Differences in systemic inflammation between psoriasis, psoriatic arthritis and rheumatic arthritis.

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ABSTRACT

Background: psoriatic arthritis (PsA) and rheumatic arthritis (RA) and to a lesser extent psoriasis (PSO), all have increased levels of systemic markers.

Objectives: to compare the distribution of parameters of serological inflammation between patients with PSO, PsA, RA and controls and to identify factors associated with elevated systemic inflammatory markers in a daily practice setting.

Methods: In this daily practice cross-sectional study, all participants with a diagnosis of PSO, PsA, and RA were included and compared with controls. Demographic data, disease characteristics, medical history, life style factors, previous treatments, quality of life indicators and serum was collected per participant. Serum was tested on IL-6, IL-10, IL12P70, IL17A, IL17F, IL22, IL23, TNFα and CRP. A mixed regression model was used to estimate the effect size of factors associated with levels of CRP, IL6 and-10 after adjusting for confounders.

Results: in total 601 patients; 180 PSO (39% female, mean age 49 years), 154 PsA (46% female, mean age 52 years), 136 RA (65% female, mean age 61 years) and 131 controls (58% female, mean age 54 years) were included. The highest levels of the pro-inflammatory markers were in RA followed by PsA. In the multivariate analysis CRP was associated with disease severity (β6.9 SE 1.8), pain medication (β4.2 SE 1.9) and SF 36's physical impairment (β-0.25 SE 0.09); and IL-6 was associated with diagnose, male gender and systemic medication and IL-10 with diagnose.

Conclusion: Overall RA has the most pronounced serological inflammatory profile followed by PsA and least inflammation was seen in PSO patients despite the use of systemic medication.

INTRODUCTION

Psoriasis (PSO) is an immune-mediated inflammatory disease (IMID), but a systematic review shows that the blood levels of several key cytokines are at most mildly elevated with unsure clinical relevance.[1,2] However, systematic inflammation is proposed to be the explanation of PSO's associated comorbidities and the concept of PSO as a systemic disease. In contrast to PSO, rheumatoid arthritis (RA) is truly a systemic disease reflected its diagnostic ACR/EULAR RA Classification Criteria and pronounced and consistent elevated inflammatory parameters such as CRP. PSO and RA are both considered IMIDs suggesting in part a common pathogenesis and share several effective therapies. From the systemic inflammation and comorbidity perspective, several authors have 'upgraded' PSO to a systemic disease comparable to RA. This disease overlap is further supported by psoriatic arthritis (PsA) that occurs in approximately 10% of PSO patients. However, few studies have compared cytokine levels in PSO patients to PsA, RA and controls while taking potential cofounders in consideration.[3]

In this study we selected the following inflammatory markers: C-reactive protein (CRP), interleukin (IL) -6, IL-10, IL12P70, IL17A, IL17F, IL22, IL23 and tumor necrosis factor (TNFα). CRP was chosen because firstly, it has been recognized as one of the most sensitive markers of inflammation. Moreover, a short half-life of 6–8 h makes it an appropriate tool for following disease course. Secondly, CRP is an independent risk factor for cardiovascular disease.[4] IL6 was chosen as an overall pro-inflammatory marker and Il-10 as an anti-inflammatory marker. IL12P70, IL17A, IL17F, Il-22, IL23, TNFα were chosen as pro-inflammatory markers in PSO and rheumatic diseases which are target for the biological therapies used in these diseases.

The objective of this cross-sectional study is to explore the differences in levels of serum biomarkers reflecting systemic inflammation in a 'real-life population' in PSO patients compared to RA patients and subsequently to patients with PsA and controls. We hypothesized that RA expressed more serological inflammatory markers than PSO and that PsA would be in between the two other diseases.

