Differing local and systemic inflammatory burden in polyarticular psoriatic arthritis and rheumatoid arthritis patients on anti-TNF treatment in clinical remission

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Abstract

Objective

To analyse clinical, serological and sonographic differences between rheumatoid arthritis (RA) and polyarticular psoriatic arthritis (PsA) patients on anti-TNF therapy in clinical remission.

Methods

Angiogenic and proinflammatory cytokine serum levels were determined by multiplex ELISA in patients with RA and PsA in clinical remission (DAS28-ESR<2.6), clinically-active RA patients (DAS28>3.2) and healthy controls. Ultrasound (US) scans were made of both wrists and hands.

Results

30 RA and 47 PsA patients in remission, 22 active RA patients and 20 healthy controls were included. PsA patients had significantly lower disease activity according to DAS28-ESR (p=0.006) but not according to DAS28-CRP (p=0.319), and lower serum levels of proinflammatory and angiogenic cytokines than RA patients in remission. PsA patients had cytokine levels similar to healthy controls, while RA patients in remission had similar levels to those of active RA patients. Globally, 31 (40.25%) patients in remission had a PD signal and 12 had SH≥2 plus PD [1 PsA vs. 11 RA (p=0.0001)], meeting the criteria for ultrasound-defined active synovitis (UdAS). Patients with UdAS had significantly higher levels of IL-6, IL-20, PIGF and SDF1. More PsA patients were on tapered doses of anti-TNF (63.8%), and more frequently as monotherapy (72.3%), compared with RA patients (26.6% and 20%, respectively).

Conclusion

Polyarticular PsA patients in remission had lower levels of local (US synovitis) and systemic inflammation than RA patients in remission, even though a significantly higher percentage of PsA patients were on tapered doses of anti-TNF, mainly in monotherapy.

Key words

psoriatic arthritis, rheumatoid arthritis, remission, ultrasonography, cytokines

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Introduction

New treatment strategies and novel drugs, such as anti-TNF therapy, have radically changed outcomes in patients with inflammatory arthritis. A large percentage of patients achieve clinical remission, especially when treated to target in the early stages of the disease (1). Although biological therapies are generally successful throughout the spectrum of chronic inflammatory arthritis (2-4), national registries of biologics and data from clinical practice show that the survival of anti-TNF therapy is greater in patients with psoriatic arthritis (PsA) than in those with rheumatoid arthritis (RA) (5-9), suggesting that the effectiveness of these drugs is better in PsA. However, although several studies have demonstrated subclinical activity in RA patients on anti-TNF therapy in clinical remission, there are no comparative studies in PsA patients.

We hypothesised that the quality of clinical remission with anti-TNF therapy, measured by 28 joint disease activity score-erythrocyte sedimentation rate (DAS28-ESR) criteria would be better in patients with polyarticular PsA than in patients with RA. The DAS28-ESR has been validated for use in clinical trials (10) and shows comparable outcomes to the 68-joint DAS in patients with PsA receiving biological therapy (11).

Therefore, the aims of this study were to analyse differences in clinical, sonographic and serum biomarkers between patients with polyarticular PsA and RA on anti-TNF therapy in clinical remission. We also compared serum biomarkers in two control cohorts: clinically active RA patients (DAS28-ESR>3.2) and healthy controls. Finally, we tested the clinical and biological associations of the previously proposed concept of ultrasound (US)-defined active synovitis (UdAS) [synovial hypertrophy (SH) ≥2+ power Doppler (PD) signal] (12) in PsA and RA patients in clinical remission.

Patients and methods

Patients

Polyarticular PsA (after excluding any other inflammatory musculoskeletal manifestations, such as enthesitis, dactylitis or spondylitis) and RA patients diagnosed according to CASPAR (13) and ACR/EULAR classification criteria (14), respectively, who were on anti-TNF therapy (etanercept, adalimumab or infliximab), were consecutively selected from our arthritis unit outpatient clinic. All were in remission for >6 months, as defined by DAS28-ESR<2.6 and as confirmed by two independent rheumatologists. Polyarticular was defined as the involvement of >4 joints. Two age- and sex-matched control cohorts were selected to compare biomarker serum levels: first, a control group of active RA patients (DAS28-ESR>3.2), with or without biological therapy, and second, a group of healthy controls. Clinical, demographic and serological data collected included low dose oral prednisone (<7.5 mg/day) treatment, disease-modifying anti-rheumatic drugs (DMARDs) and biological therapy. Rheumatoid factor (RF) was determined by nephelometry and anti-citrullinated peptide/protein antibodies by CCP2-ELISA kits (Immunoscan, Eurodiagnostica, distributed by Diasorin Madrid, Spain). Signed informed consent was obtained from all patients, including the control cohorts. The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona.

