

Cardiovascular involvement in psoriatic arthritis*

Coinvolgimento cardiovascolare nell'artrite psoriasica

F. Atzeni¹, M. Turiel², L. Boccassini¹, S. Sitia², L. Tomasoni², M. Battellino¹, A. Marchesoni³, V. De Gennaro Colonna⁴, P. Sarzi-Puttini¹

¹Rheumatology Unit, L. Sacco University Hospital, Milan, Italy;

²Cardiology Unit, Department of Health Technologies, IRCCS Galeazzi Orthopedic Institute, Università di Milano, Milan, Italy;

³U.O.C. Day Hospital of Rheumatology, Pini Orthopedic Institute, Milan, Italy;

⁴Department of Pharmacology, Chemotherapy and Medical Toxicology, University of Milan, Italy

RIASSUNTO

La psoriasi è una malattia autoimmune infiammatoria cronica della cute geneticamente determinata che coinvolge il 2-3% della popolazione Caucasica. Diversi pazienti sviluppano una forma di artrite infiammatoria nota con il nome di artrite psoriasica (APs), la cui prevalenza non è ben definita. I pazienti affetti da APs hanno un tasso di mortalità superiore rispetto alla popolazione generale, e il rischio di mortalità correla con la severità della malattia al momento dell'esordio. La disfunzione endoteliale e l'aterosclerosi precoce sono state riportate in pazienti affetti da APs che non presentano fattori di rischio per eventi cardiovascolari (CV), tanto che gli Esperti ritengono che gli eventi CV rappresentino una causa di mortalità in questi pazienti così come descritto nei pazienti affetti da artrite reumatoide (AR). Diversi meccanismi correlati alla malattia potrebbero essere coinvolti nello sviluppo del danno vascolare precoce sia nell'APs che nell'AR, quali aumentata sintesi di mediatori dell'infiammazione (quali citochine, chemochine e molecole di adesione), anticorpi contro i componenti delle cellule endoteliali, alterazioni dei subsets dei T linfociti, polimorfismi genetici, iperomocisteinemia, stress ossidativo, riparazione delle alterazioni vascolari, e fattori iatrogeni. In un recente studio che ha coinvolto 22 pazienti affetti da APs senza alcun segno o sintomo di malattia CV, è stato osservato che la concentrazione della dimetil-arginina asimmetrica (ADMA) è significativamente aumentata nei pazienti affetti da APs rispetto ai controlli e che la riserva di flusso coronarica (RFC) è significativamente ridotta. Inoltre, nei pazienti con APs esiste una significativa correlazione tra la RFC e la concentrazione di ADMA nel plasma. La significativa correlazione tra la RFC ridotta e il livello di ADMA aumentato suggerisce che, come nei pazienti affetti da AR all'esordio, i pazienti affetti da APs soffrono di disfunzione endoteliale e di alterazione del microcircolo coronarico. In conclusione, l'APs in fase attiva rappresenta un fattore di rischio per eventi CV, ed è consigliabile che i pazienti affetti da APs siano sottoposti a screening per il coinvolgimento CV subclinico e per i suoi fattori di rischio.

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■ INTRODUCTION

Psoriatic arthritis (PsA) is usually considered a benign disease, but this idea has been challenged by some recent data. Sheeb et al. (1) found there was no significant difference in survival between patients with PsA and that observed in the general population. However, it has recently been confirmed that PsA is a chronic inflammatory arthritis and that, like rheumatoid ar-

thritis (RA), it is associated with increased cardiovascular mortality (2-4). It has been reported that patients with severe psoriasis requiring hospitalization have a 50% increased risk of cardiovascular (CV) mortality (5), which seems to be associated with markers of disease activity, such as the prior use of medications, a high erythrocyte sedimentation rate (ESR) at presentation, and evidence of radiological alterations (3). Traditional CV risk factors are more com-

