A polyarticular onset and diabetes could be the main predictors of cardiovascular events in psoriatic arthritis

P. Tejón[1], I. Morante[2], I. Cabezas[2], C. Sarasqueta[3], P. Coto[4], R. Queiro[4]

[1]Rheumatology Section, Hospital General de Castellón, Castellón, Spain; [2]Rheumatology Section, Department of Internal Medicine, Hospital Universitario Central de Asturias (HUCA), Oviedo, Spain; [3]I.I.S. Biodonostia, H.U. Donostia/REDISSEC, San Sebastián, Spain; [4]Psoriasis Unit (Rheum-Derm Division), Hospital Universitario Central de Asturias (HUCA), Oviedo, Spain.

Abstract

Objective

We aimed to determine which disease features could be associated to the risk of cardiovascular (CV) events in a PsA cohort from a tertiary care institution.

Methods

We conducted an age- and sex-matched case-control study in which the cases were all PsA patients who developed cardiovascular (CV) events during the study period (2010–14). The control group was free of CV events during the same period. Univariate analysis was performed to examine unadjusted associations of potential risk factors. Significant variables in the univariate analysis were then introduced in a multivariate analysis with a backward stepwise approach.

Results

Of the 206 patients enrolled, 17 (8.3%) patients developed a total of 25 CV events (10 stroke, 9 acute coronary events and 6 ischaemic peripheral vascular events). In univariate analysis these patients showed more pustular psoriasis (OR 5.5, p=0.02), polyarticular onset (OR 3.2, p=0.03), polyarthritis during follow-up (OR 2.9, p=0.04), arthritis onset after 40 yr (OR 3.7, p=0.02), high lipid levels (OR 2.8, p=0.04), hypertension (OR 6.4, p=0.0008), diabetes (OR 12.1, p<0.0001) and lower educational level (OR 3.2, p=0.05). After controlling for age and other confounders, a polyarticular onset of PsA (OR 3.7, p=0.043) and diabetes (OR 8.1, p=0.001) remained as independently related to the risk of CV events.

Conclusion

Traditional CV risk factors as well as factors related to the inflammatory nature of the disease were the main predictors of CV complications in this PsA population.

Key words

psoriasis, psoriatic arthritis, cardiovascular risk, diabetes, polyarthritis

Patricia Tejón, MD
Isla Morante, MD
Iván Cabezas, MD
Cristina Sarasqueta, MD, PhD.
Pablo Coto, MD, PhD
Rubén Queiro, MD, PhD

Please address correspondence to::
Rubén Queiro,
Rheum-Derm Division,
Department of Internal Medicine,
Hospital Universitario Central
de Asturias (HUCA).
Avda. de Roma, s/n,
33011 Oviedo, Spain.
E-mail: rubenque7@yahoo.es

Received on July 23, 2015; accepted in revised form on November 17, 2015.

Competing interests: none declared.

Introduction

Psoriasis is a chronic inflammatory skin disease that affects 1%–3% of the general population, with the highest incidence and prevalence observed in white populations (1). A similar prevalence to western countries has been recently found in Japan (2). Psoriatic arthritis (PsA) is also a common feature of what is now called psoriatic disease (3).

One of the most important findings of the recent history of psoriatic disease was that these patients also had an increased prevalence of traditional cardiovascular risk factors (CVRF) including hypertension, diabetes, obesity, and dyslipidaemia, when compared to general population (4, 5). Moreover, subclinical atherosclerosis, diagnosed on the basis of increased intima-media thickness in the common carotid artery or the presence of carotid plaque, has also been reported in association with psoriatic disease regardless of the presence of classic CVRF (6). As a consequence, patients with psoriatic disease may also have an increased risk of major adverse cardiovascular events (MACE) beyond that attributable to measured CVRF (7-11).