Methods

• *Sonographic assessment*

All sonographic assessments were made using high-sensitivity ultrasound equipment (MyLab Twice®, ESAOTE, Italy). Sonographic assessments were made using a frequency range from 10 to 14 MHz and a pulse repetition frequency between 500 and 800 Hz. Receiver gain settings were controlled to eliminate the appearance of artefacts. Joint US findings were defined according to published OMERACT definitions (15). An experienced sonographer, who was blinded to the results of the clinical joint examination, evaluated 11 joints and tendons of each hand (including proximal interphalangeal joints, metacarpophalangeal joints and wrists) for both SH and intra-articular PD signal according to EULAR guidelines (16). SH and PD signal were graded using a 4-grade semi-quantitative scoring

Table I. Clinical, demographic and serologic data of 77 patients. Data are represented as percentages or mean and standard deviation. Tapered doses refer to the percentage of patients with no standard doses of biological treatment due to remission (lower dose or longer intervals between administration than recommended in the product package insert). Monotherapy refers to the percentage of patients with anti-TNF therapy without DMARDs. PD and SH≥2+PD refers to the percentage of patients with SH grade ≥2 plus PD signal in ≥1 joint assessed.

	RA (30)	PsA(47)	P	aRA (22)	HC (20)
Female (%)	22 (73.3)	20 (42.5)	0.008	16 (72.7)	10 (50)
Age, years (SD)	63.4 (10.5)	53.4 (10.4)	0.0001	58.8 (9.6)	39.5 (11.5)
Disease duration, years (SD)	16.9 (9.1)	15.0 (7.9)	0.372	12.5 (9.8)	-
Rheumatoid factor (%)	24 (80)	6 (12.7)*	0.0001	14 (63.6)	0
ACPA (%)	24 (80)	3 (6)*	0.0001	15 (68.1)	0
DAS28-ESR, mean (SD)	2.01 (0.3)	1.74 (0.4)	0.006	5.41 (1.3)	-
DAS28-CRP, mean (SD)	1.67 (0.4)	1.55 (0.2)	0.319	5.16 (1.2)	-
Time of remission, years (SD)	4.72 (4.35)	3.89 (2.71)	0.817	- -	
Anti TNF treatment (%)	77 (100)	14 (63.6)	-		
Etanercept (%)	18 (60)	24 (51)		8 (57)	-
Adalimumab (%)	9 (30)	16 (34)		5 (36)	-
Infliximab (%)	3 (10)	7 (14.8)		1 (7)	-
Patients on tapered doses (%)	8 (26.6)	30 (63.8)	0.001	0 (0)	-
Monotherapy (%)	6 (20)	34 (72.3)	0.0001	3 (21.4)	-
Patients with Prednisone (%)	10 (33.3)	1 (2.1)	0.0001	18 (81.8)	-
PD (%)	20 (66.6)	11 (23.4)	0.0001	22 (100)	-
SH≥2+PD (%)	11 (36.6)	1 (2.1)	0.0001	22 (100)	-

RA: rheumatoid arthritis; PsA: psoriatic arthritis; aRA: active rheumatoid arthritis; HC: healthy controls; SH: synovial hypertrophy; PD: power Doppler; ACPA: anticitrullin-protein antibody; SD: standard deviation. *Low levels (less than 50 U/mL of RF or ACPA).

system from 0-3 (grade 0=no, 1=mild, 2=moderate and 3=severe) according to the method developed by Szkudlarek *et al*. (17). Intra-rater agreement on US assessment, calculated as previously described (12), was 0.81 for SH and 0.92 for PD. Patients with SH grade ≥2 plus PD signal in any joint assessed were classified as having UdAS.