Indirizzo per la corrispondenza:
Piercarlo Sarzi-Puttini, MD
Consultant and Director
Rheumatology Unit
L. Sacco University Hospital of Milan
20175 Milano, Italy
E-mail: sarzi@iscali.it
atzenifabiola@hotmail.com

mon in patients with PsA than in controls. A study from the integrated outcomes database, matched 3,066 PsA patients with other subjects in a ratio of 1 to 4 on the basis of age, gender, location and time in the database, and found that the prevalence ratios of peripheral cardiovascular disease (CVD) (1, 6), cardiovascular heart failure (CHF) (1, 5), atherosclerosis (1, 4), ischemic heart disease (1, 3), cerebrovascular disease (1, 3) and hypertension (1, 3) were all higher in the patients with PsA. They also found a higher prevalence of risk factors for coronary artery disease, such as hypertension (1, 3), diabetes (1, 5) and hyperlipidemia (1, 2) than in controls (6). Kimhi et al. (7) found that PsA patients have thicker common carotid arteries than healthy controls. This correlates with the duration of skin and joint disease, spine involvement and fibrinogen levels, as well as with conventional risk factors for atherosclerosis, such as age, body mass index (BMI), blood pressure, and serum glucose levels.

Increased incidences of diabetes mellitus and obesity have been reported in psoriatic patients (8). PsA and psoriasis patients have an altered atherogenic lipid profile (9, 10) mainly consisting of increased LDL sub-fractions and decreased HDL levels. Gonzalez-Gay et al. (11) found that there is a correlation between serum uric acid concentrations and subclinical atherosclerosis in PsA patients without any clinically evident CVD.

Gonzalez-Juanatey et al. (12, 13) found that patients with PsA without CV risk factors or clinically evident CVD show endothelial dysfunction and a high prevalence of macrovascular disease in the form of increased carotid artery intima media thickness (IMT) in comparison with ethnically matched controls.

Metabolic syndrome (MS) is made up of a group of traditional risk factors that includes abdominal obesity, atherogenic dyslipidemia, hypertension, and insulin resistance (14). The presence of MS is a strong predictor for type 2 diabetes mellitus, stroke, and CV, although controversy remains over whether metabolic syndrome is a distinct entity and whether the predic-

tive value of the metabolic syndrome for CV risk is higher than that expected from individual risk factors alone (15).

Recently, a cross-sectional study (16) indicated that MS occurs more frequently in patients with PsA than in the general population. Among patients with RA, AS (ankylosing spondylitis), and PsA, PsA patients show the highest risk for the presence of atherosclerotic risk factors, in particular of obesity, impaired glucose tolerance, and hypertriglyceridemia, and hence of metabolic syndrome. Moreover, the use of anti-TNF α treatment was associated with a trend towards a lower prevalence of metabolic syndrome supporting the idea that persistent inflammation is an aggravating factor for atherosclerotic risk (16).

In conclusion, all of these findings demonstrate the potential association between PsA and atherosclerotic disease.

■ CYTOKINES AND PSORIATIC ARTHRITIS

Various disease-related mechanisms may be involved in the development of premature vascular damage in patients with PsA or RA, including an increased synthesis of pro-inflammatory mediators (such as cytokines, chemokines and adhesion molecules), autoantibodies against endothelial cell components, perturbations in T-cell subsets, genetic polymorphisms, hyperhomocysteinemia, oxidative stress, abnormal vascular repair, and iatrogenic factors (17-21).

Pro-inflammatory cytokines are important mediators of systemic and local inflammation, and the abundant expression of interleukin-1 (IL-1) and tumor necrosis factor- α (TNF α) has been found in psoriatic skin lesions and in the synovial tissue of patients with RA or PsA (22). The synovial infiltrate in both groups of patients is comparable in terms of the number of fibroblast-like synoviocytes and macrophages, but the number of T cells is considerably lower in the synovium of patients with PsA, and the number of their plasma cells also tends to be lower. TNF α , IL-1 β , IL-6 and IL-18 expression is high in both cases (23, 24).