As PsA may be viewed as a "disease within a disease", it may be difficult to ascertain which CVRF may be attributable to psoriasis and which of them to PsA. For example, it has been estimated that the presence of joint disease doubles the risk of hypertension when compared to psoriasis alone (12). A recent meta-analysis regarding the risk of diabetes in psoriatic disease showed that patients with PsA had higher diabetes risk as compared to psoriasis alone (13). Therefore, we also should expect to see higher prevalence of MACE among more severely affected subjects within the psoriatic spectrum. In that sense, in a recent meta-analysis patients with psoriasis (OR 1.25) as well as those with PsA (OR 1.57) had an increased risk of MI compared with the general population. The risk of MI was even more pronounced for patients having severe psoriasis, PsA and for patients with psoriasis of early onset. This risk remained significantly elevated after controlling for major CVRF (14).

As mentioned above, several studies clearly show that the risk of MI is elevated in both psoriasis and PsA. However, results about stroke risk show more disparity (14, 15). Ischaemic/haemorrhagic cerebrovascular disease or stroke is a major cause of morbidity and mortality. The major common risk factors for stroke include diabetes, hypertension, and smoking, which also predispose to cardiovascular (CV) risk in general. Less common but more specific risk factors for stroke include transient ischaemic attacks and atrial fibrillation. Most strokes (80%) are ischaemic in nature, with the minority of strokes being haemorrhagic. Ischaemic and haemorrhagic strokes share similar risk factors and can have similar clinical presentations (16). In the meta-analysis mentioned before, assessing the risk of stroke gave inconclusive results: analysis of cross-sectional studies suggested that psoriasis patients had a slightly higher risk of stroke with an OR of 1.14, whereas the meta-analysis of cohort studies failed to show an association (14). Therefore, we need studies aimed to discover disease traits that may be used as predictors of CV complications in order to establish the best preventive strategy that in turn could diminish this CV burden. In this report we aimed to determine which PsA features could be associated to CV complications.

Patients and methods

This age matched case-control study included 206 consecutive patients who fulfilled the CASPAR classification criteria for PsA (17). These patients were attended according to a standard protocol in a PsA monographic clinic within the rheumatology division of a tertiary care institution from January 2010 to December 2014. Patients of this cohort were regularly evaluated every 3 to 6 months depending on disease activity or severity. All demographic, clinical, laboratory, therapeutic and radiographic variables were collected in a standardised manner as depicted below. Patients were informed about the objectives of the study and consent informed sheets were signed by all participants. This study was conducted following the rules of good clinical practice (Hel-

sinki Declaration). An institutional ethics committee approved the final version of this study.

Study population and study variables

The cohort was composed by 112 men and 94 women with a mean age of 53±13 years. The description of joint patterns was made on the basis of the dominant pattern observed in the last 5 years previous to study entry. Patients with 4 or less swollen joints were labelled as oligoarthritis; those who presented 5 or more were tagged under the polyarthritis category. Patients with axial disease were classified according to the ASAS criteria for axial spondyloarthritis (18).

Family history of psoriasis and PsA was collected. Educational levels was assessed and classified under three categories according to the achieved degree: primary, secondary (high-school), and university studies. Data regarding skin disease included the main type of psoriasis, location of lesions, nail disease and percentage of patients with involvement of three or more body areas. Psoriasis was confirmed by a dermatologist.

The onset patterns of arthritis were based on the main articular phenotype during the first 6 months of disease evolution.

Pelvic, lumbar and cervical lateral x-rays were included in the radiographic study to assess spinal involvement. X-rays of affected areas during follow-up were also obtained. Laboratory data included the following routine tests: blood and urine biochemistry, haemogram, ESR, HLA-B*27, HLA-C*06, rheumatoid factor, antinuclear antibodies and CRP.

Glucocorticoid, NSAID, conventional as well as biologic DMARD use was collected.

Definition of cardiovascular risk factors

• Diabetes mellitus (DM): defined by the analytical finding during monitoring of glucose elevation of more than 126 mg/dl on two fasting determinations, chronic treatment with antidiabetic or insulin, or diagnosis by medical specialist.

• High blood pressure (hypertension): defined as finding at least two determinations on different days of blood pressure greater than 140/90 mmHg during follow-up, chronic use of antihypertensive treatment or diagnosis by medical specialist.

