**Table 1** Characteristics of all patients

| Characteristic | All patients (n = 164) (⩾3 SS items) | SS (n = 108) (⩾4 SS items) | SS-like syndrome (n = 56) (3 SS items) |
|---|---|---|---|
| Age (years), mean (range) | 56.3 (20.1–87.3 ) | 57.1 (24.9–87.3) | 54.6 (20.1–81.9) |
| Female/male ratio | 9.25/1 | 8/1 | 13/1 |
| Follow up | | | |
| Years | 855.8 | 627.0 | 225.4 |
| Median | 3.65 | 4.30 | 2.75 |
| Range | 0–21.6 | 0–21.6 | 0.2–15.9 |
| Anti-SSA/Ro, No (%) | 94 (57) | 77 (71) | 17 (30) |
| Anti-SSB/La, No (%) | 71 (43) | 62 (57) | 9 (16) |
| RF, No (%) | 67 (41) | 52 (48) | 15 (27) |
| Anti-CCP, No (%) | 5 (3) | 3 (3) | 2 (4) |
| Anti-CCP, No (%) | | | |
| Specificity (%) | 98.8 | 98.1 | 100 |
| Sensitivity (%) | 75 | 50 | 100 |
| PPV (%) | 60 | 50 | 100 |
| NPV (%) | 99.4 | 98.1 | 100 |
| RF | | | |
| Specificity (%) | 60.6 | 52.8 | 75.9 |
| Sensitivity (%) | 100 | 100 | 100 |
| PPV (%) | 6.0 | 3.8 | 13.3 |
| NPV (%) | 100 | 100 | 100 |
| McNemar's test (p value) | <0.0001 | <0.0001 | <0.0001 |
| κ Value (95% CI) | 0.058 (−0.013 to 0.129) | 0.021 (−0.044 to 0.086) | 0.184 (−0.041 to 0.410) |

*SS, Sjögren's syndrome; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

Figure 1 shows an overview of patients who have RA. Patients A and D have SS and RA, patients B and C have Sjögren's-like syndrome and RA while patients E and F do not have RA (RF was negative in both patients), but have a borderline anti-CCP. They could develop RA at a later stage. Patients A, B, and C have a positive anti-CCP.

In this study only four patients were diagnosed with RA. This limits the accuracy of the sensitivity, but is excellent for calculating the specificity. The rationale for this study is the fact that it is important to select only those patients with RA from a group in which most have a positive RF test, with the help of a specific diagnostic test such as the anti-CCP test. When a cut off value of 100 U/ml for anti-CCP is used, the specificity of anti-CCP for RA is 100%.

We conclude that the RF test for the diagnosis of RA in patients with SS has no value because about 40% of patients with SS have positive RF tests (94% of these tests are false positive). The anti-CCP test, on the other hand, has a high specificity for RA.

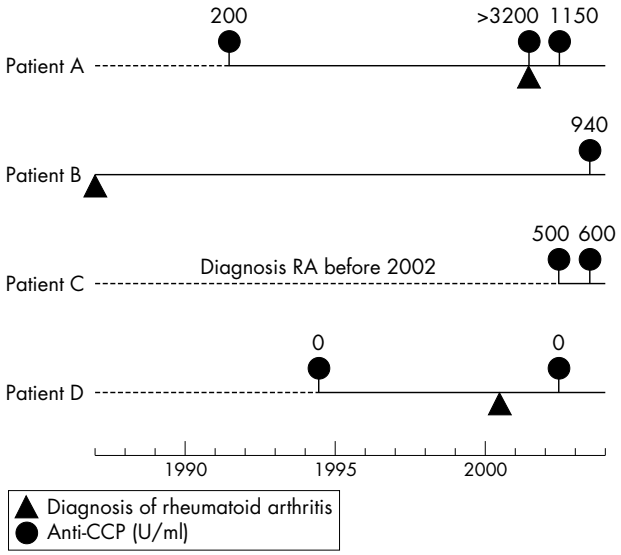


**Figure 1** Timescale of the four patients with RA with the relevant anti-CCP results. Patient A (SS) 1991 RF: 50 IU/ml, 2002 RF: 200 IU/ml; patient B (SS-like) 2003 RF: 1600 IU/ml; patient C (SS-like) 2002 RF: 50 IU/ml, 2003 RF: 50 IU/ml; patient D (SS) 1994 RF: 50 IU/ml, 2002 RF: 12 IU/ml. The evaluation criteria for anti-CCP are as follows: ⩽25 U/ml are defined as negative, >50 U/ml are positive. Samples with >25 U/ml and <50 U/ml were considered as borderline. The evaluation criteria for RF are as following: negative (<12 IU/ml) and positive (⩾12 IU/ml).

