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Background: The disease course of axial SpA (axSpA) is highly variable and can be characterized by ongoing axial inflammation and radiographic progression associated with restricted mobility of the spine, reduced function and disability leading to impairment in quality of life. Control of disease activity is a primary aim in axSpA management. To assess disease activity the Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP) is often considered as a reference tool. The data on remission are sparse in axSpA and the identification of long-term remission factors, enabling the patient's management to be adapted, seems necessary but remains unclear.

Objectives: To evaluate the proportion of patients in remission according to ASDAS-CRP at 5 years of follow-up, to describe their characteristics in comparison with patients with active disease at that time, and to identify baseline factors associated with remission at 5 years of follow-up.

Methods: We included all patients from the DESIR (*Devenir des Spondylarthropathies Indifférenciées Récentes*) cohort with available data on ASDAS-CRP at 5-year follow-up and TNF α inhibitors exposure. Patients in remission, defined as an ASDAS-CRP <1.3, and with active disease were compared according to their main demographic, clinical, biological and radiological characteristics. A logistic model stratified on TNF α inhibitors exposure was used in the main analysis. Sensitivity analyses among patients with axSpA diagnosis confirmed by rheumatologist at 5-years were performed.

Results: A total of 614 patients were followed in the DESIR cohort at M60. After excluding those with missing data on ASDAS score (n= 163) and TNF α inhibitors exposure (n= 2), analyzed patients were 449 (73%). Excluded patients had similar baseline characteristics to those included in the analysis. Among patients unexposed to TNF α inhibitors (n=247), 77 (31%) were in remission (37.8 $\pm$ 8.3 years; 55% men, 58% NSAID users), 170 (69%) weren't (39.8 $\pm$ 8.6 years; 42% men, 81% NSAID users). Among exposed patients (n=202), 34 (17%) were in remission (36.1 $\pm$ 8.1 years; 71% men, 29% NSAID users), 168 (83%) weren't (39.5 $\pm$ 9.0 years; 41% men, 63% NSAID users) (Figure 1). Overall, patients in remission were more frequently men, HLA-B27+, with high education and lower BMI at 5-year of follow-up. The baseline factors associated with remission at 5 years of follow-up from the multivariate analysis are presented in Table 1.

Table 1. Baseline factors associated with remission at 5-year follow-up (multivariate analysis)

	Baseline factors positively associated with 5-year remission	Baseline factors negatively associated with 5-year remission
Unexposed to TNF α inhibitors	<ul style="list-style-type: none"> Past history of arthritis (OR_a=2.1, 95%CI 1.2-5.3) 	<ul style="list-style-type: none"> Low BASDAI (OR_a=0.9, 95%CI 0.8-0.9)
Exposed to TNF α inhibitors	<ul style="list-style-type: none"> High education (OR_a=2.9, 95%CI 1.6-5.1) 	<ul style="list-style-type: none"> Low BASDAI (OR_a=0.9, 95%CI 0.9-0.9) Low BMI (OR_a=0.8, 95%CI 0.7-0.9) Low enthesitic index (OR_a=0.8, IC95% 0.7-0.9)

TNF α : Tumor Necrosis Factor alpha; OR_a: adjusted Odd Ratio; 95%CI: 95% confidence interval; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BMI: Body Mass Index.

Conclusion: The overall remission rate at 5 years was 25%, 31% among patients unexposed to TNF α inhibitors and 17% among those exposed. This study reveals the difficulty in achieving 5-year remission in recent axSpA, especially in the most active forms at baseline; socio-educational factors and overweight also appear to be related.