• Dyslipidaemia: defined as the ongoing finding of cholesterol figures above 240 mg/dl or triglycerides figures above 200 mg/dl during follow-up, chronic treatment with lipid-lowering drugs, or diagnosis by medical specialist.

• Obesity: defined as the presence of a body mass index (BMI) greater than 30 kg/m^2, whereas overweight involves a BMI between 25 and 29.9 kg/m^2.

• Smoking habit: we consider as active smokers, all those daily smoker patients at the time of the study (irrespective of the number of cigarettes); on the other hand, those patients with past smoking habit (at least five years), but not being active smokers at the time of the study, are regarded as former smokers.

Definition of cardiovascular outcomes

• Ischaemic heart disease: defined as at least one cardiac event such as acute MI, stable or unstable angina, diagnosed by a medical specialist.

• Cerebrovascular disease: any transient or permanent event as a result of a disorder of cerebral circulation either ischaemic or haemorrhagic diagnosed by a medical specialist.

• Peripheral vascular disease: defined as the presence of at least one episode of peripheral arterial ischaemic disease diagnosed by a medical specialist.

Statistical analysis

Descriptive statistics with mean and standard deviation for quantitative variables and percentages for qualitative variables were included. Differences between qualitative variables were analysed by using Chi-squared and Fisher's exact tests. Differences between quantitative variables were analysed by using Student's t-test. In order to determine the strength of the association of each variable depending on the presence or absence of CV events, we conducted an age and sex paired case-control study in which cases were all PsA patients who developed a CV event (case group, n: 17) during the study period 2010–2014. The control group included all PsA patients free of CV events during the same period. For the purposes of this study, 3 controls were selected per case and matched by sex and age group plus or minus three years (control group, n: 51). Odds ratio (OR) values with its 95% CI were calculated by conditional logistic regression analysis. Initially, a univariate analysis was performed to examine unadjusted associations of potential risk factors. Significant variables in the univariate analysis were then introduced in a multivariate analysis with a backward stepwise approach. The statistical analysis software package used was SPSS v.19.0

Results

We evaluated 206 patients, 112 (54.4%) males and 94 (45.6%) females. The mean age was 53±13 years. The mean age at psoriasis onset was 30.5±17.1 years and the mean age of onset of arthritis was 43.3±14.2 years. The mean lag time between the onset of psoriasis and onset of arthritis was 14.6±12.6 years.

Educational level was distributed as follow: 51.5% of patients had primary school education, 26.7% had secondary education and 21.8% had a university degree.

Demographic, clinical and cardiovascular characteristics of patients are shown in Table I.

Of the study population, 17 patients experienced 25 CV events (10 ictus, 9 coronary events, and 6 ischaemic peripheral vascular events). In the case control univariate analysis, patients with CV events showed more pustular psoriasis (OR 5.5, 95%CI: 1.3–23.8, p=0.02), polyarticular onset (OR 3.2, 95%CI: 1.1–9.1, p=0.03), polyarthritis during follow up (OR 2.9, 95%CI: 1.1–8.0, p=0.04), arthritis onset after 40 yr (OR 3.7, 95%CI: 1.2–11.0, p=0.02), high lipid levels (OR 2.8, 95%CI: 1.0–7.6, p=0.04), hypertension (OR 6.4, 95%CI: 2.2–19.2, p=0.0008), diabetes (OR 12.1, 95%CI: 4.1–35.7, p<0.0001) and lower educational level (OR 3.2 95%CI: 1.0–10.4, p=0.05). After adjusting for sex, age and other confounders, the best multivariate model showed that a polyarticular debut of PsA (OR

Table I. Demographic, clinical and cardiovascular risk profile of the study population.