## ACKNOWLEDGEMENTS

We thank Jane Meijlink for her help with the English translation.

## Authors' affiliations

**C van Noord, H Hooijkaas, B C M Dufour-van den Goorbergh, P M van Hagen, P L A van Daele, J P van de Merwe,** Departments of Immunology and Internal Medicine, Erasmus MC, University Medical Centre Rotterdam, The Netherlands

Correspondence to: Ms C van Noord, Erasmus MC, University Medical Center Rotterdam, Department of Immunology, Dr Molewaterplein 50, 3015 GE Rotterdam, The Netherlands; charlottevannoord@hotmail.com

Accepted 22 August 2004

## REFERENCES

1 **Thomas E**, Hay EM, Hajeer A, Silman AJ. Sjögren's syndrome: a community-based study of prevalence and impact. *Br J Rheumatol* 1998;**37**:1069–76.
2 **Schellekens GA**, de Jong BA, van den Hoogen FH, van de Putte LB, van Venrooij WJ. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. *J Clin Invest* 1998;**101**:273–81.
3 **Bas S**, Perneger TV, Seitz M, Tiercy JM, Roux-Lombard P, Guerne PA. Diagnostic tests for rheumatoid arthritis: comparison of anti-cyclic citrullinated peptide antibodies, anti-keratin antibodies and IgM rheumatoid factors. *Rheumatology (Oxford)* 2002;**41**:809–14.
4 **Newkirk MM**. Rheumatoid factors: host resistance or autoimmunity? *Clin Immunol* 2002;**104**:1–13.
5 **Schellekens GA**, Visser H, de Jong BA, van den Hoogen FH, Hazes JM, Breedveld FC, *et al*. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. *Arthritis Rheum* 2000;**43**:155–63.
6 **Bizzaro N**, Mazzanti G, Tonutti E, Villalta D, Tozzoli R. Diagnostic accuracy of the anti-citrulline antibody assay for rheumatoid arthritis. *Clin Chem* 2001;**47**:1089–93.
7 **van Venrooij WJ**, Hazes JM, Visser H. Anticitrullinated protein/peptide antibody and its role in the diagnosis and prognosis of early rheumatoid arthritis. *Neth J Med* 2002;**60**:383–8.

8 **Vitali C**, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, *et al*. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;**61**:554–8.
9 **Martin-Martin LS**, Latini A, Pagano A, Ragno A, Stasi R, Coppe A, *et al*. A new mathematical model based on clinical and laboratory variables for the diagnosis of Sjögren's syndrome. *Clin Rheumatol* 2003;**22**:123–6.
10 **Arnett FC**, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24.

# Chemotherapeutic induced fascial oedema

**I Lim, R Kefford, N Manolios**

*Ann Rheum Dis* 2005;**64**:162–163. doi: 10.1136/ard.2004.020362

Chemotherapeutic agents have well recognised toxicities in addition to the usual features of nausea, vomiting, and myelosuppression. Toxicity affecting the skin and subcutaneous tissue is uncommon and poorly documented. Of the chemotherapeutic drugs, bleomycin is the best known for its ability to cause skin hyperpigmentation, Raynaud's phenomenon, and thickening of subcutaneous tissues resembling scleroderma, especially affecting the fingers.[1] The taxanes, a class of antimicrotubule agents can cause macules, papules, plaques, and nail changes. Docetaxel, in particular, has been described as causing scleroderma-like changes.[2]

The triazene derived compounds, dacarbazine and temozolomide, are chemotherapeutic agents similar to the nitrosoureas, which act as alkylating agents, predominantly through the methylation of the $O^6$ position of guanine in DNA. Dacarbazine is an intravenous preparation with single agent activity against malignant melanoma with reported partial remission rates up to 20% and median response durations of 4–6 months.[3] It is also active in Hodgkin's disease and soft tissue sarcomas. Temozolomide is an oral prodrug of 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide, the active metabolite of dacarbazine. Its major advantage is improved penetration into spaces, such as the central nervous system.