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OP0053

IMPACT OF CORRECTING CRP THRESHOLD ACCORDING TO BMI ON DIAGNOSIS, DISEASE ACTIVITY, INDICATION OF BIOLOGICAL TREATMENT AND PREDICTION OF THERAPEUTIC RESPONSE, IN PATIENTS SUSPECTED OF AXIAL SPONDYLOARTHRITIS. RESULTS FROM DESIR COHORT

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Background: Acute phase reactants are crucial parameters to consider for management of chronic inflammatory back pain (IBP) patients suspect of axial spondyloarthritis (ax-SpA). Indeed, C-reactive protein (CRP) is part of ASAS classification criteria for SpA, impacts on assessment of disease activity by ASDAS-CRP score, and should be elevated when a bDMARD is discussed in patients without radiological sacroiliac lesions. Moreover, elevated CRP is regarded predictive of favorable therapeutic response. Obesity in otherwise healthy people is associated with high CRP values. An adjusted definition of normal CRP threshold based on gender and BMI has been proposed.

Objectives: The aim of this study was to assess whether correcting CRP threshold with patient's BMI would change classification according to ASAS criteria for ax-SpA, presence of clinically relevant activity according to ASDAS-CRP, indication for TNF inhibitor (TNFi) and, as primary endpoint, improve prediction of therapeutic response to first TNFi.

Methods: The study was conducted in DESIR cohort, which included 708 patients with early IBP suspect of ax-SpA. We included all patients with available data on BMI and CRP. High CRP level was defined either according to usual threshold (5mg/L) or to the formula using BMI for adjustment. With this formula, CRP could be considered "normal" or due to obesity if: $\leq 1 + (BMI-25)/25$ for men and $\leq 1 + (BMI-25)/12.5$ for women (with CRP in mg/dL). We reported distribution of CRP levels in patients with high level according to usual threshold but below BMI adjusted threshold, as it is potentially suggestive of false-positive CRP due to overweight/obesity. Among them, we identified those who had no objective sign of disease activity (defined as arthritis, dactylitis, active uveitis or inflammatory bowel disease). To evaluate the impact on classification/diagnosis, we examined HLAB27-positive patients with only 2 ASAS criteria, including high CRP (the second being IBP, since it was mandatory for inclusion in DESIR cohort). Then, we calculated ASDAS-CRP score. We presented proportions of patients with ASDAS-high or very high disease activity but high CRP level possibly due to BMI only, and among those, the number concerned by a change of disease activity level when adjusting ASDAS-CRP score with minimal value for CRP (2mg/l). Among patients treated by TNFi during first 24-month follow-up, we excluded those with sacro-iliitis, and studied in others, CRP levels at last visit before treatment initiation using both thresholds. We compared proportion of ASAS40 responders using logistic regression analysis, with abnormal CRP defined after correction for BMI in patients without any sign of activity, beside other classical predictive factor of therapeutic response (age, gender, sacro-iliitis, HLAB27, psoriasis, arthritis, smoking).

Results: Data were available for 634 patients. 205 had a high CRP level using usual threshold, of which 73 (35.6%) had a high CRP possibly due to BMI alone as they had no objective sign of disease activity. There were no differences in diagnosis as no patient had as only ASAS criteria: HLAB27 associated with high CRP and IBP. ASDAS-CRP score could be calculated in 626 patients. By correcting ASDAS score for patients with high CRP possibly due to BMI, 95.3% remained with same activity level (kappa for the ASDAS levels was 0.93). For impact of CRP on indication of bDMARD, 178 patients were treated by TNFi during first 24 months of follow-up: 61% of patients had an indication of TNFi according to EMA, with usual CRP threshold, and 56% with the adjusted one. Regarding response to TNFi, there were no association between any of the 2 CRP thresholds and ASAS40 response. Only sacro-iliitis on MRI was associated with ASAS40 response.

Conclusion: Adjustment of CRP threshold according to BMI has a very limited impact on diagnosis, evaluation of disease activity of SpA, indication of TNFi initiation and prediction of TNFi response.