METHODS

Study and population

The study participants were included from March 2009 until August 2012 as described previously.[5] PSO patients had chronic plaque PSO and were diagnosed and recruited by dermatologists from the department of dermatology of the Erasmus University

Medical Center in Rotterdam, the Netherlands. At the same center, the control group consisting of individuals with varicose veins or benign moles without PSO, PsA and/or RA were recruited. The PsA and RA patients were recruited from the rheumatology department of the Maxima Medisch Centrum Hospital in Eindhoven, the Netherlands. An rheumatologist confirmed PsA and RA diagnosis based on the Classification Criteria for Psoriatic Arthritis (CASPAR) and 2010 ACR/EULAR RA Classification Criteria.[6] The eligible PSO subjects had no history or signs of inflammatory arthritis such as PsA.

Covariates Demography, lifestyle

Patients were asked to fill in a standardized questionnaire at the day of inclusion to obtain data concerning general medical history including comorbid conditions, medication use, smoking behavior, alcohol intake, socioeconomic status and (prior) disease specific drug use. Furthermore type of arthritis/psoriasis, (earlier) disease specific medication use, disease severity, comorbidities and other medication use, were collected by the dermatologist or rheumatologist.

Furthermore body mass index (BMI) was calculated as weight (kg)/height (m2). Diabetes was defined as 1: Diabetic medication including all insulin preparations and oral agents, 2: diabetes mentioned in the medical history or 3: an elevated non-fasting glucose level (> 6.1 mmol/L) or HbA1c (Glycohemoglobine) (>42 mmol/mol Hb) in the patients' blood. Hypercholesterolemia was defined as serum total cholesterol >6.5 mmol/L, serum triglycerides greater than 2.0 mmol/L; serum high-density lipoprotein cholesterol less than 0.9 mmol/L, serum low-density lipoprotein cholesterol greater than 2.59 mmol/L or drug treatment for low high-density lipoprotein cholesterol or elevated triglycerides or elevated high low-cholesterol. Hypertension was defined as drug treatment for elevated blood pressure or medical history of hypertension.

Disease characteristics

For PSO and PsA patients, Psoriasis Severity Index Score (PASI)<7 was defined as mild; PASI 7–12 as moderate and a PASI>12 as severe disease.[7] The disease activity and course severity in PsA and RA patients were assessed with Disease Activity Score 28 (DAS28) (DAS<3.2 was defined as mild, 3.2-5.1 as moderate and >5.1 as severe disease activity[8]). In case of a discrepancy in disease severity score between skin and joints in PsA, the most severe stage was taken. This occurred only in 4 patients with skin severity higher than joint severity.

Disease specific medication was divided into four subgroups; (1) patients without medication or who only used topical products, UV and/or non-steroidal anti-inflammatory drugs (NSAIDs); (2) patients who used disease related systemic drugs excluding metho-

trexate (MTX); (3) MTX use irrespective of any other medication except biologicals; and (4) patients who used a biologicals irrespective of medication from group one to three. A separate variable was used of NSAID, as this medication is used a lot and it is known to have a different effect on inflammatory markers.[9] Data on dosing regimens were not available.

Quality of life

The impact of disease on quality of life was assessed by the generic SF36-questionnaire.[10] The lower the score the more disability. Assessment of the rheumatologic disease was done in the following manner; the impact on quality of life was evaluated by the functional index (HAQ = Health Assessment Questionnaire).[11] To assess the quality of life on the skin disease the Skindex 29 was used.[12]

Laboratory values and cytokines levels

None fasting venous blood was drawn from all participants at the day of inclusion and centrifuged to separate serum. All serum samples were frozen at -80°C and were later analyzed simultaneously as a batch. IL-6, IL-10, IL12P70, IL17A, IL17F, IL22, IL23, TNFα in sera were analyzed using ELISA (ebioscience, Affymetrix, San Diego) expressed in ng/ml in the research laboratory of the department rheumatology of the Erasmus Medical Center.

Leukocytes and high sensitivity C reactive protein (Hs-CRP), were analyzed using standard enzymatic immunoassays. For the PsA and RA patients, also the following extra tests were analyzed: blood sedimentation rate of erythrocyte (BSE) and cyclic citrullinated peptide antibody (anti-CCP).