TNF is an inflammatory cytokine released by activated monocytes, macrophages and T lymphocytes that promotes the inflammatory responses involved in the pathogenesis of both RA and PsA (25). It also promotes dyslipidemia and insulin resistance, both of which are traditional risk factors for atherosclerosis; it up-regulates adhesion molecules, leading to the formation of fatty streaks and the start of atherosclerosis; and it is involved in inflammation leading to plaque rupture (26-28). It may also promote thrombophilia, thus encouraging thrombotic events.

In fact, Ingegnoli et al. (29, 30) showed increased levels of prothrombin fragment 1+2 (F1+2) and D-dimer, plasminogen activator inhibitor (PAI-1) antigen, PAI-1 activity and tissue-type plasminogen activator (t-PA) antigen in patients with RA compared to controls. Moreover, the same authors reported a reduction in fibrinolysis inhibition and coagulation biomarkers in RA patients after infliximab treatment, supporting the hypothesis that anti-TNF agents reduce the whole thrombotic risk in these patients not only due to cytokine inhibition but also due to its effects on coagulation (29, 30).

IL-6 is a pro-inflammatory cytokine that stimulates hepatocytes to synthesize acute phase response proteins, such as C-reactive protein (CRP) and fibrinogen (30). It may also contribute to atherosclerosis and arterial thrombosis by enhancing endothelial cell adhesiveness, activating the production of tissue factor, fibrinogen and factor VIII, by increasing platelet production and aggregation, and decreasing endogenous anticoagulant levels (31).

■ BIOLOGICAL THERAPY: PSORIATIC ARTHRITIS AND CV INVOLVEMENT

The introduction of the anti-TNF α agents infliximab, etanercept and adalimumab has dramatically improved the outcome of severe RA and also reduced the burden of CVD (32). There is compelling evidence that TNF α antagonists improve both ax-

ial and peripheral psoriatic arthropathies (33), and significantly inhibit radiological progression in a sustained manner. They also seem to reduce disease-related mortality (20).

Angel et al. (34) showed that anti-TNF agents reduce inflammatory activity and improve aortic stiffness in patients with inflammatory arthritis, thus supporting the hypothesis of a favorable anti-inflammatory effect on CV risk in PsA patients.

A double-blind, placebo-controlled study involving 127 patients with PsA showed that anti-TNF agents induce a significant reduction in concentrations of CRP, lipoprotein(a), and homocysteine, and an increase in the serum sex hormone-binding globulin, apolipoprotein (Apo) AI, Apo B, and triglycerides; however, the study did not confirm the cardioprotective effect of anti-TNF agents in this cohort of patients (35).

Tocilizumab is a recombinant humanized anti-IL6 receptor mAb that prevents interactions between IL-6 and the membrane-expressed receptor or its soluble counterpart, thus inhibiting IL-6 signal transduction (32). Its clinical efficacy has been assessed in adult patients with active moderate-to-severe RA, including those with an inadequate response to TNF antagonists, and the current data suggest that its tolerability profile is acceptable, infections being the most frequently reported adverse events. Although RA and PsA are clinically separate diseases of a different etiology, the similarities in the synovial infiltrate and increased pro-inflammatory cytokine production in PsA support the view that, in addition to TNF α blockade, targeted treatments against other pro-inflammatory cytokines such as IL-6 might be effective in PsA and co-morbidities such as CVD (36).

■ PLASMA ASYMMETRIC DIMETHYLARGININE (ADMA) CONCENTRATIONS AND CORONARY FLOW RESERVE

Plasma asymmetric dimethylarginine (ADMA), a major endogenous inhibitor

of nitric oxide synthase, is a newly discovered risk factor for endothelial dysfunction associated with enhanced atherosclerosis (37, 38).

