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Janssen, Merck, Roche, Pfizer, and UCB Pharma
DOI: 10.1136/annrheumdis-2020-eular.1946

FRI0093

FACTORS ASSOCIATED WITH REFRACTORY RHEUMATOID ARTHRITIS (RRA) ACCORDING TO THREE AVAILABLE DEFINITIONS: TWO CROSS-SECTIONAL ANALYSES IN A LARGE ITALIAN MONOCENTRIC COHORT

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Background: Three definitions of refractory rheumatoid arthritis (RRA) have been proposed: Buch's (B-RRA), i.e. failure of ≥ 1 anti-cytokine and ≥ 1 cell-targeted bDMARD [1]; Kearsley-Fleet's (KF-RRA), i.e. exposure to ≥ 3 bDMARDs classes [2]; De Hair's (DH-RRA), i.e. signs and/or symptoms of RA activity and failure of ≥ 1 csDMARD and ≥ 2 bDMARDs [3].

Objectives: To evaluate the rate of RRA according to the three definitions in a monocentric cohort with two cross-sectional analyses in 2012 and 2019. We investigated also the major determinants of each definition. Secondary objective was to evaluate the most frequent treatments in RRA patients.

Methods: Patients affected by RA followed at Padova University Hospital were included at two different time points. In the 2012 cohort patients on bDMARDs on 31st December 2012 and in the 2019 cohort patients on b/target synthetic DMARDs (tsDMARD) on 1st March 2019. Factors independently associated with RRA definitions were tested with multivariable regression analysis, including all variables achieving a $p < 0.10$ in the univariate analysis.

Results: We included 260 patients in the 2012 cohort and 571 in the 2019 cohort. Rate of RRA in 2012 cohort was: 23 (8.8%) B-RRA, 57 (21.9%) KF-RRA and 12 (4.6%) DH-RRA; rate of RRA in 2019 cohort was: 165 (28.9%) B-RRA, 96 (16.8%) KF-RRA and 57 (10%) DH-RRA. Following multivariate regression analysis, in the 2012 cohort a significant association was found between number of bDMARDs treatment and all RRA definitions [Tab.1]. Also in the 2019 cohort the variable associated with all RRA definitions was the number of bDMARDs treatment [Tab.2]. Both in 2012 and 2019, IL6-inhibitors were more frequently prescribed in RRA patients; instead TNF inhibitors were less frequently prescribed in RRA.

Conclusion: Rate of RRA in the 2019 cohort was 10-30% which is higher compared to the 2012 cohort. This might be explained by the fact that RRA definitions are mainly affected by the number of bDMARDs. Thus, an accurate RRA definition should consider not only the number of treatments but also the current disease activity.

References:

- [1] Buch MH. Ann Rheum Dis 2018;77:966–969
- [2] Kearsley-Fleet L, et al. Ann Rheum Dis 2018;77:1405–1412
- [3] De Hair MJH et al. Rheumatology 2018;57:1135-1144

Table 1. Factors associated with three definitions of RRA in the 2012 cohort, multivariate analysis

Characteristics		OR (95% C.I.)	p value
B-RRA			
CRP	per mg/L increase	0,81 (0,68-0,95)	0,011
HAQ	per unit increase	3,28 (0,85-12,54)	0,84
Combination with any csDMARD		4,61 (0,65-32,59)	0,124
bDMARD treatment duration	per year increase	0,58 (0,52-1,03)	0,114
No bDMARDs		91,0 (7,87-1055,58)	<0,001
Model constant			0,009
KF-RRA			
PDN	per mg increase	1,49 (0,87-2,56)	0,144
DAS28	per unit increase	4,22 (1,4-12,71)	0,011
No bDMARDs		- (0-0)	0,99
Model constant			0,989
DH-RRA			
Combination with any csDMARD		6,24 (0,69-56,61)	0,614
Comorbidity		12,82 (0,46-1122,91)	0,065
No bDMARDs	per unit increase	6,25 (2,75-121,39)	0,003
Model constant			0,002

B-RRA refractory RA according to Buch, KF-RRA refractory RA according to Kearsley-Fleet, DH-RRA refractory RA according to De Hair

Table 2. Factors associated with three definitions of RRA in the 2019 cohort, multivariate analysis

