. The positive impact of an early treatment with a TNFα blocker is expected but the place and the interest of non-steroidal anti-inflammatory treatments (NSAIDs) and glucocorticoids is not clear.
Objectives: The aim of this study was to evaluate the radiological outcomes after an early treatment during 21 days by Etanercept, or Naproxene, or Celecoxib, or Prednisone, or Diclofenac or Methotrexate in adjuvant induced arthritis in rats.
Methods: Adjuvant-induced arthritis (AIA) was induced in 6 weeks old male Lewis rats by injection of *Mycobacterium butyricum* in adjuvant at the basis of the tail. At the onset of arthritis, rats were daily treated with Naproxene (10 mg/kg/d i.p), or Diclofenac (5mg/kg i.p twice a day), or Celecoxib (3 mg/kg/d i.p) or Prednisone (10 mg/kg/d i.p), or Etanercept (10 mg/kg/3 days, s.c.), or Methotrexate (1mg/kg/3 days, s.c.), or saline solution (Vehicle), for 21 days. Arthritic score was daily monitored. At the end of treatment, paws' radiological exam was performed with a BMA High Resolution Digital X Ray (40mV, 10mA). A score of 0 to 20 was determined for each paw using a grading scale modified from Ackerman *et al (1979)*.



Abstract FRI0042 – Table 1

	%CD5+IgM+ (median;range)	%BAFF-R+ve	BAFF-R+ve (MFI)	BAFF levels (ng/ml) (median;range)
HC	18.5 (9.1–26.8)	98.7 (97.9–99.5)	62.5 (50.5–82.4)	1.1 (0.9–1.2)
Pre-RTX	5.4 (1.9–21.4)	97.3 (85.8–100)	58 (34.2–139)	1.4 (0.9–1.7)
Post-RTX early relapse	44.4 (39.6–55.8) **###$$	60.6 (12.9–71.2)**###$$	15.6 (11.8–17.5)**###$$	2.4 (2–6.4)**###$
Post-RTX late relapse	12.7 (2.3–27.9)$$	93.1 (81.5–97.9)**$$	30.2 (19.9–36)**##$$	1.7 (1.3–2.4)**#$

*p<0.05; **p<0.01; ***p<0.001 compared with NC; #p<0.05; ##p<0.01; ###p<0.001 compared with pre-RTX; $p<0.05; $$p<0.01; $$$p<0.001 for comparisons between post-RTX groups.

Results: Compared to the Vehicle, all treatments significantly reduced ($p<0.001$) arthritic score with a reduction of the arthritic score evaluated between 40% (for methotrexate) and 70% (for diclofenac) (figure 1. Compared to the vehicle, the radiographic score was improved by Naproxene, Diclofenac, Celecoxib, Glucocorticoids, Etanercept ($p<0.001$) but not by methotrexate. Compared to Etanercept, Naproxene and diclofenac showed less radiological structural changes ($p<0.01$) (figure 2).
Conclusions: Our study demonstrates for the first time that an early treatment with NSAIDs, excluding COX2 selective inhibitor, is more beneficial than Etanercept on the radiological damages in adjuvant induced arthritis. The close efficacy of all drugs on the arthritis score suggests that the beneficial impact of NSAID is not only driven by their impact on the systemic inflammation. NSAIDs should be used during the window of opportunity.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.2611

FRI0045 ORAL MICROBIOME PROFILE IN RHEUMATOID ARTHRITIS PATIENTS: ASSOCIATION BETWEEN TONGUE BIOFILM PORPHYROMONAS GINGIVALIS AMOUNT AND DISEASE ACTIVITY

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Background: *P. gingivalis* is a Gram-negative anaerobic bacterium usually located in the oral cavity, as component of microbiome. Next to the established association with oral cavity diseases, such as periodontitis and halitosis, in the last years a growing interest has been addressed to its implication in the development of autoimmune diseases, such as Rheumatoid Arthritis (RA). The ability of *P. gingivalis* to citrullinate peptides is the most relevant link with RA. Indeed, this bacterium has several virulence factors directly contributing to its chronic inflammation regardless of citrullination. Data from the literature demonstrated the ability of *P. gingivalis* in inducing the production of several inflammatory cytokines, such as TNF, IL6 and IL17, through the TLR signaling pathways.
Objectives: In the present case-control study, we aimed at analysing tongue microbiome in a large RA cohort, focusing on the evaluation of *P. gingivalis* presence and quantification.
Methods: We enrolled 143 RA patients (1987 ACR criteria; M/F 32/111, mean±SD age 57.5±19.8 years, mean±SD disease duration 155.9±114.7 months); 36 periodontitis (M/F 11/25, mean±SD age 56±9.9 years, mean±SD disease duration 25.5±20.9 months); 57 (M/F 12/45, mean ±SD age 61.4±10.9 years, mean ±SD disease duration 62.3±66.9 months) affected by knee osteoarthritis or fibromyalgia (control subjects – CS). All subjects underwent a clinical evaluation in order to assess disease activity by DAS28. Blood serum samples were obtained to evaluate the presence of ACPA by a commercial ELISA kit. Finally, a standard cytologic swab to collect tongue biofilm samples was performed and the presence of *P. gingivalis* was evaluated by PCR method.
Results: The prevalence of *P. gingivalis* resulted significantly higher in RA and PD patients in comparison with CS (P=0.01 and P=0.003, respectively). No correlation between bacterium presence and ACPA was found. When evaluating the percentage of *P. gingivalis* on the total tongue biofilm, we observed a significant correlation between this measure and DAS28 values (r=0.4, P=0.01). Furthermore, RA patients in DAS28 remission showed a significantly lower prevalence of *P. gingivalis* in comparison with non-remission patients (P=0.02).
Conclusions: In the present study, for the first time we assessed the prevalence of *P. gingivalis*, i.e. its percentage on the total tongue biofilm, in a large RA cohort. A significant correlation between the amount of *P. gingivalis* on total tongue biofilm and disease activity was observed. There was no association with ACPA, suggesting that this bacterium, beyond citrullination, could be implicated in triggering a pro-inflammatory state in RA.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.5034