It has been reported that ADMA is a predictor of cardiovascular risk (39), and increased plasma ADMA levels have been observed in patients with diseases associated with atherosclerosis, (40) such as hypercholesterolemia (41), hypertriglyceridemia (42), peripheral arterial disease (43), hypertension (44), type 2 diabetes mellitus (45), acute coronary syndromes (46, 47) and end-stage renal failure (48). We have recently found that plasma ADMA levels are significantly higher in patients with early rheumatoid arthritis (ERA), and that this has a statistically significant negative effect on coronary flow reserve (CFR), which is significantly reduced in ERA patients without any signs or symptoms of coronary artery disease (CAD) (49).

We previously showed that CFR is reduced early in patients with long-standing RA without any clinical evidence of heart disease, (50) and in a recent study of 22 PsA patients and 35 healthy controls with no history or current signs of CVD, we found that ADMA levels were significantly higher in the PsA patients (0.71 ± 0.07 vs 0.48 ± 0.07 ; $p=0.00$) who also had a significantly reduced CFR (2.86 ± 0.70 vs 3.3 ± 0.43 ; $p<0.01$) (51). Common carotid IMT was greater in the PsA patients, but the difference was not significant (0.64 ± 0.26 vs 0.62 ± 0.5 mm). There was a significant correlation between CFR and plasma ADMA levels in the PsA group ($R=0.28$; $p<0.01$), but no correlation between plasma ADMA levels and IMT ($R=0.02$; $p=0.32$), the Disease Activity Score 28 (DAS-28) ($p=0.52$) or the Psoriasis Area and Severity Index ($p=0.98$).

It has recently been demonstrated that CFR is a highly sensitive (>90%) diagnostic marker of CAD, and that a CFR of less than 2 accurately predicts the presence of severe (i.e. >70%) coronary stenosis (52). The significant correlation between the reduced CFR and increased ADMA levels in PsA patients may indicate endothelial dysfunction and impaired coronary micro-

circulation, as found in patients with early RA (49). Kimhi et al. (7) found that PsA patients have higher common carotid artery IMT values than healthy controls and the same results were also reported from a larger study (53). We also found this in our experience, although the difference was not statistically significant. This may have been due to the relatively small number of patients, but it could also indicate that CFR (a functional parameter) is a more sensitive marker of subclinical atherosclerosis than IMT. In a study of 20 patients treated for 18 months with DMARDs (10 with methotrexate and 10 with adalimumab), we found that both drugs significantly reduced DAS-28 (6.0 ± 0.8 vs 2.0 ± 0.7 ; $p<0.0001$) and improved CFR (2.4 ± 0.2 vs 2.7 ± 0.5 ; $p<0.01$), whereas the changes in common carotid IMT and plasma ADMA levels were not significant (54). In addition to their well-known anti-phlogistic effects, DMARDs improve coronary microcirculation without having any direct effect on IMT or ADMA, clinical markers of atherosclerosis in patients with RA and possibly in those with PsA (55, 56).

However, Tam et al. (57) in a pilot study showed that treatment with anti-TNF agents may determine a reduction in IMT in PsA patients, associated with improvement in inflammatory markers, but independent of changes in lipid profiles. Moreover, Mazlan (58) et al. reported a significant association between CV risk and positive IMT in PsA patients, although there was no association with disease activity, disease severity or DMARD therapy.

Finally, Di Minno, (59) in a study involving 224 patients with PsA (120 on TNF- α blockers and 104 on DMARDs), reported that IMT in PsA patients without CV risk was higher than in controls. Furthermore, they showed that treatment duration inversely predicted IMT in PsA patients on TNF blockers but not in those on DMARDs. In conclusion, all these data indicate that active PsA is a risk factor for CVD. PsA patients should, therefore, be screened for subclinical forms of the disease and its risk factors, and an early treatment approach should be adopted.