Characteristics		OR (95% C.I.)	p value
B-RRA			
No. bDMARDs		18.77 (11.06;31.85)	$p < 0.001$
PDN daily dose	per 5mg increase	2.15 (1.17;2.15)	0.014
Model Constant			$p < 0.001$
KF-RRA			
BMI	per 5 unit increase	0.61 (0.35;1.05)	0.072
No. bDMARDs		8.69 (5.16;14.64)	$p < 0.001$
bDMARD treatment start year	per year increase	0.92 (0.84;1.01)	0.087
Model Constant			0.069
DH-RRA			
No. bDMARDs		3.9 (2.67;5.71)	$p < 0.001$
bDMARD treatment start year	per year increase	0.91 (0.83;0.99)	0.026
DAS28	per 0.6 unit increase	5.55 (3.34;9.23)	$p < 0.001$
RX progression		2.7 (1.21;6.03)	0.015
Model Constant			0.04

B-RRA refractory rheumatoid arthritis according to Buch, KF-RRA refractory rheumatoid arthritis according to Kearsley-Fleet, DH-RRA refractory rheumatoid arthritis according to De Hair, RX progression (mTSS ≥ 0.5 over the last 24 months)

Disclosure of Interests: LARA FRISO: None declared, Francesca Ometto: None declared, DAVIDE ASTORRI: None declared, Costantino Botsios: None declared, Andrea Doria Consultant of: GSK, Pfizer, Abbvie, Novartis, Ely Lilly, Speakers bureau: UCB pharma, GSK, Pfizer, Janssen, Abbvie, Novartis, Ely Lilly, BMS
DOI: 10.1136/annrheumdis-2020-eular.3253

FRI0094

SIGNIFICANT IMPROVEMENT OF NT-PROBNP LEVELS IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH TOCILIZUMAB AND TOFACITINIB

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Background: N-terminal pro-brain natriuretic peptide (NT-proBNP) is a recognized predictor of congestive heart failure (CHF) and cardiovascular death. Rheumatoid arthritis (RA) patients (pts) were shown to have higher NT-proBNP concentrations than in general population, but it remains unclear, whether NT-proBNP levels are related to RA duration, activity or treatment.

Objectives: To investigate the effect of interleukin 6 receptor inhibitor - tocilizumab (TCZ) and JAK inhibitor - tofacitinib (TOFA) on NT-proBNP levels in RA pts during a 12-month (m) follow-up period.

Methods: The study enrolled 60pts (50women/10men) with the lack of efficacy/resistance and/or intolerance of basic anti-inflammatory drugs (DMARDs); median age was 55[42;61] years, median disease duration 55[29;120]m, with moderate to high activity (DAS28-5,1[4,6;6,1], serum positivity for rheumatoid factor (RF)(85%)/ anti-cyclic citrullinated peptide antibodies (ACCP)(80%). The study did not include RA pts with CHF and clinically overt cardiovascular disease (CVD). Twenty nine RA pts received TCZ(8mg/kg) every 4 weeks: 61% received TCZ in combination with methotrexate (MTX), 35% - with low-dose glucocorticoids (GCs). Thirty one RA pts were prescribed oral TOFA at 5 mg BID with dose escalation to 10mg BID in 8 (26%)pts. TOFA was used in combination with MTX in 90% pts, with GCs - in 29% pts. Pts treated with TCZ and TOFA were comparable in terms of age, sex, body mass index. RA activity rates (DAS28, SDAI, ESR, CRP) were higher in pts on TCZ -therapy compared with pts treated with TOFA. Echocardiography data and NT-proBNP levels using electrochemiluminescence method Elecsys proBNP II (Roche Diagnostics, Switzerland) were obtained at baseline and after 12m.

Results: Significant positive changes in major disease activity, clinical and laboratory parameters were found in RA pts after 12 m of TCZ infusion and TOFA intake: remission (DAS28<2,6) was achieved in 54% and 39% pts, low activity levels (DAS28<3,2) - in 46% and 51% pts, respectively.

The NT-proBNP levels were significantly higher in RA pts than in the control group (median 69,1 (37,9;105,8) pg/mL vs 55,3 (36,6;67,3) pg/mL, $p < 0.05$).

Six pts (10%) (three in each pts group) had NT-proBNP levels over 125pg/ml, but were asymptomatic and had unremarkable echocardiography.

There was a good correlation between NT-proBNP level at baseline with age ($r = 0,55$, $p < 0,001$), SDAI ($r = 0,5$, $h = 0,01$), ACCP ($r = 0,23$, $p = 0,01$).

Decrease of median NT-proBNP levels was documented after 12m of TCZ therapy (81,5[43,0;102,0]vs41,6[25,4;64,2]pg/ml ($p < 0,01$) and after 12m TOFA therapy (66,1[30,5;105,0]vs16,8 [5,0;81,0]pg/ml, $p = 0,001$).