• *Quantification of serum levels of biomarkers of inflammation/angiogenesis*

Cytokines and angiogenic mediators were analysed using Quantibody® Human Custom Array (RayBiotech, Norcross, GA, USA). These biomarkers were selected according to the results of a previous exploratory study (12) that analysed a wide sample of angiogenic and inflammatory biomarkers in patients with RA in remission: activin A, angiopoietin (ANG), angiopoietin-2 (ANG-2), angiopoietin-like protein-4 (ANGPTL4), basic fibroblast growth factor (bFGF), transforming growth factor β1 (TGF-b1), placental growth factor (PIGF), vascular endothelial growth factor (VEGF), vascular endothelial growth factor D (VEGF-D), epithelial cell-derived neutrophil-activating peptide-78 (ENA-78), stromal-cell derived factor-1 (SDF-1), CC-chemokine ligand 16 (CXCL16), tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-17F (IL-17F), interleukin-18 (IL-18), interleukin-20 (IL-20), interleukin-23 (IL-23), interleukin-33 (IL-33) and matrix metalloproteinases-2 (MMP-2). These were analysed according to the manufacturer's specifications. Each sample was diluted twofold and prepared in quadruplicate. An Axon scanner 4000B with GenePix software was used to collect fluorescence intensities. Detection limits for cytokines are displayed on the manufacturer's website (RayBiotech [http://www.raybiotech.com]). After sample dilution, the effect of rheumatoid factor on the final results was estimated to be around 1% (18). We analysed serum levels of proinflammatory and angiogenic biomarkers in all patients in remission and the two control cohorts.

Statistical analysis

Clinical variables and sonographic data were compared between patients with RA and polyarticular PsA in clinical remission. The analysis was performed using the Mann-Whitney test and 95% median confidence intervals (Hodges-Lehmann) or the chi-square test, Fisher's exact test and relative risk estimation with 95% confidence intervals (CI). Subsequently, we compared serum levels of biomarkers in a direct head-to-head comparison between the four groups using non-parametric tests. For all tests, *p*-values ≤0.05 were considered significant. The statistical analysis was made using SPSS v. 18 software.

Results

Clinical and demographic data

We included 77 patients [47 PsA and 30 RA in clinical remission, mean age (SD) 57.3 (11.5) years, disease duration 15.7 (8.3) years, DAS28-ESR 1.85 (0.41), time of remission 4.2 (3.3) years] of whom 42 were on etanercept, 25 adalimumab and 10 infliximab. Forty (51.9%) patients were on monotherapy and 38 (49.3%) were on tapered doses of TNF antagonists due to persistent clinical remission. Tapered doses indicate either a dose reduction (infliximab) or a longer time between the administration of the drug (adalimumab and etanercept) compared with that recommended by the manufacturer. Clinical and demographic characteristics of both active RA patients and healthy donors are shown in Table I.

Lower disease activity and higher percentage of patients on tapered doses of anti-TNF therapy in PsA than in RA patients in remission

Patients with PsA had significantly-lower disease activity as measured by DAS28-ESR than those with RA

(p=0.006) although not according to DAS28-CRP (0.319), even though more PsA patients were on tapered doses of TNF antagonists due to persistent clinical remission [30/47 PsA (63.8%) *vs*. 8/30 RA patients (26.6%) p=0.001], and more PsA patients were on anti-TNF monotherapy [34/47 (72.3%) PsA *vs*. 6/30 (20%) RA patients, p=0.0001] (Table I).

Lower serum levels of proinflammatory and angiogenic cytokines in PsA than in RA patients in remission

PsA patients had significantly lower levels of both proinflammatory (IL6, TNF-α, IL33, IL17F and IL23 – Fig. 1) and angiogenic cytokines (angiogenin, ANGPTL4, CXCL16, ENA78, PIGF and SDF1 – Fig. 2) compared with RA patients. Comparison of serum levels of these biomarkers with those of the 22 patients with active RA and 20 healthy controls showed no significant differences between PsA patients and healthy controls, except for higher serum levels of angiogenin in PsA patients (p=0.048). However, serum levels of these biomarkers in RA patients in remission were closer to those of active RA patients than to those of PsA patients (Figs. 1-2).

Lower prevalence of ultrasound-defined active synovitis in PsA than in RA patients in remission

Globally, 31 polyarticular (PsA+RA) patients (40.2%) had PD signal and 12 (15.5%) also had SH ≥2, thus meeting the criteria for UdAS. In concordance with the greater disease activity and higher proinflammatory/angiogenic cytokine serum levels, significantly more RA patients had PD signal (RA, n=20; 66.6% *vs*. 11 PsA; 23.4%, p=0.0001) and met the criteria for UdAS (RA, n=11; 36.6% *vs*. 1 PsA; 0.02%; p=0.0001).