RIASSUNTO

Psoriasis is a chronic, genetically determined and immunomediated inflammatory skin disease that affects 2-3% of the Caucasian population. A considerable proportion of these patients develop a form of inflammatory arthritis known as psoriatic arthritis (PsA), although the prevalence of this has not been well defined. Patients with PsA have a higher mortality rate than the general population and the risk of mortality is related to disease severity at the time of presentation. Endothelial dysfunction and early atherosclerosis have been found in patients with PsA without any cardiovascular disease (CVD) risk factors, and experts believe that CVD is one of the leading causes of death, as it is in patients with rheumatoid arthritis (RA). Various disease-related mechanisms may be involved in the development of premature vascular damage in both cases, including an increased synthesis of proinflammatory mediators (such as cytokines, chemokines and adhesion molecules), autoantibodies against endothelial cell components, perturbations in T-cell subsets, genetic polymorphisms, hyperhomocysteinemia, oxidative stress, abnormal vascular repair, and iatrogenic factors. In a recent study of 22 patients with PsA without any signs of CVD, we found that the plasma concentration of asymmetric dimethylarginine (ADMA) levels were significantly high and coronary flow reserve (CFR) was significantly reduced. Moreover, there was a significant correlation between CFR and plasma ADMA levels in the PsA group. The significant correlation between the reduced CRF and increased ADMA levels suggests that, like patients with early RA, PsA patients suffer from endothelial dysfunction and impaired coronary microcirculation. Active PsA is a risk factor for CVD, and so PsA patients should be screened for subclinical forms of the disease and its risk factors, and an early treatment approach should be adopted.

Parole chiave: artrite psoriasica; coinvolgimento cardiovascolare; dimetil-arginina asimmetrica; fattori di rischio.

Key words: psoriatic arthritis; cardiovascular involvement; asymmetric dimethylarginine; risk factors.

■ REFERENCES

1. Sheeb M, Uramoto KM, Gibson LE, O'fallon WM, Gabriel SE. The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982-1991. *J Rheumatol* 2000; 27: 1247-50.
2. Wong K, Gladman DD, Husted J, Long JA, Farewell VT. Mortality studies in psoriatic arthritis: results from a single outpatient clinic. I. Causes and risk of death. *Arthritis Rheum* 1997; 40: 1868-72.
3. Gladman DD, Farewell VT, Wong K, Husted J. Mortality studies in psoriatic arthritis: results from a single outpatient center. II. Prognostic indicators for death. *Arthritis Rheum* 1998; 41: 1103-10.
4. Gladman DD, Ang M, Su L, Tom BD, Schentag CT, Farewell VT. Cardiovascular morbidity in psoriatic arthritis. *Ann Rheum Dis* 2009; 68: 1131-5.
5. Mallbris L, Akre O, Branath F, Yin L, Lindelof B, Ekblom A, et al. Increased risk for cardiovascular mortality in psoriatic inpatients but not outpatients. *Eur J Epidemiol* 2004; 19: 225-30.
6. Han C, Robinson DW Jr, 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.
7. Kimhi O, Caspi D, Bornstein NM, Maharshak N, Gur A, Arbel Y, et al. Prevalence and risk factors of atherosclerosis in patients with psoriatic arthritis. *Semin Arthritis Rheum* 2007; 36: 203-9.
8. Jones SM, Harris CPD, Lloyd J, Stirling CA, Reckless JPD, McHugh NJ. Lipoproteins and their subfractions in psoriatic arthritis: identification of an atherogenic profile with active joint disease. *Ann Rheum Dis* 2000; 59: 904-9.
9. Brustein DM, Scher RK, Auerbach R. Hyperlipoproteinaemia and psoriasis. *Lancet* 1976; 1: 154.
10. Reynoso-von Drateln C, Martinez-Abundis E, Balcazar-Munoz BR, Bustos-Saldana R, Gonzalez-Ortiz M. Lipid profile, insulin secretion, and insulin sensitivity in psoriasis. *J Am Acad Dermatol* 2003; 48: 882-5.
11. Gonzalez-Gay MA, Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Gomez-Acebo I, Miranda-Fillooy JA, Paz-Carreira J, et al. Asymptomatic Hyperuricemia and Serum Uric Acid Concentration Correlate with Subclinical Atherosclerosis in Psoriatic Arthritis Patients Without Clinically Evident Cardiovascular Disease. *Semin Arthritis Rheum* 2009; 39:157-62.
12. Gonzalez-Juanatey C, Llorca J, Miranda-Fillooy JA, Amigo-Diaz E, Testa A, Garcia-Porrúa C, et al. Endothelial dysfunction in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. *Arthritis Rheum* 2007; 57: 287-93.
13. Gonzalez-Juanatey C, Llorca J, Amigo-Diaz E, Dierssen T, Martin J, Gonzalez-Gay MA. High prevalence of subclinical atherosclerosis in psoriatic arthritis patients without clinical