Statistics

Covariate distribution among the groups was examined using descriptive statistics of SPSS software version 20. The distribution of the general characteristics were compared between the different groups using the Chi-square tests and one way ANOVA or Kruskal Wallis tests for statistical significance of categorical data and continuous data, respectively. P-values were two-sided and values <0.05 were considered statistically significant.

In order to estimate if covariates predicted CRP and ILs concentrations a regression models were fitted. A linear backward regression model was used for CRP. As the distribution of ILs contained many zero values and non-zero values were non-normally distributed, a mixed regression model with a zero adjusted gamma distribution was used. This model presented the data in two parts, percentage positive values and the level of the positive values. And this model estimates the odds ratio (OR) of non-zero values vs. zero values

and also estimates the percentage change in IL for non-zero values. The maximum degrees of freedom was determined by dividing the number of non-zero values by 10. The distribution of IL-6, IL-10 and contained enough non-zero values to perform a regression model. The mixed regression models were performed using the gamlss package from R (www.r-project.org, www.gamlss.org). Other analyses were performed using SPSS 20.0 (IBM, UK). P-values were two-sided and values <0.05 were considered statistically significant.

The study was approved by the Medical Ethics Committee of the Erasmus Medical Center in Rotterdam (MEC- 2007-181) and Maxima Medical Center in Eindhoven. Written informed consent was obtained from all participants.

RESULTS

Demographic and life style

The primary analyses included in total 601 patients; 180 patients with PSO (39% female, mean age 49 years), 154 patients with PsA (46% female, mean age 52 years), 136 patients with RA (65% female, mean age 61 years) and 131 controls (58% female, mean age 54 years) (Table 1). BMI was slightly higher in PSO patients. Alcohol use/abuse did not differ significantly between the four groups. However, we observed a trend towards increased prevalence of alcohol abuse (>3 beverage a day) in PSO patients. Although PSO patients were more often current smokers compared to controls and RA patients, total pack years and the amount being smoked did not differ between all groups. RA patients had the highest level of socio-economic status.

Disease characteristics, quality of life and medication

PSO patients suffered the longest from their disease (mean 20.6 years compared to 10.0 and 10.9 years by PsA and RA patients). A mean PASI score, being independent of medication use, of 1.5±2.4 in PsA patients and (mean PASI 5.9 ± 5.8) in PSO patients. Half of the PSO, PsA and RA patients had a positive family history of PSO or arthritis.

Most patients included in this study were using systemic drugs (76% for PSO, 92% PsA and 97% RA). MTX was most often used in RA and PsA patients. Combination therapy, (MTX with another biological) was also more often used in RA and PsA patients. 31% of PSO patients used fumaric acid, 15% MTX, 8% acitretin, 4.4% ciclosporine and 22% used a biological (81% anti-TNF blocker).

