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FRI0365

REAL-WORLD EFFECTIVENESS AND SAFETY OF APREMILAST IN A LARGE COHORT OF GERMAN PATIENTS WITH PSORIATIC ARTHRITIS: 1-YEAR ANALYSIS OF AN ONGOING MULTICENTER, PROSPECTIVE, NON-INTERVENTIONAL STUDY

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Background: Apremilast (APR) has been studied extensively in phase III randomized, controlled trials. However, real-world information is limited on the effectiveness and safety of APR in patients with psoriatic arthritis (PsA).

Objectives: To assess the effectiveness and safety of APR in a large cohort of patients with active PsA from routine clinical practice settings in Germany.

Methods: In this multicenter, prospective, non-interventional study, the primary endpoint was the proportion of patients reaching ≥ 1 point ($\geq 20\%$) improvement from baseline (BL) in the Physician's Global Assessment of Disease Activity (PhGA) score. Other endpoints included effects on swollen and tender joint counts (SJC/TJC), psoriasis-involved body surface area (BSA), enthesitis, dactylitis, Patient's Global Assessment of Disease Activity score (PtGA), Psoriatic Arthritis Impact of Disease (PsAID) tool, pain, and pruritus. The current analysis is based on observed data through 1 year of study duration.

Results: A total of 545 German patients were enrolled and followed up to 12 months of APR treatment; 488 patients were included in the safety analysis and 418 in the final analysis set. The mean age was 55 years, mean body mass index was 29.5 kg/m², and 60% were female. The mean duration of psoriasis and PsA was 26 years and 18 years, respectively. At BL, 46.7% of patients had enthesitis based on the Leeds Enthesitis Index (LEI; mean [SD]: 2.9 [1.72]) and 23% had dactylitis (mean [SD]: 2.2±2.03); 74% of patients were biologic-naïve. Effectiveness is shown after ~1 month (Visit 1 [V1]) and ~4 months (Visit 2 [V2]) and for up to 225 patients after 12 months (Visit 5 [V5]) of treatment (Table). Improvements were also seen in PtGA, overall pain, and pruritus. A subanalysis suggests APR was associated with greater benefits in biologic-naïve patients compared with patients who previously received biologic therapy. Observed safety and tolerability through V5 were consistent with the known overall safety profile of APR. Common adverse events in clinical trials were similar, with a lower incidence of diarrhea (11.1%), nausea (7.0%), headache (3.9%), and respiratory tract infection (0.8%).

Conclusion: Data from this large, real-world cohort of patients with PsA show the effectiveness of APR. In patients with up to 12 months of follow-up, APR was associated with rapid and maintained improvements in physician-assessed and patient-reported outcomes. Safety and tolerability were consistent with the known profile of APR.

Table. Effectiveness of APR Treatment

	BL n=418*	V1 n=326*	V2 n=360*	V5 n=214*
≥ 1 -point PhGA improvement, %	NA	56.2	77.2	86.4
PhGA score, mean (95% CI)	2.5 (2.4, 2.5)	1.8 (1.7, 1.9)	1.4 (1.3, 1.5)	1.1 (1.0, 1.2)
PhGA score=0-1, %	NA	34.3	60.8	77.0
SJC mean improvement, % (95% CI)	NA	42.1 (34.7, 49.5)	54.7 (45.4, 64.1)	75.7 (65.5, 86.0)
TJC mean improvement, % (95% CI)	NA	38.3 (27.2, 40.4)	36.0 (23.8, 48.3)	57.1 (41.1, 73.1)
Psoriasis-involved BSA (%), mean (95% CI)	10.0 (8.6, 11.4)	7.7 (6.3, 9.1)	4.7 (3.8, 5.7)	2.4 (1.8, 2.9)
Achievement of LEI=0 [†] , %	NA	38	50	58
Achievement of dactylitis count=0 [†] , %	NA	48	71	88
PsAID score, mean (95% CI)	5.33 (5.12, 5.53)	4.65 (4.41, 4.89)	3.97 (3.73, 4.20)	3.22 (2.94, 3.50)

*Based on the number of patients with data available at the given visit; the n may vary for individual parameters at a given visit. [†]In patients affected at BL. CI=confidence interval; NA=not applicable.