- cally evident cardiovascular disease or classic atherosclerosis risk factors. *Arthritis Rheum* 2007; 57: 1074-80.
14. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al, for the American Heart Association and National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 2005; 112: 2735-52.
 15. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. *Diabetes Care* 2005; 28: 385-90.
 16. Mok CC, Ko GT, Ho LY, Yu KL, Chan PT, To CH. Prevalence of atherosclerotic risk factors and the metabolic syndrome in patients with chronic inflammatory arthritis. *Arthritis Care Res (Hoboken)* 2011; 63: 195-202.
 17. Atzeni F, Turiel M, Caporali R, Cavagna L, Tomasoni L, Sitia S, et al. The effect of pharmacological therapy on the cardiovascular system of patients with systemic rheumatic diseases. *Autoimmun Rev* 2010; 9: 835-9.
 18. Hahn BH, Grossman J, Chen W, McMahon M. The pathogenesis of atherosclerosis in autoimmune rheumatic diseases: roles of inflammation and dyslipidemia. *J Autoimmun* 2007; 28: 69-75.
 19. Wolfe F, Michaud K. the risk of myocardial infarction and pharmacologic and non-pharmacologic myocardial infarction predictors in rheumatoid arthritis: a cohort and nested case-control analysis. *Arthritis Rheum* 2008; 58: 2612-21.
 20. Gisondi P, Girolomoni C. Psoriasis and atherothrombotic diseases: disease-specific and non-disease-specific risk factors. *Semin Thromb Hemost* 2009; 35: 313-24.
 21. Sarzi-Puttini P, Atzeni F, Gerli R, Bartoloni E, Doria A, Barskova T, et al. Cardiac involvement in systemic rheumatic diseases: An update. *Autoimmun Rev* 2010; 9: 849-52.
 22. van Kuijk AW, Reinders-Blankert P, Smeets TJ, Dijkman BA, Tak PP. Detailed analysis of the cell infiltrate and the expression of mediators of synovial inflammation and joint destruction in the synovium of patients with psoriatic arthritis: implications for treatment. *Ann Rheum Dis* 2006; 65: 1551-7.
 23. Danning CL, Illei GG, Hitchon C, Greer MR, Boumpas DT, McInnes IB. Macrophage-derived cytokine and nuclear factor kappaB p65 expression in synovial membrane and skin of patients with psoriatic arthritis. *Arthritis Rheum* 2000; 43: 1244-56.
 24. Kruithof E, Baeten D, De RL, Vandooren B, Foell D, Roth J, et al. Synovial histopathology of psoriatic arthritis, both oligo and polyarticular, resembles spondyloarthropathy more than it does rheumatoid arthritis. *Arthritis Res Ther* 2005; 7R569-R580.