Table 1. General characteristics of the study population

	Psoriasis (n=180)	Psoriatic arthritis (n=154)	Rheumatoid arthritis (n=136)	Controls (n= 131)	Total** (n=601)	*P*-value*
Covariables						
Age (years)	49,3 ± 14,3	52,3 ± 11,7	61,4 ± 11,0	53,9 ± 14,4	53,8 ± 13,7	**<0,001**
Female (%)	38,9	46,1	64,7	58,0	50,7	**<0,001**
BMI (kg/m2)	27,2 ± 5,8	26,5 ± 4,2	25,9 ± 4,5	27, 5 ± 6,1	26,8 ± 5,3	**0,054**
Alcohol intake (drinks/day)						0.060
None (%)	43,5	31,7	38,5	36,3	37,8	
< 3 (%)	49,4	65,5	59,2	60,5	58,1	
>3 (%)	7.1	2.9	2.3	3.2	4.1	
Smoking						**<0,001**
Never (%)	28,1	40,5	31,9	52,3	37,4	
Former (%)	29,2	42,5	53,3	32,3	38,8	
Current (%)	42,7	17,0	14,8	15,4	23,8	
Education status						**0,008**
Low (<6 years) %	23,3	29,3	21,1	33,6	26,6	
Medium (6-12 years) %	41,5	30,0	27,1	32,0	33,2	
High (>12 years) %	35,2	40,7	51,9	34,4	40,2	
Personal medication use (yes, %)						
Diabetes	13.4%	5.5%	8.1%	0%	7.2%	**0.01**
Anticoagulant	16.8%	14.6%	26.1%	30.4%	21.1%	**0.01**
Antihypertensive	33.6%	34.9%	43.2%	55%	40.3%	**0.02**
Hypercholesterolemia	25.7%	17.4%	18.9%	23.1%	21.1%	0.58
Pain medication	8.0%	19.3%	18.0%	10.1%	14.2%	0.055
Psycho medication	9.8%	11.9%	8.1%	7.2%	9.4%	0.58
Disease						
Onset of disease	27.6 ± 15.7	40.3 ± 22.3	50.1 ± 13.2	-	38.2 ± 19.8	**<0.001**
Duration of disease, years	20.6 ± 14.8	10.0± 9.40	10.9 ± 9.4	-	14.4 ± 12.8	**<0.001**
Severity of disease PASI	5.9 ± 5.8[#]	1.5 ± 2.4[#]	-	-	3.89 ± 5.07	**<0.001**
Severity of disease DAS	-	2.16 ± 0.91	2.66 ± 1.00	-	2.39 ± 0.98	0.72
Overall disease severity						**<0.001**
mild	121 (67.2%)	127 (82.5%)	84 (65.6%)	-	332 (55.2%)	
moderate	37 (20.6%)	25 (16.2%)	42 (32.8%)	-	104 (17.3%)	
severe	22 (12.2%)	2 (1.3%)	2 (1.6%)	-	26 (4.3%)	
Quality of life						
Skindex 29	98.6 (IR 89)	46.3 (IR 61)	0 (IR 20)	7.14 (IR 43)	35.7 (IR 90)	**<0.001**
SF-36						
PCS	48.3 ± 9.5	41.0 ± 10.7	37.7 ± 11.4	48.9 ± 10.2	44.1 ± 11.4	**<0.001**
MCS	48.5 ± 9.5	50.4 ± 9.5	51.3 ± 10.4	50.1 ± 9.5	50.0 ± 9.7	**0.03**

Table 1. General characteristics of the study population (continued)

	Psoriasis (n=180)	Psoriatic arthritis (n=154)	Rheumatoid arthritis (n=136)	Controls (n= 131)	Total** (n=601)	*P*-value*
HAQ	-	0.66 ± 0.60	1.04 ± 0.62	-	0.84 ± 0.68	**<0.001**
Medication use (n, (%))						
None	3.3%	5.2%	2.9%	-	6.7%	
Cutaneous only	21.1%	3.2%	-	-	12.9%	
Prostagladinesynthetase inhibors only	-	9.1%	2.9%	-	6.2%	
DMARD and PSO medication						
MTX (only)	10%	30.5%	27.9%	-	21.9%	
Other	43.9%	37.7%	56.6%	-	45.5%	
Prednison	-	9.7%	15.4%	-	12.4%	
Biologicals	23.3%	12.9%	12.5%	-	16.8%	
Laboratory data						
Leukocytes	7.14 ± 2.06	7.2 ±5.8	9.24 ± 13.8	-	7.8 ± 8.5	**0.09**
CRP	2.00 (IR 3)	3.00 (IR 3)	4.00 (IR 6)	-		**>0.001**
BSE	-	6.0 (IR 10)	11.0 (IR 19)	-		**>0.001**
CCP	-	24.0 (IR 1)	390 (743)	-		