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Vasculitis - I

OP0054

NEW ROLE FOR PROTEINASE 3 IN IL-16 BIOACTIVITY CONTROL IN GRANULOMATOSIS WITH POLYANGIITIS

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Background: The immunomodulatory cytokine IL-16 is increased in several inflammatory and autoimmune diseases¹. IL-16 recruits and activates CD4+ immune cells such as T cells, dendritic cells, or monocytes. IL-16 is produced by various immune and non-immune cells, but synthesis and storage of IL-16 is regulated differentially depending on the cell type and stimulation. For its biological activity, IL-16 cleavage by caspase-3 is required¹. Necrotizing granulomatous inflammation is a hallmark of granulomatosis with polyangiitis (GPA) with neutrophil dysregulation as a central driver of chronic inflammation and autoimmunity². Earlier studies showed a correlation between increased serum IL-16 and disease parameters in AAV, including GPA³, but functional evidence for a direct link between IL-16 and neutrophils in granulomatous inflammation is missing so far.

Objectives: In this study we aim to identify a functional link between increased IL-16, neutrophils, and the autoantigen proteinase 3 (PR3) with regard to chronic inflammation and autoimmunity in GPA.

Methods: IL-16 was measured in sera of GPA patients (n = 40) and healthy controls (HC, n = 50) by ELISA and correlated with clinical features, such as disease activity (BVAS), creatinine, GFR, VDI and PR3-ANCA status. IL-16 protein expression was analyzed in peripheral blood mononuclear cells (PBMC) and polymorphonuclear cells (PMN) from GPA patients and HC (n = 5, each) by SDS-PAGE and western blot. Binding affinity of recombinant pro-IL-16 to native human PR3 was assessed by microscale thermophoresis. Cleavage of pro-IL-16 by active human PR3 was performed at various time points at 37°C. Cleavage products were analyzed by SDS-PAGE and western blot.

Results: Circulating IL-16 was significantly increased in GPA patients compared to HC. Elevated IL-16 positively correlated with BVAS, creatinine, VDI and PR3-ANCA status and negatively correlated with GFR. In PMBC and PMN from GPA and HC we identified different expression patterns of precursor and active forms of IL-16. In healthy PBMC we found high amounts of precursor (80kD), pro-IL-16 (55kD) and active IL-16 (17kD). In contrast, PBMC from GPA patients had lower amounts of pro-IL-16 and no active IL-16, indicating activation and secretion of IL-16 due to inflammatory stimulation, as shown earlier². In GPA PMN we detected no precursor IL-16, but pro-IL-16 and its active form, in contrast to very low amounts of all IL-16 forms in healthy PMN. Processing and release of IL-16 in neutrophils has been linked to apoptosis and secondary necrosis⁵. By interaction studies we demonstrated direct binding of pro-IL-16 to PR3 with a Kd of 10nM. In a subsequent cleavage assay we confirmed IL-16 processing by PR3 in a time-dependent manner.

Conclusion: Correlation of serum IL-16 with clinical features of GPA suggests that IL-16 is associated with markers of disease activity, tissue damage and auto-reactivity. We showed that PBMC and PMN represent a source of IL-16 in GPA. By the identification of PR3 as an additional IL-16-activating enzyme we could demonstrate a potential link between excessive PR3 expression, cell death and IL-16-dependent mechanisms, contributing to chronic granulomatous inflammation and autoimmunity in GPA.

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OP0055

ULTRASOUND HALO SIGN AS A POTENTIAL MONITORING TOOL FOR PATIENTS WITH GIANT CELL ARTERITIS: A PROSPECTIVE ANALYSIS

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Background: Ultrasound of the temporal ± axillary arteries showing a non-compressible halo sign is recommended for diagnosing patients with giant cell arteritis (GCA); however, its value for monitoring disease activity is still poorly understood.

Objectives: To assess the sensitivity to change of ultrasound halo features and their association with disease activity and glucocorticoid (GC) treatment in patients with newly diagnosed GCA.