 25. Silva LC, Ortigosa LC, Benard G. Anti-TNF- α agents in the treatment of immune-mediated inflammatory diseases: mechanisms of action and pitfalls. *Immunotherapy* 2010; 2: 817-33.
 26. Popa C, Netea MG, van Riel PL, van der Meer JW, Stalenhoef AF. The role of TNF-alpha in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. *J Lipid Res* 2007; 48: 751-62.
 27. Dixon WG, Symmons DP. What effects might anti-TNFalpha treatment be expected to have on cardiovascular morbidity and mortality in rheumatoid arthritis? A review of the role of TNFalpha in cardiovascular pathophysiology. *Ann Rheum Dis* 2007; 66: 1132-6.
 28. Popa C, van den Hoogen FH, Radstake TR, Netea MG, Eijsbouts AE, den Heijer M, et al. Modulation of lipoprotein plasma concentrations during long-term anti-TNF therapy in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2007; 66: 1503-7.
 29. Ingegnoli F, Fantini F, Griffini S, Soldi A, Meroni PL, Cugno M. Anti-tumor necrosis factor alpha therapy normalizes fibrinolysis impairment in patients with active rheumatoid arthritis. *Clin Exp Rheumatol* 2010; 28: 254-7.
 30. Ingegnoli F, Fantini F, Favalli EG, Soldi A, Griffini S, Galbiati V, et al. Inflammatory and prothrombotic biomarkers in patients with rheumatoid arthritis: effects of tumor necrosis factor-alpha blockade. *J Autoimmun* 2008; 31: 175-9.
 31. Moots RJ, Ostor AJK, IJD Will. treatment of rheumatoid arthritis with an IL-6R inhibitor help facilitate the 'age of remission'? *Expert Opin Investig Drugs* 2009; 18: 1687-99.
 32. Oldfield V, Dhillon S, Plosker GL. Tocilizumab. A review of its use in the management of rheumatoid arthritis. *Drugs* 2009; 69: 609-32.
 33. Atzeni F, Sarzi-Puttini P, Vena GA. Resistant cases of psoriatic arthritis: how to manage them. *J Rheumatol* 2009; 83: 73-S5.
 34. Angel K, Provan SA, Gulseth HL, Mowinckel P, Kvien TK, Atar D. Tumor necrosis factor-alpha antagonists improve aortic stiffness in patients with inflammatory arthropathies: a controlled study. *Hypertension* 2010; 55: 333-8.
 35. Sattar N, Crompton P, Cherry L, Kane D, Lowe G, McInnes IB. Effects of tumor necrosis factor blockade on cardiovascular risk factors in psoriatic arthritis: a double-blind, placebo-controlled study. *Arthritis Rheum* 2007; 56: 831-9.
 36. Bannwarth B, Richez C. Clinical safety of tocilizumab in rheumatoid arthritis. *Expert Opin Drug Saf* 2011; 10: 123-31.
 37. Anthony S, Leiper J, Vallance P. Endogenous production of nitric oxide synthase inhibitors. *Vasc Med* 2005; 10: S3-9.