The dose limiting toxicity of both dacarbazine and temozolomide is myelosuppression. Nausea and vomiting occurs in up to 90% of patients.[1] Skin toxicity is not described with either agent. In this case report, we describe the occurrence of fascial oedema and scleroderma-like skin changes with the use of these agents in the treatment of metastatic melanoma.

## CASE REPORT

A 52 year old white woman presented with a 3 week history of ''heaviness'' of both thighs. She had also noted increasing tightness and swelling affecting both thighs, both shoulders, and the right side of her face and neck. There was no preceding history of Raynaud's phenomenon or musculoskeletal problems.

Four months earlier, she had been diagnosed with metastatic melanoma involving the liver and lung. Palliative chemotherapy with single agent dacarbazine was started (1700 mg infusion over 5 days every 3 weeks). There was a good response and the lung and liver metastases resolved. Four cycles of the dacarbazine chemotherapy were completed before the start of her lower limb symptoms. Other medical history consisted of hyperthyroidism treated with propylthiouracil, and a previous episode of idiopathic pancreatitis.

On examination, the skin was shiny and taut over the back of both thighs, extending over both buttocks. There was similar skin tightness over both shoulders, with less involvement of the right side of her face. No pitting was demonstrable. There were no peripheral stigmata of chronic sclerodermatous disease (telangiectasia, calcinosis, synovitis, sclerodactyly, or abnormal nailfold capillaries). The quadriceps and hamstring musculature were only mildly tender.

A full blood count and serum biochemistry, including creatine kinase, were normal. The patient was clinically and biochemically euthyroid. Erythrocyte sedimentation rate and C reactive protein were normal. She had a positive antinuclear antibody (speckled pattern with titre 1/160, as well as nucleolar pattern with titre 1/640). Extractable nuclear antigens, double stranded DNA, and antineutrophil cytoplasmic antibodies were not detectable. Magnetic resonance imaging (using the STIR technique) of her lower limbs disclosed marked subcutaneous oedema with involvement of the fascia (fig 1). Open muscle biopsy of the right upper lateral thigh was unhelpful, with no evidence of inflammatory infiltration. The biopsy was unfortunately too superficial, with no fascia included. No malignant cells were seen in the biopsy sample and all cultures were negative.

A diagnosis of fascial oedema was made and the only change to her management was that dacarbazine chemotherapy was stopped. Over 2 weeks, the skin tightness and softening of subcutaneous tissues visibly reduced, with associated improvement in her symptoms.

Dacarbazine was again restarted, with five further cycles given, for the liver metastases. She then developed cerebral metastases, and dacarbazine was changed to temozolomide to enhance central nervous system penetration. After the first course of temozolamide at the usual dosage of 250 mg on days 1–5, she redeveloped the skin tightness in a similar distribution. Unfortunately, the patient soon developed a dense left hemiplegia. Chemotherapy was stopped and the patient admitted to a palliative hospital.

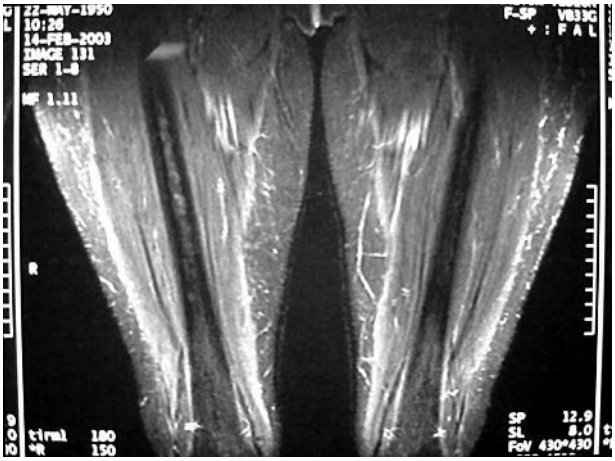

**Figure 1** Magnetic resonance imaging (STIR technique) of thighs showing enhancement of the fascia.

## DISCUSSION

Fascial oedema is an uncommon condition of unknown cause that mimics scleroderma, with swelling, stiffness, reduced flexibility of limbs, and thickening of the subcutaneous tissue. Fascial oedema is not usually related to drug toxicity.