FRI0046 IDENTIFICATION OF HERV-K ENV SURFACE PEPTIDES HIGHLY RECOGNIZED IN RA PATIENTS

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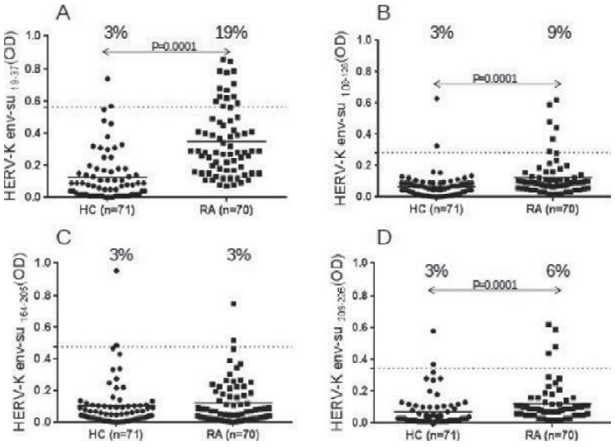
Background: Endogenous Retroviruses (HERV) are believed to be pathogenic in several autoimmune diseases. Among them, HERV-K viruses have been recently reported to be involved in the pathogenesis of rheumatoid arthritis (RA).
Objectives: In this study we have explored the role of humoral immune response against HERV-K as a potential pathogenetic mechanism in RA.
Methods: Four different peptides from the extracellular portion of the *env* protein of HERV-K (env-su $_{19–37}$, env-su $_{109–26}$, env-su $_{164–205}$, env-su $_{209–226}$) were selected by bioinformatic analysis on the basis of their putative immunogenicity. Indirect ELISA was then carried out to quantify antibodies against those peptides on blood samples from RA patients and healthy controls (HC). Differences between the two groups were analysed using the Mann-Whitney rank-sum and chi-square tests. Potential correlations between RA laboratory, clinical descriptors and IgGs levels were explored by bivariate regression analysis.
Results: Seventy consecutive RA patients and seventy-one HC crossed by age and sex were enrolled in the study. Serum autoantibodies against three out of the four tested peptides, anti HERV-Ksu$_{19–37}$, HERV-K env-su$_{109–126}$ and HERV-K env-su$_{205–226}$, were significantly more prevalent in RA than in HC (19% vs 3%,p=0.0001;9% vs 3%, p=0.0001; and 6% vs 3%, p=0.0001 respectively) (See Fig. 1)
Subgroup analysis showed no association between anti-HERV-K peptide humoral response and clinical, serological and clinimetric RA disease descriptors.



Conclusions: Serum from RA patients in our series significantly reacted against different HERV-K peptides in comparison to the general population suggesting a role for the HERV-K related, secondary antigenic driven immune response in the pathogenesis of RA. Further studies are needed to confirm these results and to explore the role of HERV-K surface peptides as potential therapeutic targets.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.2043

FRI0047 ELEVATED 14-3-3ETA LEVELS PREDICT WORSE RADIOGRAPHIC OUTCOMES IN PATIENTS WITH RECENT-ONSET INFLAMMATORY ARTHRITIS IN CLINICAL REMISSION

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Background: 14–3-3η is a joint-derived serum protein that up-regulates pro-inflammatory factors. We have previously reported that baseline 14–3-3η levels ≥0.50 ng/ml (HIGH 14–3-3η) were predictive of radiographic progression over 5 years.
Objectives: Our objective was to verify if the persistence of HIGH 14–3-3η at 18 months in recent-onset polyarthritis patients in REMISSION predicts more rapid radiographic progression over the following years, up to 42 months.
Methods: Serum 14–3-3η titres were assessed at baseline and at 18 months into disease, a median of 14 months after diagnosis and initiation of treatment. Three definitions of "clinical remission" at 18 months were used: Swollen Joint Count (SJC) =0; SJC + Tender Joint Count (TJC) =0; ACR/EULAR Boolean definition. The progression of radiographic damage (Erosion and Total Sharp/van der Heijde (SvH) scores) in patients with LOW (<0.50 ng/ml) or HIGH (≥0.50 ng/ml) 14–3-3η were compared using the Mann-Whitney test. P values <0.05 were considered significant.
Results: Out of 331 patients, 36.0% of which had HIGH 14–3-3η at Baseline, 308 had complete data up to 5 years. Median age was 60 years, 62% women. Depending on the stringency of the definition used, variable numbers of patients reached remission at 18 months: 162 (53%) had SJC=0; 108 (35%) SJC+TJC=0; and 56 (18%) Boolean.
Remission at 18 months was negatively associated with persistence of HIGH