In the whole group of patients in remission, patients fulfilling the criteria for UdAS had significantly higher serum levels of IL-20, IL-6, PIGF and SDF1 (Fig. 3), although no significant clinical differences between patients with or without UdAS were found. No significant differences in clinical features or serum levels of biomarkers were found when PD was used as the main sonographic outcome (data not shown).

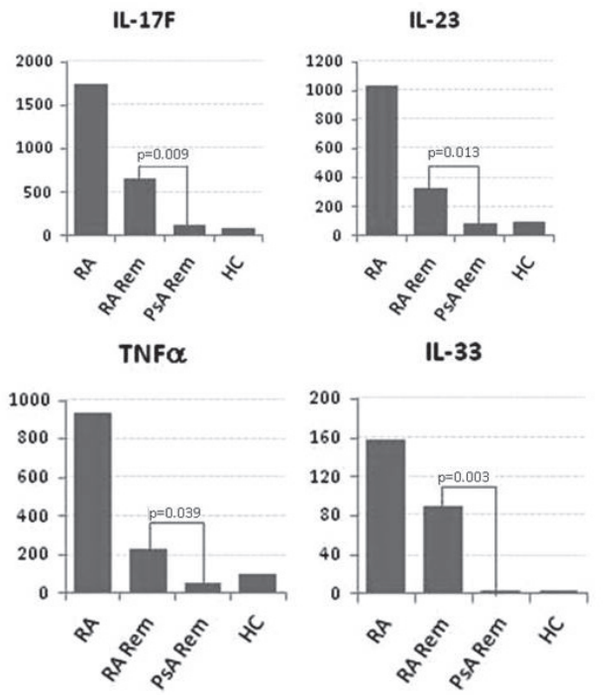

Fig. 1. Serum proinflammatory biomarkers differentially expressed in patients with active RA, RA in remission, PsA in remission and healthy controls.
Data are represented as medians. Serum levels of cytokines are shown in pg/ml.

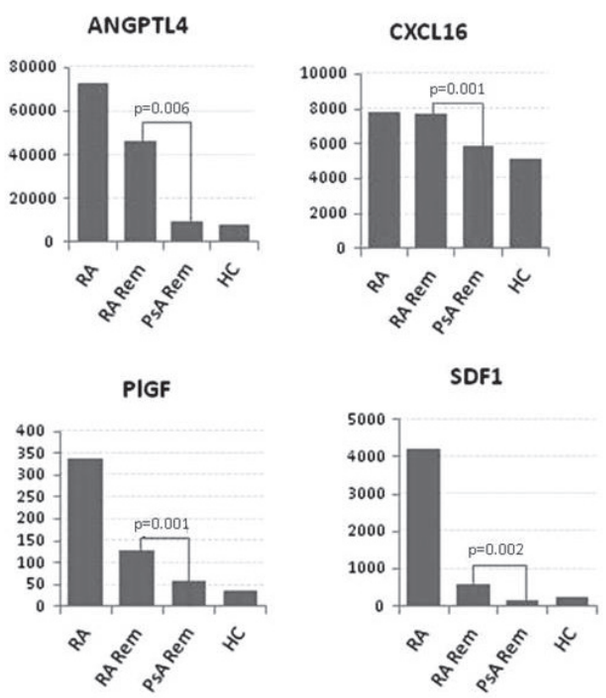

Fig. 2. Serum angiogenic biomarkers differentially expressed in patients with active RA, RA in remission, PsA in remission and healthy controls.
Data are represented as medians. Serum levels of cytokines are shown in pg/ml.

Discussion

Our results show that polyarticular PsA patients in remission as defined by DAS28-ESR had significantly less subclinical synovitis and lower serum levels of biomarkers of angiogenesis and inflammation than RA patients in remission. More PsA patients in remission were on tapered doses of anti-TNF and monotherapy.

To the best of our knowledge, no previous comparative studies have analysed the sonographic and biological characteristics of clinical remission in polyarticular PsA and RA patients.