We report here the first case of diffuse fascial oedema with scleroderma-like skin changes in a female patient with metastatic melanoma being treated with dacarbazine and its analogue temozolamide. In this case a strong temporal relationship was found between the skin changes seen and drug use. Possible explanations of these skin changes include a direct drug effect; altered immune regulation secondary to drug or disease, leading to the development of autoantibodies and subsequent disease; paraneoplastic effect of melanoma; or coincidence. However, the improvement of clinical signs and symptoms followed by recurrence of these on rechallenge strongly favours a drug effect.

**Authors' affiliations**
**I Lim, N Manolios,** Department of Rheumatology, Westmead Hospital, Westmead, NSW, Australia 2145
**R Kefford,** Department of Oncology, Westmead Hospital, Westmead, NSW, Australia 2145

Correspondence to: A/Prof. N. Manolios, Department of Rheumatology, Westmead Hospital, Westmead, NSW, Australia 2145; Nickm@westgate.wh.usyd.edu.au

Accepted 26 March 2004

## REFERENCES

1 **Souhami R**, Tannock I, Hohenberger P, Horiot J-C. *Oxford textbook of oncology*, 2nd ed. Oxford: Oxford University Press, 2002.
2 **Hassett G**, Harnett P, Manolios N. Scleroderma in association with the use of docetaxel (Taxotere) for breast cancer. *Clin Exp Rheumatol* 2001;**19**:197–200.
3 **DeVita V**, Hellman S, Rosenberg S. *Cancer: principles and practice of oncology*, 6th ed. Lippincott: Williams & Wilkins, 2001.

# Risk factors for accelerated atherosclerosis in patients with systemic lupus erythematosus

**B Marasini, M De Monti, G Ghilardi**

*Ann Rheum Dis* 2005;**64**:163–164. doi: 10.1136/ard.2004.024299

Accelerated atherosclerosis is a recognised leading cause of morbidity and mortality in systemic lupus erythematosus (SLE),[1] and therefore the identification of patients with SLE at risk for cardiovascular (CV) events is important. However, the mechanisms of premature atherosclerosis associated with SLE are still unknown, with lupus itself a possible candidate and the role of traditional and non-traditional risk factors still uncertain.[2–4] It has been recently suggested that mechanisms inherent to SLE might predispose the vascular wall to acceleration of the atherosclerotic process through traditional risk factors.[5]

## METHODS AND RESULTS

We performed high resolution carotid ultrasonography in 48 consecutive patients (43 women, 5 men, aged 19–77 years) fulfilling the American Rheumatism Association criteria for SLE,[6] without clinical evidence of overt atherosclerosis or diabetes. Plaque at carotid bifurcation was found in 6/48 (13%) and abnormal intimal medial thickness (IMT, considered "abnormal" if $> 0.7$ mm) in 8/48 (17%) patients.

Older age and high blood pressure were confirmed to be strongly associated with carotid lesions. Patients with plaque or abnormal IMT were significantly older (mean (SD) 69 (7) *v* 39 (12) years or 62 (14) *v* 39 (14) years, $p<0.0001$ and $p = 0.0014$, respectively) and higher blood pressure (>140/90 mm Hg or treatment with antihypertensive drugs) was also more common in plaque positive (67%) than in plaque negative (7%) patients ($p = 0.0001$).

Moreover, among traditional risk factors, we found that men with SLE tended to have plaque more often (20%) than women with SLE (12%), in accord with recent observations both on patients with SLE and the general population.[4 7]

We did not find any relationship between carotid abnormalities, cumulative prednisone intake, or inflammation markers (erythrocyte sedimentation rate, fibrinogen, and C reactive protein). As recently pointed out,[2] inflammation markers, which fluctuate as a consequence of disease activity and treatment, cannot serve as suitable risk markers in SLE, even if increasing evidence indicates that atherosclerosis is an inflammatory disease.