After 12m of TCZ correlations of Δ NT-proBNP were established with Δ ESR ($R = 0,43$; $p < 0,05$), Δ CRP ($R = 0,46$; $p < 0,05$), Δ Ee left ventricle (LV) ($r = 0,88$, $p = 0,03$).

In the group of pts treated with TOFA Δ NT-proBNP level significantly correlated with the percentage change in DAS 28 ($r=0.41, p=0.038$), there was no direct correlation with changes in the parameters of the LV diastolic function.

Conclusion: TCZ and TOFA treatment for 12 m reduced NT-proBNP levels in RA pts without clinically manifest CVD and CHF. Falling NT-proBNP concentrations are associated with positive dynamics of RA activity (DAS 28) and inflammatory markers (CRP, ESR), therefore allowing to suggest that increased NT-proBNP levels should be considered as a component of disease activity. Correlation between Δ NT-proBNP and Δ EeLF may be indicative as possible impact of these biomarkers on the LV diastolic function's development in RA pts.

Disclosure of Interests: None declared
DOI: 10.1136/annrheumdis-2020-eular.5859

FRI0095

SARILUMAB IMPROVED PATIENT-PERCEIVED IMPACT OF RHEUMATOID ARTHRITIS WHATEVER THE BASELINE DISEASE ACTIVITY: FIRST RESULTS FROM AN INTERVENTIONAL NON CONTROLLED STUDY: SARIPRO, IN MODERATE AND SEVERE RHEUMATOID ARTHRITIS PATIENTS

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Background: Sarilumab, an anti-IL-6R antibody, is approved for the treatment of moderate to severe RA and shown efficacy on disease activity and patient-reported outcomes (PROs). Detailed analyses of drug efficacy from the patient point of view is important. SariPRO is a pragmatic interventional study close to the daily practice.

Objectives: To assess the effectiveness of sarilumab on several PROs using the RAID (Rheumatoid Arthritis Impact of Disease) score.

Methods: The SariPRO study (NCT 03449758) was a French multicenter interventional study assessing the effects of sarilumab 200 mg on PROs in patients with moderately to severely active RA with an inadequate response or intolerance to conventional synthetic or biologic DMARDs. The primary endpoint was change in total RAID score from baseline to week 24 (RAID ranges 0-10 where 10 is maximal impact). Changes from baseline for RAID, DAS28-ESR and CDAI according to baseline disease activity were analyzed as secondary outcomes. Safety was assessed by monitoring adverse events (AE). All statistical analyses were descriptive, 95% CI was given when appropriate.

Results: 84 patients were included in 31 centers and 62 were evaluable and analyzed for effectiveness. They had similar characteristics to the 84 patients at baseline and were as expected for an RA population initiating a biologic: mean (SD) age: 59.9 (12.4) years, 71.0% female, disease duration 9.7 (10.3) years, rheumatoid factor positivity 82.5%, ACPA positivity 86.4%, and DAS28=4.9 (11). Total RAID score decreased significantly from 5.7 (2.0) at baseline to 3.3 (2.5) at W24; mean change was -2.4 [95% CI: -3.0; -1.8]. Furthermore, this improvement was noted both for highly and less active patients at baseline: for patients with DAS28-ESR < 5.1 (n=31), mean change was -1.56 [-2.28; -0.83] and for patients with DAS28-ESR ≥ 5.1 (n=27), mean change was -1.98 [-2.91; -1.05]. Changes in DAS28-ESR and CDAI were significant (-2.8 [-3.2; -2.4] and -15.2 [-18.5; -11.8], respectively). AEs were consistent with the safety profile of anti-IL-6R antibodies and with results from RCTs (data not shown).

Conclusion: In this real world study, treatment with sarilumab during 24 weeks in RA patients led to an improvement in the total RAID score irrespective of baseline levels of disease activity. This is the first time RAID score is used as the primary endpoint in a study.

References:

[1] Study was sponsored by Sanofi Genzyme
Disclosure of Interests: Laure Gossec Grant/research support from: Lilly, Mylan, Pfizer, Sandoz, Consultant of: AbbVie, Amgen, Biogen, Celgene, Janssen, Lilly, Novartis, Pfizer, Sandoz, Sanofi-Aventis, UCB, René-Marc Flipo Consultant of: Johnson and Johnson, MSD France, Novartis, Sanofi, Speakers