Variables	Patients. n=206
Mean age, years (SD)	53 ± 13
Mean age of onset of psoriasis	30.5 ± 17.1
Mean age of onset of arthritis	43.3 ± 14.2
Mean latency time psoriasis-arthritis	14.6 ± 12.6
Sex, number (%)	
Male	112 (54.4%)
Female	94 (45.6%)
Educational level (%)	
Primary school	51.5%
Secondary education	26.7%
University degree	21.8%
Psoriasis onset, number (mean onset age ± SD)	
<40 years	139 (20.7 ± 9.7)
>40 years	67 (53.5 ± 7.6)
PsA onset, number (mean onset age ± SD)	
<40 years	83 (29 ± 7.2)
>40 years	123 (52.8 ± 8.6)
Plaque psoriasis	176 (85.4%)
Nail disease	100 (48.5%)
≥ 3 areas of psoriasis	97 (47.1%)
Family history of psoriasis	97 (47.1%)
Family history of PsA	32 (15.5%)
Oligoarthritis	44 (21.4%)
Polyarthritis	72 (35%)
Spondylitis	19 (9.2%)
Mixed pattern	67 (32.5%)
Dactylitis	58 (28.2%)
DIP disease	48 (23.3%)
Mutilating arthritis	3 (1.4%)
Erosive disease	30 (14.6%)
HLA-B*27	41 (20%)
HLA-C*06	78 (38%)
Diabetes Mellitus	25 (12.1%)
Hypertension	63 (30.6%)
Dyslipidaemia	63 (30.6%)
Obesity (BMI ≥30)	49 (23.8%)
Overweight	38 (18.4%)
Ischaemic heart disease	9 (4.4%)
Cerebrovascular disease	10 (5%)
Peripheral vascular disease	6 (3%)
Smokers	52 (25.2%)
Ex-smokers	53 (25.7%)
NSAID use	86 (41.7%)
Glucocorticoid use	32 (15.5%)
Methotrexate use	133 (64.6%)
Biologic use	70 (34%)

DIP: distal interphalangeal joint; NSAID: non-steroidal anti-inflammatory drugs; BMI: Body mass index.

3.7, 95%CI: 1.04–13.15, p=0.043) and diabetes (OR 8.1, 95%CI: 2.24–29.3, p=0.001) were independently related to the risk of CV events. When data were compared between sexes, men showed more frequently nail disease (OR 2.1, 95%CI: 1.2–3.7, p=0.009) and higher lipid levels (OR 1.9, 95%CI: 1.1–3.4, p=0.045), but there were no sex differences regarding CV outcomes during follow up.

Table II. summarises the unadjusted comparisons between both populations.

Discussion

Spondyloarthritis patients are at a greater CV risk owing to the higher prevalence of smoking, other conventional CVRF and a higher atherogenic index (19, 20). In this study we analysed in detail those disease factors that may help in predicting CV disease development in PsA. Given that the prevalence of CV disease in psoriatic disease is high, the evaluation of CV risk should include not only those factors inherent to this risk in general, but also those additional traits related to the inflammatory nature of the disease that may suppose an additional risk beyond that attributable to classic CVRF. As in previous studies, diabetes, high lipid levels and hypertension, classic factors linked to CV risk, were also found as risk factors for CV disease in this cohort. Patients with the lowest level of education also showed a higher risk for CV complications. On the other hand, patients who developed MACE were those more severely affected by the disease. Indeed, they had one of the most severe phenotype of psoriasis (pustular variants) as well as the most severe form of arthritis (polyarthritis) when compared to non-CV cases. These findings represent the known association that exists between the inflammatory burden of psoriatic disease and accelerated atherosclerosis (19, 20). Most studies done so far, indicate that both Th1 and Th17 cytokines have a proinflammatory effect that favours the development of inflammation in synovial tissue, skin, and vessel walls (20, 21). The activation of the Th1 response by IL-12 is well known in both psoriasis and atherosclerosis. In atherosclerosis, this mechanism plays an essential role not only in plaque formation but also in maintaining inflammation and developing the unstable phenotype that makes the plaques prone to rupture (20-23). Th17 lymphocytes produce IL-17, IL-6, IL-21, IL-22, and TNF, and have a profound synergistic effect on atherogenesis. Although Th1 cells predominate over Th17 cells in the proportion of 10 to 1 in atherosclerotic plaques, the Th17 cells act synergistically (20-23). Most of the experimental evidence and biomarker studies indicate a link between IL-17 and instability in atherosclerotic plaques, a finding that may partially explain the increased risk of CV events in patients with psoriatic disease (20-23). We observed here for example that two of the most infrequent, inflammatory and severe phenotypes of skin psoriasis (pustular and erythrodermic) were clearly prevalent among those patients who developed CV disease. These findings are in line with recent developments that confer a dominant role to the IL-23/IL-17 axis

Table II. Unadjusted comparisons between patients with and without cardiovascular disease.

