

THU0037 IMMUNOGENICITY IN A TERTIARY CARE HOSPITAL: OUR EXPERIENCE

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Background: The drugs called Anti-TNF inhibitors are capable of inducing an immune response (immunogenicity) Its effectiveness may be affected by the development of Anti-Drug Antibodies (Ab)

Objectives:

- To assess the frequency of appearance of Anti-Drug Antibodies: Infliximab (IFX), Adalimumab (ADA), etanercept (ETN)
- To classify the failures of response
- To analyse the relationship between anti-TNF α antibodies and concomitant treatment with DMARDs
- To observe whether there is a link between risk factors and drug levels

Methods: This is a retrospective, descriptive, observational study of patients with Rheumatoid Arthritis (RA), Spondyloarthritis (SpA), Psoriatic arthritis (PsA), Seronegative arthritis (SA) and Enteropathic arthritis (EA) with active disease and that were treated in the "University Health Care Hospital of León" between Jan-2015 and Jan-2016. Using ELISA Technology and the kits Promonitor[®], it was possible to detect serum levels of IFX ADA, ETN (reference values >2.5 μ g/mL, 5–8 μ g/mL and 0.8–1.2 μ g/mL respectively) and of anti-drug antibodies. The samples were collected the same day of the administration, prior to it, always in a trough level. The gathered data was: demographic data, activity, time-to-disease progression, prior treatment with biologics, concomitant DMARDs, duration of the biologic treatment and dosage, quantization levels, anti-TNF antibodies, cardiovascular risk factors (CVRf) and smoking habits.

Results: Variables to study:

N=40: IFX 50%, ADA 30%, ETN 20%.

Age 53.6 \pm 3.7 years old [95% CI], Women: 55%, time-disease progression: 12.3 \pm 2.7 years old.

Type of disease: RA 47.5%, SpA 15%, PsA 20%, SA 7.5%, EA 10%.

DAS28: 3.5 \pm 0.4, BASDAI 4.7 \pm 0.5, BASFI 4.3 \pm 1.4.

Prior treatment with biologics (30%): IFX 15%, ADA 66%, ETN 12.5%.

Frequency of administration: IFX 8.6 \pm 0.36 weeks, ADA 2.25 \pm 0.36 weeks, ETN 1.1 \pm 1.0 weeks.

Reasons for requesting the levels:

- Secondary failure (82%): IFX 90%, ADA 66.7%, ETN 75%
- Primary failure (17%): IFX 5%, ADA 33%, ETN 25%
- Infusion reactions (2.5%)

Drug levels within the therapeutic range: IFX 10%, ADA 41%, ETN 50%.

Formation of anti-TNF Ab of the sample: IFX 30%, ADA 16%, ETN 0%.

DMARDs: presence of 62.5% (MTXsc 64%, MTXvo 20%, Leflunomide, Sulfasalazine e Hydroxychloroquine 16%).

Conclusions: We found the following conclusions:

- In the data collected, we observe that the IFX (30%) is the most immunogenic drug, followed by the ADA (16%) and being the ETN (0%) the one that so far has not presented anti-drug Ab, outcomes in agreement with the medical literature
- The main reason for requesting has been the secondary failure (90%)
- The suboptimal levels of the drug and the presence of specific ab are correlated with the loss of clinical response. In our case, the proper range of drug is only objective in 10% of the patients treated with IFX, 41% with ADA and 50% with ETN
- The concomitant use of DMARDs in our study has not been shown to decrease levels of Ab, being the MTX the most used in our patients (84%). We observed no correlation between the occurrence of Ab, the use of DMARDs or the type of disease
- The monitoring of the levels of anti-TNF drug may be useful to individualize the treatment, to avoid possible side effects and to make decisions regarding the continuation or change of therapy.

Disclosure of Interest: None declared

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THU0038 BIMEKIZUMAB DUAL INHIBITION OF IL-17A AND IL-17F PROVIDES EVIDENCE OF IL-17F CONTRIBUTION TO CHRONIC INFLAMMATION IN DISEASE-RELEVANT CELLS

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Background: IL-17A and IL-17F share structural homology and have similar biological function¹. Although the contribution of IL-17A to immune-mediated inflammatory diseases has been widely reported^{1–3}, the role of IL-17F is less well characterised in human tissue inflammation. Bimekizumab, a humanised monoclonal IgG1 antibody, was developed to neutralise both IL-17A and IL-17F potently and selectively, and is under clinical development as a treatment for psoriatic arthritis (PsA) and other immune-mediated conditions such as psoriasis.

Objectives: To assess the involvement of IL-17F in chronic inflammation in tissue from patients with PsA and disease-relevant cells, and to determine the effect of

dual neutralisation of IL-17A and IL-17F in suppressing inflammation, compared with blockade of IL-17A.