Data are represented as mean (± standard deviation), median (25^th -75^th percentile) or percentages. Based on One-Way ANOVA, Kruskal-Wallis or Chi-square test. Abbreviations: cat, categorical; BMI, Body Mass Index; PASI, psoriasis area severity index; SF-36, Short Form (36) Health Survey ; HAQ, Health Assesment Questionnaire; MTX, methotrexate; PCS, physical component summary; MCS, mental component summary; CRP, C reactive protein; BSE, blood sedimentation rate of erythrocyte ; CCP, cyclic citrullinated peptide antibody; ** Total of the applicable groups

The SF 36 showed on the condition of physical functioning, health, pain and general health a lower score at the arthritis patients. The subgroups of emotional problems, energy/fatigue, emotional well-being and social functioning scored equal between PSO patients and the arthritis patients. PSO patients had significantly the lowest on the mental component.

Inflammatory markers

The results of the inflammatory markers included multiple zero's. The data is presented in two parts, percentage positive values and the level of the positive values. The percentage of positive values of the pro-inflammatory markers IL6 and IL17A, presented as dichotomous variables ,were significantly higher in RA patients (32.9% and 5.1%) compared to PsA (22.6% and 0%) and PSO (14.1% and 0%) patients. We observed the opposite effect for anti-inflammatory marker IL10 . The highest values of IL10 were observed in PSO patients (29%) lowest values in RA patients (3%). TNF-alfa had in the

Table 2. Inflammation markers stratified for disease.

% (n)	Controls		Psoriasis		Psoriatic arthritis		Rheumatoid arthritis		***P*-value***		***Total***	
	% pos	mean with SD	***% pos***	mean with SD	***% pos***	mean with SD	***% pos***	mean with SD			***% pos***	mean with SD
IL-6	14.1%	19.4±55.6	14.5%	1.8±1.8	22.6%	30.5±86.7	32.9%	13.4±19.8	0.01	0.52	21.3% (66)	17.3±52.5
IL-10	18.3%	2.59±2.77	28.9%	5.87±3.92	3.6%	9.83±1.33	2.5%	3.11±2.28	0.00	0.007	12.9% (40)	4.97±3.9
IL12P70	5.6%	27.9±51.1	6.6%	2.07±3.14	2.4%	45.0±61.0	5.1%	2.72±4.60	0.64	0.35	4.8% (15)	14.86±33.3
IL17A	0%	0.0 ±0.0	0%	0.0 ±0.0	0%	0.0 ±0.0	5.1%	20.8±16.2	0.008	-	1.3% (4)	20.8±16.2
IL17F	1.4%	589.1	1.3%	57.8	4.8%	283.3±497.0	7.6%	93.4±168.0	0.13	0.52	3.9% (12)	195±323
IL22	0%	0.0 ±0.0	0%	0.0 ±0.0	0%	0.0 ±0.0	2.6%	95.8±5.6	0.25	-	0.8% (2)	95.8±5.6
IL23	1.4%	0.88	1.3%	1.0	2.4%	0.35±0.07	2.5%	1.65±1.9	0.92	0.82	1.9% (6)	0.98±1.03
TNF-alfa	0%	0.0 ±0.0	7.1%	80.7±79.5	13.0%	89.9±48.3	9.0%	102.8±79.7	0.036	0.89	6.8% (16)	93.8±65.1

Data are represented as positive values of dichotomous variables and data are represented as total mean with SD

PsA the most positive values (13%) followed by RA (9%). Il12P70, Il17F, IL22 and IL23 showed no significant different between the groups in percentage positive values. Table 2 showed the percentage values above the measure threshold and the overall means of the different inflammatory markers stratified for disease. In figure 2 showed the percent-