Variables	CV disease, n=17 (%)	Non CV disease, n=189 (%)	*p*-values
Age (yr ± SD)	66.7 ± 11.2	52.3 ± 12.7	0.001
Age at psoriasis onset (yr ± SD)	37 ± 20.6	30 ± 16.9	NS
Age at PsA onset (yr ± SD)	52 ± 14.6	43 ± 114.1	0.06
Psor-arthritis latency (yr ± SD)	21 ± 20.2	14 ± 12	NS
Men	10 (58.8)	102 (54)	NS
Women	7 (41.2)	87 (46)	
Educational level:			0.01
- Primary	13 (76.5)	92 (48.7)	
- Secondary	2 (11.8)	53 (28)	
- University	2 (11.8)	44 (23)	
Psor. onset > 40 y	5 (29.4)	62 (32.8)	NS
Psor. onset < 40 y	12 (70.6)	127 (67.2)	
PsA onset > 40 y	12 (70.6)	111 (58.7)	NS
PsA onset < 40 y	5 (29.4)	78 (41.3)	
Plaque psoriasis	14 (82.4)	160 (84.7)	NS
Pustular psoriasis	5 (29.4)	6 (3.2)	0.0001
Guttate psoriasis	0 (0)	11 (5.8)	NS
Erythrodermic psor.	2 (11.7)	4 (2)	0.07
Inverse psoriasis	0 (0)	1 (0.5)	NS
Nail disease	8 (47)	92 (48.7)	NS
≥3 affected areas	7 (41.2)	90 (47,6)	NS
Family history (psor)	7 (41.2)	90 (47.6)	NS
Family history (PsA)	3 (17.6)	29 (15.3)	NS
Form of PsA onset:			
- Oligoarticular	2 (11.7)	89 (47.1)	0.040
- Polyarticular	12 (70.6)	68 (36)	0.013
- Axial	3 (17.6)	32 (17)	NS
PsA evolution:			
- Oligoarticular	2 (11.7)	42 (22.2)	NS
- Polyarticular	11 (64.7)	61 (32.3)	0.043
- Axial	2 (11.7)	17 (9)	NS
- Mixed	4 (23.5)	63 (33.3)	NS
Dactylitis	0 (0)	58 (30.7)	0.05
DIP disease	4 (23.5)	44 (23.3)	NS
Erosive disease	0 (0)	30 (15.9)	NS
HLA-B27	3 (17.6)	38 (20)	NS
HLA-Cw6	5 (35.3)	73 (38.6)	NS
Obesity (BMI ≥ 30)	4 (23.5)	45 (23.8)	NS
Overweight	3 (17.6)	35 (18.5)	NS
Current smoker	2 (11.7)	50 (26.5)	NS
Past smoker	5 (29.4)	48 (25.4)	NS
Diabetes	10 (58.8)	15 (7.9)	<0.0001
Hypertension	12 (70.6)	51 (27)	0.002
Dyslipidaemia	9 (52.9)	54 (28.6)	0.08
NSAID use	6 (35.3)	80 (42.3)	NS
GC use	4 (23.5)	28 (14.8)	NS
MTX use	10 (58.8)	123 (65.1)	NS
Biologic use	6 (35.3)	64 (33.9)	NS

DIP: distal interphalangeal joint; NSAID: non-steroidal anti-inflammatory drugs; BMI: Body mass index; GC: glucocorticoid; MTX: methotrexate.

in CV risk as well as in the pathogenesis of pustular psoriasis (23, 24).