Methods: Synovial and lesional skin tissue from patients with PsA was probed by immunostaining for expression of IL-17F protein. Normal dermal fibroblasts and synoviocytes, in the presence of TNF α , were stimulated with recombinant IL-17A and IL-17F to assess the inflammatory response. Using cytokine-specific blocking antibodies, the individual and combined effects of IL-17A and IL-17F were explored with: pro-inflammatory cytokine expression in a complex *in vitro* model (synoviocytes from patients with PsA and normal dermal fibroblasts were treated with pro-inflammatory mediators from supernatant [SN] of sorted Th17 cells), microarray and cell migration studies.

Results: IL-17F expression was observed in tissue biopsies from patients with PsA. In normal dermal fibroblasts, normal synoviocytes and synoviocytes from patients with PsA, stimulation with recombinant IL-17F promoted production of pro-inflammatory mediators, such as IL-6 and IL-8, though to a lesser extent than with recombinant IL-17A. Treatment of Th17 SN-stimulated synoviocytes from patients with PsA with bimekizumab (neutralising IL-17A and IL-17F) led to greater reductions of IL-6 (42% lower p<0.05) and IL-8 (35% lower p<0.05) production than IL-17A inhibition. Bimekizumab treatment of Th17 SN-stimulated normal dermal fibroblasts also reduced production of IL-6 (35% lower p<0.0001) and IL-8 (57% lower p<0.0001) more than IL-17A alone. Combining IL-17A + IL-17F monoclonal antibodies produced similar results to bimekizumab. Levels of expression of 27 inflammation-linked genes, including *CXCL1*, *CXCL2*, *CXCL3* and *IL-15RA*, were lower with dual neutralisation of IL-17A and IL-17F by bimekizumab versus inhibition of IL-17A. Suppression of migration of neutrophils (Fig.) and monocytes, both involved in tissue destruction in immune-mediated diseases, was substantially greater with bimekizumab treatment than with single blockade of IL-17A.

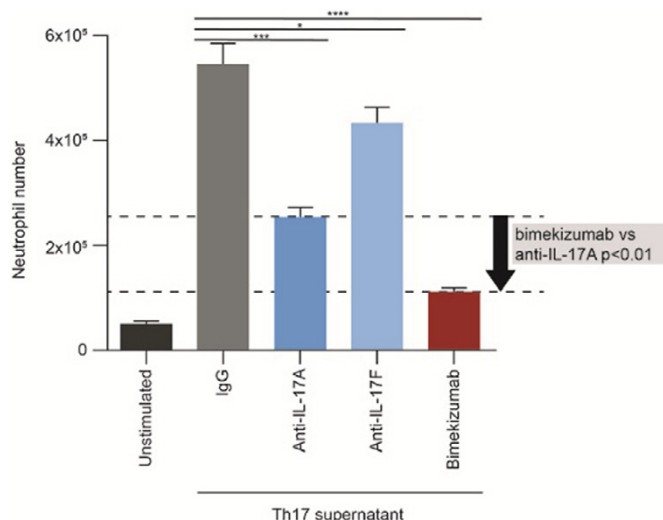


Fig. Quantification of neutrophil migration following treatment with cytokine-specific antibodies and bimekizumab. * represents a significant reduction of cell migration vs IgG control, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

Conclusions: Dual neutralisation of IL-17A and IL-17F provides evidence for the contribution of IL-17F to inflammation in joints and skin beyond IL-17A alone. As a result, dual inhibition of IL-17A and IL-17F by bimekizumab may provide an effective treatment for immune-mediated inflammatory diseases such as PsA.

References:

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THU0039 LIPIDOMICS ANALYSIS OF HDL PARTICLE IN INFLAMMATORY RHEUMATIC DISEASES: ALTERATION OF PHOSPHOLIPID COMPOSITION AND ROLE OF INFLAMMATION

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Background: Rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing

spondylitis (SA) are associated with an increased cardiovascular (CV) mortality. Quantitative abnormalities in lipid profiles are insufficient to explain this excess of CV risk and a qualitative approach of HDL composition is required to identify loss of atheroprotective functions and to correctly identify patients at risk. Atheroprotective functions of HDL are directly linked to the structure of HDL mainly composed of phospholipids (PL).

Objectives: The main objective of this study is to analyze the PL composition of HDL in patients with chronic inflammatory rheumatic diseases and to compare to matched healthy controls.

Methods: HDL structure was assessed in patients with active RA (ACR criteria), PsA (CASPAR criteria) and SA (ASAS criteria) patients before initiating first biologic and in healthy controls matched for age, sex and body mass index. Dyslipidemia treatment or pathology which could interfere with lipid profile were excluded. Demographics data, disease activity, cardiometabolic profile and plasma samples were collected. HDL particle were isolated from plasma after two step ultracentrifugation using gradient of density. Lipidomics analysis were performed using liquid chromatography coupled with mass spectrometry. Phospholipid composition between patients and controls was compared using multivariate analyses to take into account possible confounding variables determined according to univariate results and clinical relevance (age, tobacco consumption, steroids use). Multidimensional analyses as factorial mixed data analysis (FMDA) were performed to complete these analyses.