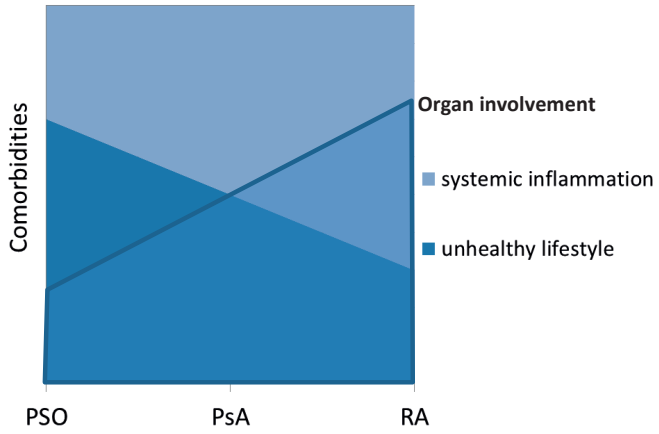

Figure 1. A hypothetical model of the etiology of the prevalence of comorbidities in PSO, PsA and RA
Abbreviations: PSO, psoriasis; PsA, psoriatic arthritis; RA, rheumatic arthritis

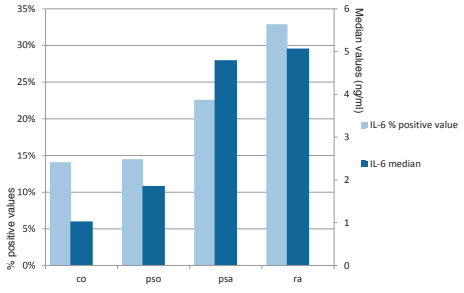

Figure 2a

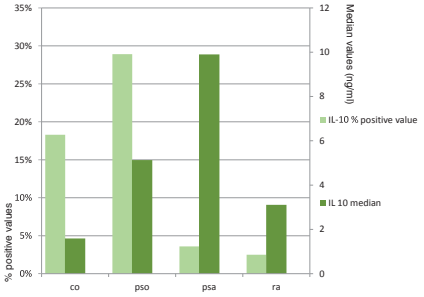

Figure 2b

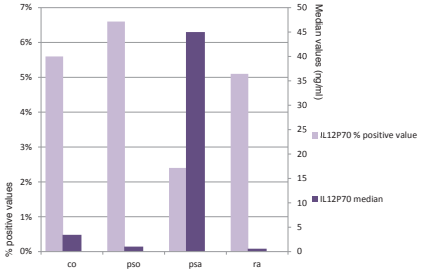

Figure 2c

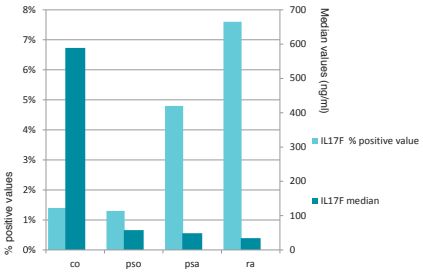

Figure 2d

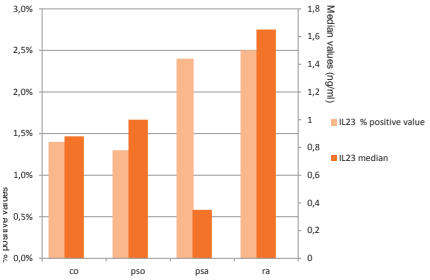

Figure 2e

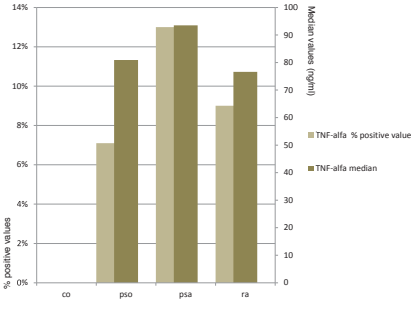

Figure 2f

Figure 2 a to f. Inflammatory makers in PSO, PSA, RA and controls.
Percentage of non-0 values and the median of these non-0 values of the inflammatory makers in PSO, PSA, RA and controls.
Abbreviations: PSO, psoriasis; PsA, psoriatic arthritis; RA, rheumatic arthritis
P values of 0 values: Chi-square test; P values of the median of the positive values: Kruskal-Wallis test
$p<0.05$ for IL6 value 0 and median; IL 10 value 0 and median; IL17A value 0, TNF-alfa value 0.