An intriguing finding of our study was the negative association between carotid abnormalities and antinuclear antibodies (ANA). Plaque was more common in ANA negative patients (40%) than in ANA positive patients (9%) ($p = 0.0495$). Our observation may be consistent with the recent study of Roman *et al*,[3] who found that anti-Sm and anti-RNP autoantibodies were less common in patients with plaque, and none of the six Sm positive patients of our series had plaque. Interestingly, it has been recently suggested that Sm antibodies exert a protective effect against coronary artery calcification in SLE.[8]

## DISCUSSION

Although the role of autoantibodies in atherosclerosis,[9] and particularly in accelerated atherosclerosis of SLE, is still a matter of debate,[3 10] the proposed existence of two clinical patterns of SLE, one at higher risk of CV events, characterised by limited autoantibody production, and the other at lower risk but with a wider autoantibody spectrum,[3] opens a new promising research agenda.

Because in atherosclerosis there is evidence for an involvement of humoral immunity, an inappropriate autoimmune response inherent to the process of SLE might have a role in chronic plaque development. On the other hand, aggressive immunosuppressant drugs for more severe diseases might lower or even suppress autoantibody production. Moreover, a genetic predisposition linked to autoantibody repertoires and to clinical subsets of disease cannot be ruled out.

More studies are needed to assess whether ANA testing might represent an additional tool for identifying patients with SLE at risk for CV events.

**Authors' affiliations**
**B Marasini, M De Monti, G Ghilardi,** Department of Medicine, Surgery and Dentistry, S Paolo Hospital, University of Milan, Italy

Correspondence to: Professor B Marasini; bianca.marasini@unimi.it

Accepted 6 May 2004

## REFERENCES

1 **Bruce IN**, Gladman DD, Urowitz MB. Systemic lupus erythematosus: premature atherosclerosis in systemic lupus erythematosus. *Rheum Dis Clin North Am* 2000;**26**:257–78.
2 **Doria A**, Shoenfeld Y, Wu R, Gambari PF, Puato M, Ghirardello A, *et al*. Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. *Ann Rheum Dis* 2003;**62**:1071–7.
3 **Roman MJ**, Shanker B-E, Davis A, Lockshin MD, Sammaritano L, Simantov R, *et al*. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;**349**:2399–406.
4 **Anasuma Y**, Oeser A, Shintani AK, Turner E, Olsen N, Fazio S, *et al*. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;**349**:2407–15.
5 **Selzer F**, Sutton-Tyrrell K, Fitzgerald SG, Pratt JE, Tracy RP, Kuller LH, *et al*. Comparison of risk factors for vascular disease in the carotid artery and aorta in women with systemic lupus erythematosus. *Arthritis Rheum* 2004;**50**:151–9.
6 **Tan EM**, Cohen AS Fries JF, Masi AT, McShane DJ, Rothfield NF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;**25**:1271–7.
7 **Iemolo F**, Martiniuk A, Steinman DA, Spence JD. Sex differences in carotid plaque and stenosis. *Stroke* 2004;**35**:477–81.
8 **Manger K**, Kusus M, Forster C, Ropers D, Daniel WG, Kalden JR, *et al*. Factors associated with coronary artery calcification in young female patients with SLE. *Ann Rheum Dis* 2003;**62**:846–50.
9 **Brusca I**, Sarullo FM, Fazio M. Presence of antinuclear antibodies and coronary heart disease. *Ann Rheum Dis* 2002;**61**:1038.
10 **Grainger DJ**, Bethell HWL. High titres of serum antinuclear antibodies, mostly directed against nucleolar antigens, are associated with the presence of coronary atherosclerosis. *Ann Rheum Dis* 2002;**61**:110–14.


# Angiotensin converting enzyme (ACE) gene polymorphisms and lupus disease severity: a promising link

**M Saeed, S F Mekan, M A Rabbani, F M Arain, M Arif, S Shaharyar**

*Ann Rheum Dis* 2005;**64**:164–165. doi: 10.1136/ard.2004.020834

The ACE insertion/deletion (I/D) polymorphism has been inconsistently reported to be associated with systemic lupus erythematosus (SLE).[1–3] We proposed the hypothesis that the genetic sequence variation of ACE may not cause SLE, but may participate in disease progression. Among the 13 polymorphisms of the ACE gene recently reported, a polymorphism in exon 17, ACE 2350 G>A, has the most significant effect on plasma ACE concentrations[4] and has been shown to be associated with essential hypertension.[5] We carried out a retrospective, case-control study of the two polymorphisms for putative associations with SLE and allied phenotypes among a homogeneous Asian population.