The CV risk assessment should be routinely done by any clinician treating patients with psoriatic disease. This includes not only evaluation and treatment of classic CVRF, but also assessment of the inflammatory burden of the disease, as well as other markers of atherogenesis (CRP, intima-media thickness, carotid plaque area). However, the most adequate form to do this is not clearly established at present (25, 26). In addition, classic CV risk scores underestimate the risk in these patients (27). Therefore, studies aimed to establish the best way to assess CV burden of psoriatic disease are urgently needed.

Our report has some limitations as the small number of patients included, the fact of being a hospital-based series or the absence in our final analysis of some risk factors associated with the general risk of CV disease (*i.e.* acute phase reactants). As regards to this latter point, elevated levels of several inflammatory mediators have been found in subjects with atherosclerosis. Increased basal levels of cytokines, cell adhesion molecules, selectins, acute-phase reactants such as high sensitive C-reactive protein (hsCRP), fibrinogen, and serum amyloid A are related to an increased risk of cardiovascular events. Therefore, inflammation plays a key role in atherogenesis, among other factors, by providing matrix-degrading metalloproteinases and also by inducing death of matrix-synthesising smooth muscle cells in vessel walls, factors that may ultimately contribute to plaque instability. Systemic markers of inflammation are thus the most logical forms of potential biomarkers which may predict the presence of vulnerable or high-risk plaques. In that sense, several studies have suggested the potential prognostic value of a variety of systemic markers, but regrettably, their overall clinical predictive value is modestly incremental at best, especially for individual subjects compared to groups of patients (28).

Our study highlights the associations between very severe forms of psoriatic disease with a higher risk of CV disease emphasising again the close relationship between inflammation and atherogenesis. There is now some evidence to suggest that antiTNF alpha therapies may have a beneficial effect on metabolic syndrome and diminish CV risk in arthritic populations (29, 30). Therefore a careful attention should be paid to PsA patients with these phenotypes in order to establish the most adequate therapy that would cover all disease manifestations.

References

1. NESTLE FO, KAPLAN DH, BARKER J: Psoriasis. *N Engl J Med* 2009; 361: 496-509.
2. OHARA Y, KISHIMOTO M, TAKIZAWA N *et al*.: Prevalence and clinical characteristics of psoriatic arthritis in Japan. *J Rheumatol* 2015 Jun 15. pii: jrheum.141598
3. QUEIRO R, TEJÓN P, ALONSO S, COTO P: Age at disease onset: a key factor for understanding psoriatic disease. *Rheumatology* (Oxford) 2014; 53: 1178-85.