bureau: Johnson and Johnson, MSD France, Novartis, Sanofi, Thierry Schaevebeke: None declared, Christine Albert: None declared, Athan Baillet Consultant of: Athan BAILLET has received honorarium fees from Abbvie for his participation as the coordinator of the systematic literature review, marie-Christophe Boissier: None declared, Cyrille Confavreux: None declared, Gregoire CORMIER: None declared, Emmanuelle Dernis Speakers bureau: Lilly, Novartis, Elisabeth Gervais Solau: None declared, Sophie Godot: None declared, Jacques-Eric Gottenberg Grant/research support from: BMS, Pfizer, Consultant of: BMS, Sanofi-Genzyme, UCB, Speakers bureau: Abbvie, Eli Lilly and Co., Roche, Sanofi-Genzyme, UCB, Philippe Goupille Grant/research support from: AbbVie, Amgen, Biogen, BMS, Celgene, Chugai, Lilly, Janssen, Medac, MSD France, Nordic Pharma, Novartis, Pfizer, Sanofi and UCB, Consultant of: AbbVie, Amgen, Biogen, BMS, Celgene, Chugai, Lilly, Janssen, Medac, MSD France, Nordic Pharma, Novartis, Pfizer, Sanofi and UCB, Slim Lassoued: None declared, Thierry Lequerre: None declared, Frederic Lioté Consultant of: CME: Nordic Pharma, Christian Marcelli: None declared, Yves Maugars: None declared, Minh Nguyen: None declared, Aleth Perdriger: None declared, Yves-Marie Pers: None declared, Edouard Pertuiset: None declared, Lucile Poiroux: None declared, Carole Rosenberg: None declared, Christian Roux: None declared, Adeline Ruysse-Witrand Grant/research support from: Abbvie, Pfizer, Consultant of: Abbvie, BMS, Lilly, Mylan, Novartis, Pfizer, Sandoz, Sanofi-Genzyme, Martin SOUBRIER: None declared, Pascale Vergne-Salle: None declared, Charles Zarnitsky: None declared, Eric Fakra Consultant of: Janssen, Lundbeck, Otsuka, Sanofi, Hubert MAROTTE Grant/research support from: Bristol Myers Squibb, Lilly France, MSD, Novartis, Nordic Pharma, Pfizer, SanofiAventis, Consultant of: AbbVie, Amgen, Bristol Myers Squibb, Lilly France, MSD, Novartis, Nordic Pharma, Pfizer, SanofiAventis, Paid instructor for: Sanofi-Aventis, Speakers bureau: Sanofi-Aventis, Florence E Lévy-Weil Employee of: Sanofi Genzyme employee
DOI: 10.1136/annrheumdis-2020-eular.5518

FRI0096

CLINICAL BENEFITS REPORTED IN AMPLE TRIAL OBSERVED IN A REAL-WORLD (RW) COHORT OF US RHEUMATOID ARTHRITIS (RA) PATIENTS

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Background: Efficacy observed in controlled trials may not reflect RW effectiveness, given documented differences in patient populations and management.¹

Objectives: This study aimed to assess disease measures over time as measured in a trial setting (AMPLE) and in a separate RW observational setting, both among patients with RA treated with abatacept.

Methods: The RW cohort comprised retrospective patient-level data abstracted by 31 community rheumatologists for adult RA patients treated with abatacept who had an anti-cyclic citrullinated peptide-2 titer ≥250 AU/mL. AMPLE was a phase III, randomized controlled trial of RA patients treated with abatacept that assessed disease measures over a 2-year follow-up. Data included demographics, treatments, labs, and disease measures (tender and swollen joint counts (TJC, SJC), C-reactive protein (CRP), American College of Rheumatology-20 (ACR20) and ACR50 at baseline and 3 and 6 months) and were summarized descriptively. Disease measures were evaluated across AMPLE and RW cohorts.

Results: Of the 291 RW patients and 318 AMPLE patients, the majority were female (70%, 81%), white (72%, 81%), and RF-positive (91%, 76%), respectively (Table 1). The mean ages at abatacept initiation were 54.7 and 51.4 years

Table 1: Patient Characteristics.

	RW cohort (n=291)	AMPLE cohort (n=318)
Female (n, %)	205 (70%)	259 (81%)
White (n, %)	209 (72%)	257 (81%)
Age at abatacept initiation, years (mean, SD)	54.7 (14.8)	51.4 (12.6)
RF-positive* (n, %)	249 (91%)	240 (76%)
Concomitant medications (n, %)		
Corticosteroids [†]	132 (45%)	207 (65%)
Methotrexate	179 (62%)	318 (100%)
Prior biologic use (n, %)	241 (83%)	0 (0%)
Route of administration (n, %)		
Intravenous	183 (63%)	0 (0%)
Subcutaneous	108 (37%)	318 (100%)

LEGEND: *among 274 with known RF status; [†]corticosteroids in AMPLE cohort at any time in the 2-year study period