## METHODS AND RESULTS

We investigated a sample group of 39 patients with SLE (mean (SD) age 33 (10) years; nine men) and 79 healthy control Pakistani subjects from the Aga Khan University Hospital, Karachi, matched for age (35 (9) years) and sex (20 men). Informed consent was taken from all participants and international guidelines for sample collection were followed.[6] All patients fulfilled the American College of Rheumatology criteria for SLE.[7] We used the Systemic Lupus Activity Measure (SLAM)[8] score at diagnosis as an indicator of disease severity; a SLAM score $\geqslant$20 indicating severe SLE and $\leqslant$10, mild disease. Our patients predominantly had moderate disease activity (SLAM 11–19) at diagnosis and only three patients had mild SLE.

Genotyping for ACE I/D and 2350 G>A polymorphisms was done as previously described.[5 6] Table 1 shows that the differences in the distributions of the six genotypes were not significant for either of the ACE polymorphisms, as assessed by $\chi^2$ analyses on 3×2 tables. The groups were in Hardy-Weinberg equilibrium for both markers as shown by the $D_A$ statistics.[9] The frequency of the 2350A allele increased from 17% in mild SLE to 28% in moderate disease to 32% in severe SLE.

Haplotype analysis and linkage disequilibrium (LD) statistics obtained using Powermarker version 2.0[10] showed that the D and 2350A alleles were in strong linkage disequilibrium (LD) ($D = -0.23$, $D' = 0.72$, $\chi^2 = 64.4$, $p<0.001$). The extent of LD was more in severe SLE ($D' = -0.52$, $\chi^2 = 5.04$, $p = 0.025$) than in mild to moderate disease ($D' = -0.26$, $\chi^2 = 1.42$, $p = 0.23$). The DA haplotype was more frequent in severe SLE than in mild to moderate disease (odds ratio = 1.43, 95% confidence interval = 0.38 to 5.35, $\chi^2 = 0.36$, 1 df, $p = 0.55$).

## DISCUSSION

SLE is present in an aggressive form (moderate to severe disease) in the Pakistani population. Although assessing SLE severity is not simple, as various factors such as response to treatment and type of organ affected and organ damage determine the nature of the disease, we used the SLAM index at diagnosis as an indicator of disease severity. All our patients presented within 6 months of symptom onset, which made SLAM at diagnosis a comparable index of SLE severity.

The ACE gene does not appear play a part in the development of SLE as shown by the lack of association of

**Table 1** Distribution of ACE 2350 G>A and I/D genotypes and allele frequencies (standard errors) as well as $D_A$ statistics in the patients with SLE and controls

| SNP | Genotypes/ alleles | Patients with SLE (n = 39) | Controls (n = 79) | Association ($\chi^2$ (2df)/p) |
|---|---|---|---|---|
| ACE I/D | II/ID/DD | 14/14/11 | 27/38/14 | 2.26/0.32 |
| | I/D | 0.54 (0.04)/0.46 (0.04) | 0.58 (0.06)/0.42 (0.06) | |
| $D_A/\chi^2$ | | 0.07/3.14 | 0.0008/<0.001 | |
| ACE 2350 G>A | GG/GA/AA | 18/20/1 | 38/35/6 | 1.41/0.49 |
| | G/A | 0.72 (0.07)/0.29 (0.07) | 0.70 (0.04)/0.30 (0.04) | |
| $D_A/\chi^2$ | | −0.059/3.06 | −0.014/0.354 | |

*Significant ($p<0.05$).

the ACE I/D and G>A polymorphisms, which is consistent with previous findings for ACE I/D.[2] Though the frequency of the 2350A allele was similar in both groups, its distribution was skewed towards severe SLE (SLAM >20). The D and the 2350A alleles were in strong LD and the predominant transmission of the DA haplotype in severe SLE indicated its association with severe SLE. These results support the involvement of ACE polymorphisms with increasing disease severity of SLE.