Results: 19 RA, 19 PsA and 12 SA were analyzed (table 1). 220 phospholipids species were identified among which 2 major classes were modified in rheumatic diseases. Phosphatidylcholine (PC) decreased in RA and PsA ($p<0.01$ and <0.05 respectively) while lysophosphatidylcholine (LPC) increased significantly ($p<0.01$, and <0.05 respectively). Some phospholipids species as PC 40: 8 ($p<0.001$), LPC 16:0 ($p<0.001$), LPC 18:0 ($p<0.001$) were identified as discriminant marker of HDL composition in rheumatic disease as compared to controls.

	RA (mean±SD)	Controls (mean±SD)	PsA (mean±SD)	Controls (mean±SD)	SA (mean±SD)	Controls (mean±SD)
Number of patients	19	18	19	17	12	12
Age	55.32±10.91	58.78±4.61	49.63±8.04 **	57.65±4.77 **	45.33±6.56 ***	57.17±5.69 ***
Sex (W/M) (N/M)	1/18 (5.3%)	1/17 (5.5%)	10/9 (53%)	10/7 (58%)	8/4 (67%)	8/4 (67%)
BMI (kg/m²)	24.22±4.81	22.13±2.92	27.78±7.60	24.55±3.63	25.49±4.16	23.69±2.92
ApoB/ApoA1	0.67±0.15	0.63±0.15	0.77±0.21	0.75±0.14	0.74±0.12	0.75±0.17
CRP (mg/L)	31.16±43.98 ***	0.80±0.72 ***	19.74±17.33 ***	1.40±1.83 ***	2.88±1.97 *	1.91±2.17 *
CV family history Y/N (%)	1/18 (5.3%)	0/18 (0%)	1/18 (5.2%)	0/17 (0%)	0/12 (0%)	0/12 (0%)
CV personal history Y/N (%)	0/19 (0%)	0/18 (0%)	0/19 (0%)	0/17 (0%)	0/12 (0%)	0/12 (0%)
High blood pressure Y/N (%)	4/15 (21%) *	0/18 (0%) *	2/17 (11%)	0/17 (0%)	4/8 (33%) *	0/12 (0%) *
Diabetes mellitus Y/N (%)	1/18 (5.3%)	0/18 (0%)	1/18 (5.2%)	0/17 (0%)	0/12 (0%)	0/12 (0%)
Current tobacco use Y/N (%)	5/14 (26%) *	0/18 (0%) *	5/14 (26%)	0/17 (0%)	6/6 (50%) **	0/12 (0%) **
Disease duration (years)	6.68±6.33					
DAS 28 CRP score	4.56±1.45		4.00±0.99			
BASDAI			55.67±18.58		61.14±14.09	
Corticosteroid treatment Y/N (%)	10/9 (53%)		2/17 (11%)		1/11 (8.3%)	
NSAI treatment Y/N (%)	9/10 (47%)		6/13 (32%)		6/6 (50%)	
Methotrexate treatment Y/N (%)	15/4 (79%)		9/10 (47%)		1/11 (8.3%)	

Table 1 : Demographics data, cardiometabolic profile and diseases characteristics
* p<0.05, **p<0.01, ***p<0.0001 using T test or Chi-squared

Conclusions: Phospholipids composition of HDL is altered in RA and PsA. These alterations could explain a loss of atheroprotective functions and the excess of CV risk observed in RA and PsA patients. Chronic inflammation, through the activation of phospholipase A2 type II which hydrolyze PC into LPC, could modify the structure of HDL phospholipids and thus could impact HDL functionality such as cholesterol efflux, LDL oxidation modulation, anti-inflammatory and vasculoprotective properties. These preliminary data suggest the major role of inflammation in these alterations.

References:

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THU0040 **NOVEL AKT ACTIVATOR SC-79 IS A POTENTIAL TREATMENT FOR ALCOHOL-INDUCED OSTEONECROSIS OF THE FEMORAL HEAD**