age positive values and de median of the different inflammatory markers stratified for disease, except for IL17A, only RA has 5.1% positive values with a medium of 20.4. In the control group, PSO and RA there were no values above 0. Overall RA has the most

pronounced serological inflammatory profile followed by PsA and least inflammation was seen in PSO patients despite the use of systemic medication

The regression model

After adjusting for sex, disease severity, pain medication, SF36 physical, SF36 mental, alcoholic use, diagnose, medication use, BMI, age, diabetic, education and smoking in the linear regression model, higher disease severity and more pain medication were associated with an increased CRP (β=6.9 p<0.001 and β=4.2 p=0.03) A higher SF36 physical score (i.e., less impairment) was correlated with a lower CRP value (β=-0.2 p=0.006). (Table 3) Using Nagelkerke R square on the final adjusted backward model, 13% for the CRP value was explained by the included risk factors.

For IL6, diagnoses, age, sex and medication were included in the full adjusted multivariable linear combined regression model and for IL10, these were diagnoses and age. (Table 4) For IL6, only men had a higher likelihood of not having a zero value (OR 0.5 95%CI 0.27-0.88). After excluding the zero values, a diagnose of RA, PsA, female gender and systemic medication were significant predictors for an increased risk of an elevated IL6 score. The odds of not having an absence of IL10 was elevated in PsA (OR 6.08 95%CI 5.9-6.2) and even more in RA (OR 8.4 95%CI 1.8-39.4) compared to controls. If the value was positive, PSO and PsA had a positive correlation with a higher IL-10 value.

Table 3. linear regression model for CRP

	CRP value		
	β	***SE***	***P*-value**
Crude univariate model			
diagnose	0.39	0.94	0.68
Age and sex adjusted			
Age, years	0.13	0.06	0.03
Sex, female	1.4	1.48	0.35
diagnose	0.43	0.92	0.65
Multivariable adjusted			
Sex, female	3.52	1.91	0.07
Disease severity	6.88	1.75	<0.0001
Pain medication	4.23	1.91	0.03
SF 36 physical	-0.25	0.09	0.006

Multivariate linear regression model with backward method.
The following variables were excluded in the analyses in the following order: SF36 mental, alcoholic use, diagnose, medication use, BMI, age, diabetic, education and smoking
Multivariate adjusted R square 0.127

Table 4. Multivariate adjusted model

	Beta	SE	OR non-0 vs 0	95%CI	Beta	SE	% Change if not 0	95%CI
IL-6								
Diagnose								
control			REF		2,80	0,69	1550%	323% - 6335%***
Psoriasis	0,05	0,63	1,05	0,30 - 3,65			REF	
RA	-1,09	0,71	0,34	0,08 - 1,37	2,43	0,55	1040%	287% - 3253%***
PSA	-0,59	0,69	0,55	0,14 - 2,15	2,76	0,55	1477%	438% - 4526%***
AGE								
years	-0,01	0,01	0,99	0,97 - 1,01	-0,02	0,02	-2%	
SEX								
Female			REF				REF	
Male	-0,71	0,30	0,49	0,27 - 0,88*	-1,04	0,35	-65%	-82% - -29%**
Medication								
Local	-0,05	0,61	0,95	0,29 - 3,17	-0,39	0,69	-33%	-83% - 162%
Systemic	-0,23	0,38	0,79	0,38 - 1,66	1,21	0,47	236%	34% - 742%**
MTX			REF				REF	
biological	0,39	0,50	1,48	0,56 - 3,95	0,94	0,62	156%	-25% - 773%
IL-10								
Diagnose								
control			REF				REF	
Psoriasis	-0,59	0,40	0,56	0,25-1,22	0,83	0,29	129%	29% - 308%**
RA	2,13	0,79	8,39	1,79-39,38**	0,18	0,62	20%	-64% - 304%
PSA	1,81	0,01	6,08	5,93-6,24**	1,36	0,54	288%	35% - 1019%*
AGE								
years	0,003	0,013	1,00	0,98-1,03	0,002	0,009	0%	-2% - 2%

Abbreviations: OR, odds ratio; PsA, psoriatic arthritis; RA, rheumatic arthritis. p-value WALD, *<0.05, **<0.01, ***<0.001

DISCUSSION

In this study, we analyzed cross-sectional and under 'daily life' conditions, the level of inflammatory parameters adjusted for disease, medication and comorbidities.