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FRI0366

CARDIOVASCULAR RISK RECLASSIFICATION USING CAROTID ULTRASOUND IN PSORIATIC ARTHRITIS: A CASE-CONTROL STUDY

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Background: Patients with psoriatic arthritis (PsA) have an increased risk of cardiovascular disease (CVD). Risk stratification algorithms for general population, such as cardiovascular risk calculators, have been developed to improve primary prevention and early detection of CVD; however, it underestimates cardiovascular risk in PsA patients¹. Carotid ultrasound, which measures both carotid intima-media thickness (cIMT) and carotid plaque (CP), is useful in the detection of subclinical carotid atherosclerosis improving risk stratification.

Objectives: This study aimed to evaluate the use of carotid ultrasound in the reclassification of cardiovascular risk in PsA patients and compare it with controls.

Methods: This cross-sectional study included 70 PsA patients that fulfilled the CASPAR criteria and 70 controls subjects matched by age and comorbidities. Patients with a history of previous atherosclerotic CVD and pregnancy were excluded. Clinical examination, blood tests and Framingham Risk Score Lipids and BMI based (FRS-Lipids/FRS-BMI) and ACC/AHA 2013 calculators were performed. Carotid B-mode ultrasonography was used for measurements of cIMT and CP presence. *Increased cIMT was defined as ≥ 0.9 mm. CP was defined as a focal narrowing ≥ 0.5 mm of the surrounding lumen or a cIMT ≥ 1.2 mm.* Descriptive analysis was done with measures of central tendency and dispersion and comparisons with Chi-square, Student's t and Mann-Whitney U tests.

Results: A total of 138 subjects were included. Clinical and demographic characteristics are shown in Table 1. Differences were found in the cardiovascular risk classification between the calculators and the carotid ultrasound. However, these were not significant when compared to controls, with the exception of the FRS-Lipids which had a significant difference when recategorized as high risk by the increase in the cIMT ($p = 0.016$). A 70.8% and a 56% of patients with PsA who had CP were not classified as high risk according to FRS-Lipids ($p = 0.010$) and ACC / AHA 2013 ($p < 0.001$) respectively.

Table 1. Clinical and demographic characteristics.

	PsA (n=69)	Controls (n=69)	P
Age, (mean±SD)	53.58±10.946	53.86±7.313	NS
Women, n (%)	38(55.1)	59(85.5)	<0.001
Type 2 Diabetes Mellitus, n (%)	14(20.3)	9(13)	NS
Hypertension, n (%)	27(39.1)	19(27.5)	NS
Dyslipidemia, n (%)	29(42)	24(34.8)	NS
Obese, n (%)	26(37.7)	28(40.6)	NS
Active smoker, n (%)	15(21.7)	12(17.4)	NS
Disease duration, median (q25-q75)	5(2.5-8)	-	-
DAS28-ESR, (mean±SD)	3.74±1.477	-	-
DAPSA, median (q25-q75)	35(27.5-58.5)	-	-

Conclusion: None of the traditional calculators used in the general population correctly estimates cardiovascular risk in patients with PsA. Among the calculators we performed, FRS-Lipids was the worst, underestimating PsA individuals with CP up to 70.8%. Therefore, it is advisable to perform a carotid ultrasound without relying on the results obtained by any of these calculators in order to achieve an adequate classification and accomplish a correct management of the disease.