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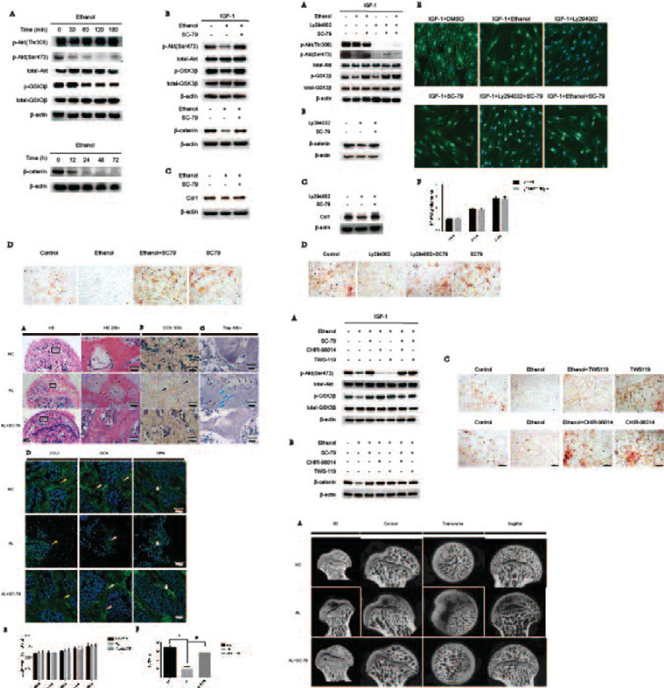
Background: Alcohol is known to be one of the leading risk factors for osteonecrosis of the femoral head. However, the underlying etiology and protective strategies of alcohol-induced osteonecrosis of the femoral head have not been clarified.

Objectives: The aim of this study was to explore the molecular mechanism of alcohol-induced osteonecrosis of the femoral head, and to investigate the protective effect of SC-79 on the disease.

Methods: In vitro, we employed RT-PCR, alizarin red staining, alkaline phosphatase activity testing, western blot, immunofluorescence staining to investigate the effect of ethanol on hBMSCs. In vivo experiments, immunofluorescence staining, TRAP, TUNEL and micro-CT were performed to investigate the development of ONFH.

Results: In vitro, we found that ethanol could significantly impair the expression of osteogenic genes of RUNX2 and OCN, downregulate osteogenic differentiation,

impair IGF-1 induced membrane recruitment of the Akt, suppress the Akt-Ser473 phosphorylation and the subsequent activation of Akt/GSK3β/β-catenin signaling in bone mesenchymal stem cells. Functional studies further confirmed this signaling was the critical mediator during the ethanol-induced inhibitory effects on osteogenesis of BMSCs. Thus, the dephosphorylation of Akt-Ser473 in Akt/GSK3β/β-catenin signaling pathway might be a potential mechanism in the pathogenesis of alcohol-induced osteonecrosis of the femoral head. SC-79, a novel Akt activator was introduced in this study to block the dephosphorylation effect of ethanol on Akt-Ser473 both in vitro and in vivo. In the rat model of alcohol-induced osteonecrosis of the femoral head, micro-CT and histopathological analyses revealed obvious osteonecrosis changes in alcohol-administrated rats while significantly less developed in SC-79 injected rats. OPN, OCN and COL1 immunofluorescence staining revealed that osteogenic response of femoral heads was markedly reduced after alcohol administration, but significantly reversed by SC-79 treatment.



Conclusions: Hence, we discovered alcohol-induced osteonecrosis of the femoral head was associated with the suppression of the Akt-Ser473 in Akt/GSK3β/β-catenin pathway in BMSCs. The administration of SC-79, to elevate Akt activation, might be a clinical strategy to prevent the development of alcohol-induced osteonecrosis of the femoral head.

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THU0041 **PROGRANULIN AND DERIVATIVES CAN BE EMPLOYED AS LATENT DUAL-FUNCTION CHONDROGENIC AND ANTI-INFLAMMATORY THERAPEUTICS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS**

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Background: Rheumatoid Arthritis (RA) is a debilitating inflammatory disease of the joints afflicting around 1% of Western populations. Some of the best treatments are anti-TNF agents, but these only achieve remission in 60% of patients and cause deleterious side effects. Progranulin (PGRN), a cysteine-rich, multi-domain growth factor was reported to bind TNF-receptors (TNFR) blocking pro-inflammatory signalling², as well as stimulating chondrogenesis³. PGRN is cleavable and its peptides have pleiotropic effects, some of which may be beneficial and others refractory to ameliorating RA. Granulin A (GRN A) was shown to interact with cartilage ECM protein COMP⁴. Atsttrin – comprising 3 fused PGRN regions, was shown to ameliorate arthritic disease². The latency associated peptide (LAP) of TGFβ1 can be fused to short peptides and cytokines via a MMP cleavage site to facilitate targeting to inflamed sites such as RA joints, reducing side effects and enhancing *in vivo* half-life¹. We hypothesised that a peptide based on PGRN could be fused to LAP and used to both block TNF and stimulate cartilage regeneration in RA joints in a targeted way.

Objectives: To produce a panel of PGRN derivatives fused to LAP. To determine the chondrogenic and anti-TNF capacities of the fragments in the presence and absence of MMP activation. To evaluate their efficacy in the CIA model of RA.