Methods: Two centre prospective study of new patients with ultrasound confirmed-GCA who underwent serial ultrasound assessments of the temporal (TA) and axillary (AX) arteries at fixed time-points. The number of arterial segments with halo and the maximum halo intima-media thickness (IMT) per segment was recorded at each visit. Only time-points in which >80% of patients were assessed were considered for analysis. Sensitivity to change of the halo sign was calculated as standardised mean difference (SMD) for each time-point separately. Correlation between ultrasound findings and erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Birmingham Vasculitis Activity Score (BVAS), and GC treatment was performed using Spearman's correlation coefficient. Logistic regression was used to determine the probability of being in remission for each unit increase (standardised) of the halo feature of interest. Remission was defined as the absence of relapse with a prednisolone dose <30 mg/day, and relapse as the recurrence of GCA-related symptoms or rise of CRP/ESR values not otherwise explained and requiring GC increase. Halo features at disease onset and first relapse were compared using Wilcoxon test.

Results: A total of 49 patients (73.5% females) with a mean age of 78.2 ± 7.4 years at baseline were assessed at 354 visits. TA involvement was reported in 47 (95.9%) patients and AX involvement in 11 (22.4%); 220 arterial segments with halo were recorded (201 TA, 19 AX). Halo sensitivity to change was calculated for weeks 1, 3, 6, 12 and 24, and showed a significant SMD between all time-points and baseline for the TA halo features, but only after week 6 for the AX halo features (Table and Figure). The number of TA segments with halo, sum of TA halo IMT and maximum TA halo IMT showed a significant correlation with ESR (0.41; 0.44; 0.48), CRP (0.34; 0.39; 0.41), BVAS (0.29; 0.36; 0.35) and GC cumulative dose (-0.34; -0.37; -0.32). The likelihood of achieving disease remission was lower in patients with a higher number of TA segments with halo (OR 0.39, p<0.05) and increased values of sum and maximum TA halo IMT (OR 0.34, p<0.05). By contrast, AX halo features showed no correlation with disease activity, nor any association with attaining clinical remission. During the study period, 32 relapses were observed (mean time for first relapse of 31.8 weeks ± 18.5 days). Halo sign was present in 16/17 (94.1%) cases of first disease relapse, all showing an increased halo IMT (sum and maximum) in relation to the previous ultrasound assessment performed. When compared to disease onset, a lower mean number of segments with halo and mean sum of halo IMT was reported for patients presenting with their first clinical relapse (2.93 ± 1.59 vs. 4.85 ± 1.51, p=0.0012; 2.01 ± 1.13 vs. 4.49 ± 1.95 mm, p=0.0012).

Table 1. SMD of halo features between baseline and different time-points

	Week 1	Week 3	Week 6	Week 12	Week 24
N of arterial segments					
Sum of all segments with halo (n=49)	-0.51	-0.78	-1.13	-1.69	-1.52
Sum of TA segments with halo (n=47)	-0.49	-0.78	-1.18	-1.87	-1.69
Sum of AX segments with halo (n=11)	-0.35	-	-0.62	-0.73	-0.91
Halo thickness (mm)					
Sum of all halo IMT (n=49)	-0.98	-1.44	-1.37	-1.60	-1.48
Sum of TA halo IMT (n=47)	-1.01	-1.55	-1.54	-1.81	-1.69
Sum of AX halo IMT (n=11)	-0.15	-0.45	-0.81	-0.84	-0.98
Max. TA halo IMT (n=47)	-1.07	-1.32	-1.47	-1.91	-2.19
Max. AX halo IMT (n=11)	-0.04	-0.29	-0.94	-1.13	-1.01

In bold p<0.05; n=n at baseline

Conclusion: Ultrasound is a reliable imaging tool to assess disease activity and response to treatment in patients with GCA. Future clinical trials in GCA should evaluate direct treatment effect on halo features as an outcome measure of interest.

Figure: Mean variation (not standardised) of halo features at different time-points

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