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Table 2. Ultrasound Characteristics in PsA patients

	CP	Without CP	P
FRS-Lipids, n (%)			0.010
Low and Moderate risk	17(70.8)	39(95.1)	
High risk	7(29.2)	2(4.9)	
FRS-BMI, n (%)			NS
Low and Moderate risk	15(62.5)	32(80)	
High risk	9(37.5)	8(20)	
ACC/AHA 2013, n (%)			<0.001
Low, Borderline and Moderate risk	14(56)	35(97.2)	
High risk	11(44)	1(2.8)	

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FRIDAY, 05 JUNE 2020

Bone diseases, including osteoporosis and osteoimmunology: aetiology, pathology and animal models

FRI0367

ADALIMUMAB IS MORE EFFECTIVE THAN ETANERCEPT AT PREVENTING TNF-ENHANCED OSTEOCLAST DEVELOPMENT THROUGH DOWNREGULATION OF PRO-OSTEOCLASTOGENIC FACTORS ICAM-1 AND IGFBP2 AND UPREGULATION OF ANTI-OSTEOCLASTOGENIC FACTOR FABP4

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Background: TNF has been shown to contribute to osteoclastogenesis independently and in conjunction with M-CSF and RANKL. We have previously demonstrated that TNF enhances the kinetics of RANKL-induced human osteoclastogenesis and that its effects are mitigated more effectively by the anti-TNF biologic adalimumab (ADA) as compared to etanercept (ETN).

Objectives: To determine the mechanism responsible for the difference in effectiveness between the two biologics, a label-free quantitative proteomics study was conducted on TNF-activated human osteoclasts (OC) upon biologic treatment.

Methods: Human bone marrow-derived OC precursors (OCP, 3 donors) were exposed for 5 days to M-CSF, M-CSF+RANKL (RANKL) alone or in combination with 100 ng/mL TNF +/- 5 ug/mL ADA, ETN or human IgG1 (IGG) as pre-formed complexes. OC differentiation was confirmed by measuring TRAP5b activity. Shotgun proteomics was performed on peptides generated from detergent based cell extracts subjected to methanol/chloroform precipitation and trypsin/Lys-C digestion. Data acquisition was performed with Orbitrap Q Exactive™ HF-X mass spectrometer. MaxQuant was utilized to quantify proteins based on MS1 peak intensities. Data matrix was normalized, imputed and subjected to differential expression analysis by limma. DAVID pathway analysis (DPA) was used to identify pathways impacted by various treatment conditions based on proteins exhibiting significant (p<0.05) 1.2-fold change in expression as compared to RANKL. Protein levels within culture supernatant or cell lysate were verified by ELISA or MSD.

Results: Principle component analysis (PCA) of the proteomic profiling data for the 3 donors indicated that exposure of OCP to TNF induced a distinct profile from that of M-CSF and RANKL. The addition of ADA:TNF complexes restored the profile to that of RANKL, whereas those exposed to ETN:TNF complexes exhibited an intermediate profile matching differences observed in TRAP 5b activity levels. DPA identified 3 pathways most associated with osteoclastogenesis: receptor-mediated endocytosis (e.g. CD163, IGFBP2), oxidation-reduction process (e.g. FABP4), and cell adhesion (e.g. ICAM-1, TGFBI) that were significantly impacted by TNF with ADA:TNF being more effective than ETN:TNF in restoring most pathway-associated proteins to RANKL levels. Based on ELISA, two pro-osteoclastogenic factors IGFBP2 and ICAM-1 were increased 2-fold in OCP culture supernatants in response to TNF with only ADA:TNF complexes reducing these levels of both to RANKL. TNF-induced reduction of intracellular levels of CD163, an M2 macrophage polarization marker, and TGFBI were not only restored to RANKL levels by ADA:TNF but brought to a level closer to M-CSF alone, unlike ETN:TNF. One anti-osteoclastogenic factor FABP4 was found to be increased intracellularly above that of RANKL only following exposure to ADA:TNF complexes.