Serum IL6 levels are higher in RA and PsA patients compared to PSO patients and controls, which is in line with the existing literature.[13] Even after adjusting for covariates, the diagnose of a rheumatic diseases, this remained significant for the different diseases. As an anti-inflammatory cytokine, the proportion of positive IL10 or the mean/median (including zeros) serum levels was significant higher in PSO compared to PsA and RA as expected. However when the IL10 value was positive, the value was significant the highest in the PsA groups followed by PSO. It is described previously that PsA have higher values of IL-10 compared to healthy controls.[14] Also here the value of the control group

were lower than expected. Moreover the median CRP was significant higher in RA , following by PsA and PSO.[15] Only controls had the highest score, which may be explained by the phlebology tertiary center patients and the fact that most of the patients with PSO, PsA and RA were on treatment, which could have decreased the levels of CRP.[3] These three (anti)-inflammatory markers confirm the idea that RA is a more systemic disease compared to PSO.

Another pro-inflammatory marker TNFα shows a significant more positive values in PSO, PsA and RA compared to the controls. The diseases are mutually comparable, with also comparable use of anti-TNF therapy.

The proportion of positive values of the other cytokines; IL12P70, IL17A, IL17F, IL 22, IL 23, was low, and there were no significant differences, however we could see some trends with overall higher values in arthritis disease (PsA and RA) compared to PSO. The low amount of positive values may be explained due to low levels and sensitivity issues of the detection assays and the fact that almost all patients are on (systemic) therapy. It is known that these cytokine levels decrease after successful therapy.[16-18]

Strengths and Limitations

This study included a relatively large cohort of real life data on well-defined PSO, PsA and RA patients. PSO, PsA and RA patients were diagnosed by a rheumatologist or dermatologist, including use of disease activity measurement scales. This minimizes the introduction of misclassification bias. Psoriasis is a clinical diagnosis easily made after physical examination and for PsA patients there is specificity and sensitivity of over 99% using CASPAR.[19] In contrast to other studies, we collected and adjusted for the most important confounders for systemic inflammation in IMIDS.

A limitations is the different location were the PSO and the PsA patients were included. This may implicated that the psoriasis patients are more relatively severe affects compared to the arthritis patients because the former were recruited in a tertiary center. To minimize this potential bias, disease severity and site of inclusion was added in our multivariate model. Furthermore the Dutch areas where both recruiting hospitals are situated do not differ with respect to demographic characteristics and degree of urbanization (Rotterdam vs Eindhoven). Therefore, the effect of the use of different hospital departments for PSO and control versus PsA on the study findings appears to be limited. Also the controls patients had some remarkable increased levels of inflammatory markers which could be explained be the fact that they were recruited in a tertiary center, however we have tried to minimalize this by using patients with naevi and phlebology patients. The duration and dosage of the used drugs was not documented, but in this

study we did not focus on treatment effects and we were able to adjust for treatment exposure in the comparison across diseases.

Notwithstanding the fact that the inflammatory markers showed an expected trend, an unexpected large proportion of the serological measurements' were below the detectable level. By using mixed regression model with a zero adjusted gamma distribution, the effects of the negative assessments were minimized. We cannot rule out the possibility that non-significant results could the results from the heterogeneity of the studied population and small sample size in subgroups analyses though correcting for a lot of confounders.

CONCLUSIONS

Globally RA demonstrated to have the most pronounced inflammatory status followed by PsA and least inflammation was seen in PSO patients . Future, prospective, randomized, controlled studies are needed to better understand the impact of systemic therapy, disease and lifestyle factor on the extent of systemic inflammation in PSO, PsA and RA.

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