4. GONZÁLEZ-GAY MA, GONZÁLEZ-VELA C, GONZÁLEZ-JUANATEY C: Psoriasis: a Skin Disease Associated With Increased Cardiovascular Risk. *Actas Dermosifiliogr* 2012; 103: 595-98.
5. HAN C, ROBINSON JR DW, HACKETT MV, PARAMORE LC, FRAEMAN KH, BALA MV: Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. *J Rheumatol* 2006; 33: 2167-72.
6. GONZÁLEZ-JUANATEY C, LLORCA J, AMIGO-DÍAZ E, DIERSSEN T, MARTÍN J, GONZÁLEZ-GAY MA: High prevalence of subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. *Arthritis Rheum* 2007; 57: 1074-80.
7. NEIMANN AL, SHIN DB, WANG X, MARGOLIS DJ, TROXEL AB, GELFAND JM: Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol* 2006; 55: 829-35.
8. GELFAND JM, NEIMANN AL, SHIN DB, WANG X, MARGOLIS DJ, TROXEL AB: Risk of myocardial infarction in patients with psoriasis. *JAMA* 2006; 296: 1735-41.
9. KIMBALL AB, GUERIN A, LATREMOUILLE-VIAU D *et al*.: Coronary heart disease and stroke risk in patients with psoriasis: retrospective analysis. *Am J Med* 2010; 123: 350-7.
10. OGDIE A, YU Y, HAYNES K *et al*.: Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis* 2015; 74: 326-32.
11. GLADMAN DD, ANG M, SU L, TOM BD, SCHENTAG CT, FAREWELL VT: Cardiovascular morbidity in psoriatic arthritis. *Ann Rheum Dis* 2009; 68: 1131-5.
12. HUSTED JA, THAVANESWARAN A, CHANDRAN V *et al*.: Cardiovascular and other comorbidities in patients with psoriatic arthritis: a comparison with patients with psoriasis. *Arthritis Care Res* 2011; 63: 1729-35.
13. COTO-SEGURA P, EIRIS-SALVADO N, GONZÁLEZ-LARA L *et al*.: Psoriasis, psoriatic arthritis and type 2 diabetes mellitus: a systematic review and meta-analysis. *Br J Dermatol* 2013; 169: 783-93.
14. HORREAU C, POUPLARD C, BRENAUT E *et al*.: Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. *JEADV* 2013; 27 (Suppl. 3):12–29.
15. GELFAND JM, DOMMASCH ED, SHIN DB *et al*.: The risk of stroke in patients with psoriasis. *J Invest Dermatol* 2009; 129: 2411-8.
16. DONNAN GA, FISHER M, MACLEOD M, DAVIS SM: Stroke. *Lancet* 2008; 371: 1612-23.
17. TAYLOR W, GLADMAN D, HELLIWELL P, MARCHESONI A, MEASE P, MIELANTS H; CASPAR STUDY GROUP: Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006; 54: 2665-73.
18. RUDWALEIT M, VAN DER HEIJDE D, LANDEWÉ R *et al*.: The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; 68: 777-83.
19. PAPAGORAS C, MARKATSELI TE, SAOUGOU I *et al*.: Cardiovascular risk profile in patients with spondyloarthritis. *Joint Bone Spine* 2014; 81: 57-63.
20. PAPAGORAS C, VOULGARI PV, DROSOS AA: Atherosclerosis and cardiovascular disease in the spondyloarthritides, particularly ankylosing spondylitis and psoriatic arthritis. *Clin Exp Rheumatol* 2013; 31: 612-20.
21. BOEHNCKE WH, BOEHNCKE S: Cardiovascular mortality in psoriasis and psoriatic arthritis: epidemiology, pathomechanisms, therapeutic implications, and perspectives. *Curr Rheumatol Rep* 2012; 14: 343-8.
22. ARMSTRONG AW, VOYLES SV, ARMSTRONG EJ, FULLER EN, RUTLEDGE JC: A tale of two plaques: convergent mechanisms of T-cell-mediated inflammation in psoriasis and atherosclerosis. *Exp Dermatol* 2011; 20: 544-49.
23. CHEN S, CROTHER TR, ARDITI M: Emerging role of IL-17 in atherosclerosis. *J Innate Immun* 2010; 2: 325-33.
24. YILMAZ SB, CICEK N, COSKUN M, YEGIN O, ALPSOY E: Serum and tissue levels of IL-17 in different clinical subtypes of psoriasis. *Arch Dermatol Res* 2012; 304: 465-9.
25. HELLIWELL P, COATES L, CHANDRAN V *et al*.: Qualifying unmet needs and improving standards of care in psoriatic arthritis. *Arthritis Care Res* (Hoboken) 2014; 66: 1759-66.
26. CAÑETE JD, DAUDÉN E, QUEIRO R *et al*.: Recommendations for the coordinated management of psoriatic arthritis by rheumatologists and dermatologists: a Delphi study. A*ctas Dermosifiliogr* 2014; 105: 216-32.
27. EDER L, CHANDRAN V, GLADMAN DD: The Framingham Risk Score underestimates the extent of subclinical atherosclerosis in patients with psoriatic disease. *Ann Rheum Dis* 2014; 73: 1990-6.
28. SHAH PK: Biomarkers of plaque instability. *Curr Cardiol Rep* 2014; 16: 547.
29. KIORTSIS DN, MAVRIDIS AK, VASAKOS S, NIKAS SN, DROSOS AA: Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. *Ann Rheum Dis* 2005; 64: 765-6.
30. ROUBILLE C, RICHER V, STARNINO T *et al*.: The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015; 74: 480-9.