Conclusion: Shotgun proteomic profiling of human OCP differentiated *in vitro* with TNF revealed at least 3 novel pathways by which TNF exerts its pro-osteoclastogenic effects. Only with the addition of ADA:TNF, not with ETN:TNF, were most pathway-associated proteins significantly restored to RANKL levels

including pro-osteoclastogenic factors ICAM-1 and IGFBP2. Moreover, ADA:TNF complexes enhanced the intracellular levels of CD163 and the anti-osteoclastogenic factor FABP4, suggesting these complexes are exerting an effect on OCP beyond simple TNF neutralization. Additional *in vitro* and *in vivo* studies need to be performed to verify our findings.

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FRI0368

GLUCOCORTICOID THERAPY MIGHT SUPPRESS WNT SIGNALING BY REDUCING THE RATIO OF SERUM WNT3A TO WNT INHIBITORS, SFRP-1 AND WIF-1, AND IMPAIR BONE FORMATION

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Background: Glucocorticoids decrease bone density by multiple mechanisms, including suppression of bone formation via Wnt/β-catenin signaling. Binding of Wnt ligands to a specific receptor and its co-receptors is required for activation of the Wnt pathway, whereas this pathway is inactivated by some negative regulators of Wnt signaling. Sclerostin (Scl) and Dickkopf-1 (Dkk-1) bind to Wnt co-receptors, and secreted Frizzled-related protein 1 (sFRP-1) and Wnt inhibitory factor 1 (Wif-1) bind to Wnt ligand, thereby inactivating the Wnt pathway [1-4]. However, the detailed changes of Wnt signaling in patients with glucocorticoid-induced osteoporosis have not been clarified.

Objectives: We measured serum levels of Scl, Dkk-1 and Wnt3a before and after starting glucocorticoid therapy in our previous study, and the results suggested that suppression of Wnt/β-catenin signaling by increasing serum Scl and Dkk-1 might impaired bone formation at least in the first week of the initiation of glucocorticoid therapy [5]. However, the involvement of Wnt signaling in subsequent suppression of bone formation was unclear. The objective of this study was to investigate the involvement of the Wnt/β-catenin signaling pathway and its clinical significance after the early phase of glucocorticoid therapy in glucocorticoid-induced osteoporosis.

Methods: A total of 53 patients with systemic autoimmune diseases who received initial glucocorticoid therapy with prednisolone (30-60mg daily) were prospectively enrolled. We measured serum levels of sFRP-1, Wif-1 and Wnt3a before starting glucocorticoid therapy and every week for four weeks after its initiation. Patients underwent measurement of bone mineral density (BMD) of the lumbar spine (L2-4) by dual-energy X-ray absorptiometry before starting therapy and after 16.3 ± 1.4 months (the mean ± SEM).

Results: Serum sFRP-1 and Wif-1 level tended to decrease compared to before therapy from the first week. Serum level of Wnt3a also decreased from the first week. Both the ratio of Wnt3a to sFRP-1 and the ratio of Wnt3a to Wif-1 decreased from the first week onward. Moreover, we stratified the subjects into two groups according to the baseline serum sFRP-1 level at median and found that the decrease of BMD after initiation of glucocorticoid therapy in the High sFRP-1 group was larger than that in the Low sFRP-1 group. There was no difference in BMD changes between High Wif-1 and Low Wif-1 group, when stratified into two groups according to the median baseline serum Wif-1 level.

Conclusion: Our previous study indicated that increase of Scl and Dkk-1 could inhibit Wnt signaling pathway in the early phase of glucocorticoid therapy. Current study suggested that the reduction in the ratio of Wnt3a to Wnt inhibitors, sFRP-1 and Wif-1, would suppress Wnt signaling, which might result in impairment of bone formation subsequent. Taken together, bone formation was impaired via suppressing Wnt signaling in patients treated with glucocorticoid. Furthermore, higher serum sFRP-1 level before glucocorticoid administration might be a predictor of future severity of glucocorticoid-induced osteoporosis.

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