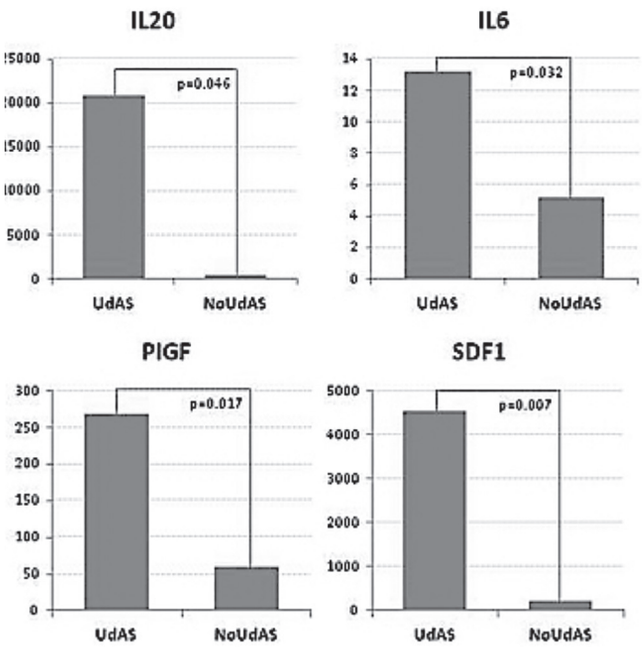

Fig. 3. Serum biomarkers differentially expressed in patients with and without ultrasound-defined active synovitis.
Data are represented as medians. Serum levels of cytokines are shown in pg/ml.

Recent data from a retrospective review show that, in clinical practice, the 10-year survival of anti-TNF drugs is longer in spondyloarthritis and PsA patients (30.5 months) than in RA patients (20.4 months) (5). Likewise, indirect data indicating a better response to anti-TNF therapy in PsA than in RA patients is provided by the lack of evidence of additional efficacy of methotrexate combined with anti-TNF therapy in PsA (19, 20).

Ultrasound subclinical synovitis is a frequent finding in RA patients in clinical remission (21-25) and we previously found that 66.6% had PD (12).

The differential expression of serum biomarkers reflecting immuno-inflammatory activity in PsA and RA patients in remission supports the concept of a distinct physiopathology in PsA and RA, and suggests that TNF dysregulation may be more relevant in the pathogenesis of PsA than in RA (26).

We also aimed to validate the concept of UdAS in patients with polyarthritis in remission. We previously reported that around 45% of patients with RA in clinical remission and ultrasound activity as defined by SH≥2+PD had significantly greater disease activity (DAS28-ESR) and higher serum levels of angiogenic biomarkers (12). Although the population analysed here is somewhat different, patients fulfilling UdAS criteria also had significantly higher serum levels of angiogenic factors such as SDF1 and PIGF, and proinflammatory cytokines (IL20 and IL6). However, no differences were found when only the PDUS signal was analysed. This suggests that UdAS is a more stringent definition of subclinical synovitis that better reflects the residual inflammatory burden in polyarthritis patients in remission.

Our study has several limitations. First, we used DAS28-ESR as the main evaluation tool in patients with PsA. Although remission has not yet been well defined in such a complex disease as PsA, several composite indices and cut-offs have been proposed (27), but require further validation. Although originally designed for RA, the DAS28-ESR has also been shown to be useful in polyarticular forms of PsA (10) without axial or entheseal involvement. Other studies support and validate the use of the DAS28 in measuring disease activity in patients with PsA on biological therapy (10, 28). Secondly, the sample size was limited by the inclusion criterion of clinical remission on anti-TNF therapy, especially in the RA group, because a significant proportion of RA patients in remission are currently treated with other biologicals (anti-IL6, anti-CD20, CTL4-IgG). Finally, no ultrasound assessment of the joints and entheses of the lower limbs was made at study inclusion. However, our sample included only patients with polyarticular PsA (RA-like), without entheseal involvement at diagnosis, and the findings of almost-normal serum levels of proinflammatory/angiogenic cytokines fit very well with the absence of subclinical inflammation.

In summary, pure polyarticular PsA patients in clinical remission on anti-TNF therapy had a significantly lower residual inflammatory burden than RA patients. More PsA patients were on tapered doses of anti-TNF-therapy and more were on monotherapy. These results are clinically relevant and point to greater achievement of remission in PsA patients than in RA patients, which could have practical implications such as more ultrasound monitoring in RA patients in remission. Patients in remission with UdAS have significantly higher serum levels of proinflammatory/angiogenic cytokines, reinforcing the idea that UdAS identifies true active synovitis. Studies to confirm these findings are ongoing.

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