38. Miyazaki H, Matsuoka H, Cooke JP et al. Endogenous nitric oxide synthase inhibitor: a novel marker of atherosclerosis. *Circulation* 1999; 99: 1141-6.
39. Vallance P. Importance of asymmetrical dimethylarginine in cardiovascular risk. *Lancet* 2001; 358: 2096-7.
40. Anthony S, Leiper J, Vallance P. Endogenous production of nitric oxide synthase inhibitors. *Vasc Med* 2005; 10: S3-9.
41. Boger RH, Bode-Boger SM, Thiele W, Junker W, Alexander K, Frolich JC. Biochemical evidence for impaired nitric oxide synthesis in patients with peripheral arterial occlusive disease. *Circulation* 1997; 95: 2068-74.
42. Lundman P, Eriksson MJ, Stuhlinger M, Cooke JP, Hamsten A, Tornvall P. Mild-to-moderate hypertriglyceridemia in young men is associated with endothelial dysfunction and increased plasma concentrations of asymmetric dimethylarginine. *J Am Coll Cardiol* 2001; 38: 111-16.
43. Boger RH, Bode-Boger SM, Thiele W, Junker W, Alexander K, Frolich JC. Biochemical evidence for impaired nitric oxide synthesis in patients with peripheral arterial occlusive disease. *Circulation* 1997; 95: 2068-74.
44. Surdacki A, Nowicki M, Sandmann J, Tsikas D, Boeger RH, Bode-Boeger SM, et al. Reduced urinary excretion of nitric oxide metabolites and increased plasma levels of asymmetric dimethylarginine in men with essential hypertension. *J Cardiovasc Pharmacol* 1999; 33: 652-8.
45. Stuhlinger MC, Abbasi F, Chu JW, Lamendola C, McLaughlin TL, Cooke JP, et al. Relationship between insulin resistance and an endogenous nitric oxide synthase inhibitor. *JAMA* 2002; 287: 1420-6.
46. Valkonen VP, Paiva H, Salonen JT, Lakka TA, Lehtimaki T, Laakso J, et al. Risk of acute coronary events and serum concentration of asymmetrical dimethylarginine. *Lancet* 2001; 358: 2127-8.
47. Bae SW, Stuhlinger MC, Yoo HS, Yu KH, Park HK, Choi BY, et al. Plasma asymmetric dimethylarginine concentrations in newly diagnosed patients with acute myocardial infarction or unstable angina pectoris during two weeks of medical treatment. *Am J Cardiol* 2005; 95: 729-33.
48. MacAllister RJ, Rambaek MH, Vallance P, Williams D, Hoffmann KH, Ritz E. Concentration of dimethyl-L-arginine in the plasma of patients with end-stage renal failure. *Nephrol Dial Transplant* 1996; 11: 2449-52.
49. Turiel M, Atzeni F, Tomasoni L, de Portu S, Delfino L, Bodini BD, et al. Non-invasive assessment of coronary flow reserve and ADMA levels: a case-control study of early rheumatoid arthritis patients. *Rheumatology (Oxford)*. 2009; 48: 834-9.
50. Atzeni F, Sarzi-Puttini P, De Blasio G, Delfino L, Tomasoni L, Turiel M. Preclinical impairment of coronary flow reserve in patients with rheumatoid arthritis. *Ann NY Acad Sci.* 2007; 1108: 392-7.
51. Atzeni F, Sarzi-Puttini P, Sitia S, Tomasoni L, Gianturco L, Battellino M, et al. Coronary flow reserve and ADMA levels: new parameters for identifying subclinical atherosclerosis in patients with psoriatic arthritis. *J Rheumatol* 2011 (in press).
52. Turiel M, Peretti R, Sarzi-Puttini P, Atzeni F, Doria A. Cardiac imaging techniques in systemic autoimmune diseases. *Lupus* 2005; 14: 727-31.
53. Tam LS, Shang Q, Li EK, Tomlinson B, Chu TT, Li M, et al. Subclinical carotid atherosclerosis in patients with psoriatic arthritis. *Arthritis Rheum* 2008; 59: 1322-31.
54. Turiel M, Tomasoni L, Sitia S, Cicala S, Gianturco L, Ricci C, et al. Effects of long-term disease-modifying antirheumatic drugs on endothelial function in patients with early rheumatoid arthritis. *Cardiovasc Ther* 2010; 28: 53-64.
55. Quinn MA, Cox S. The evidence for early intervention. *Rheum Dis Clin North Am* 2005; 31: 575-89.
56. Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002; 359: 1173-7.
57. Tam L, Li EK, Shang Q, Tomlinson B, Chu TT, Li M, et al. TNF-alpha blockade is associated with reduction of carotid intima-media thickness for patients with active psoriatic arthritis - a pilot study. *Ann Rheum Dis* 2009; 68 (Suppl 3): 659.
58. Mazlan SA, bin Mohamed Said MS, Hussein H, binti Shamsuddin K, Shah SA, Basri H. A study of intima media thickness and their cardiovascular risk factors in patients with psoriatic arthritis. *Acta Medica (Hradec Kralove)*. 2009; 52: 107-16.
59. Di Minno MN, Iervolino S, Peluso R, Scarpa R, Di Minno G; CaRRDs study group. Carotid intima-media thickness in psoriatic arthritis: differences between tumor necrosis factor- α blockers and traditional disease-modifying antirheumatic drugs. *Arterioscler Thromb Vasc Biol* 2011; 31: 705-12.