## ACKNOWLEDGEMENTS

We are grateful to our patients for their participation and to Drs Philippe Frossard, Ata Khan, and Adil Abbas for help with patient recruitment.

### Authors' affiliations

**M Saeed, S F Mekan, F M Arain, M Arif, S Shaharyar,** Department of Biological and Biomedical Sciences, The Aga Khan University, Karachi, Pakistan
**M A Rabbani,** Department of Medicine, The Aga Khan University, Karachi, Pakistan

Correspondence to: Dr M Saeed, Department of Biological and Biomedical Sciences, The Aga Khan University, Stadium Road, Karachi, 74800, Pakistan; drsaeed2k @yahoo.com

Accepted 23 May 2004

## REFERENCES

1 **Parsa A**, Peden E, Lum RF, Seligman VA, Olson JL, Li H, *et al*. Association of angiotensin-converting enzyme polymorphisms with systemic lupus erythematosus and nephritis: analysis of 644 families. *Genes Immunity* 2002;**3**(suppl 1):S42–6.
2 **Kaufman KM**, Kelly J, Gray-McGuire C, Asundi N, Yu H, Reid J, *et al*. Linkage analysis of angiotensin-converting enzyme (ACE) insertion/deletion polymorphism and systemic lupus erythematosus. *Mol Cell Endocrinol* 2001;**177**:81–5.
3 **Akai Y**, Sato H, Iwano M, Kurumatani N, Kurioka H, Kubo A, *et al*. Association of an insertion polymorphism of angiotensin-converting enzyme gene with the activity of lupus nephritis. *Clin Nephrol* 1999;**51**:141–6.
4 **Zhu X**, Bouzekri N, Southam L, Cooper RS, Adeyemo A, McKenzie CA, *et al*. Linkage and association analysis of angiotensin I-converting enzyme (ACE)-gene polymorphisms with ACE concentration and blood pressure. *Am J Hum Genet* 2001;**68**:1139–48.
5 **Saeed Mahmood M**, Saboohi K, Osman Ali S, Bokhari AM, Frossard PM. Association of the angiotensin-converting enzyme (ACE) gene G2350A dimorphism with essential hypertension. *J Hum Hypertens* 2003;**17**:719–23.
6 **Gostin LO**. National health information privacy: regulations under the Health Insurance Portability and Accountability Act. *JAMA* 2001;**285**:3015–21.
7 **Hochberg MC**. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [abstract]. *Arthritis Rheum* 1997;**40**(suppl 9):1725.
8 **Gladman DD Goldsmith CH**, Urowitz MB, Bacon P, Bombardier C, Isenberg D, *et al*. Crosscultural validation and reliability of 3 disease activity indices in systemic lupus erythematosus. *J Rheumatol* 1992;**19**:608–11.
9 **Haviland MB**, Kassling AM, Davingnon J, Sing CF. Estimation of Hardy-Weinberg pairwise disequilibrium in apolipoprotein AI-CIII-AIV gene cluster. *Am J Hum Genet* 1991;**49**:350–65.
10 **Lui J**. Powermarker version 2.0 beta. www.powermarker.net (accessed 11 October 2004). Copyright 2001–2003.

# Rheumatoid arthritis in Poland and Lithuania: different clinical course and HLA associations despite similar genetic background

**R Płoski, I Butrimiene, E Kamińska, K Valiukiene, P Sliwińska, E Kubasiewicz, A Kozakiewicz, A Smerdel, V Kučinskas, J Jaworski, E Jastrzębska, O Forre, A Venalis, J Pazdur**

*Ann Rheum Dis* 2005;**64**:165–166. doi: 10.1136/ard.2003.019158

A recognised feature of rheumatoid arthritis (RA) is its clinical heterogeneity, which may be caused by HLA factors. This theory is supported by observations that relatively severe and mild RA are associated with, respectively, DRB1*04[1] and DRB1*01.[2–4] Further, comparisons between populations show that the disease course in the Mediterranean is milder than in northern Europe,[5–8] correlating with a higher frequency of DRB1*01 and lower frequency of DRB1*04 in the former than in the latter region.[6 7 9]

## METHODS AND RESULTS

Poland and Lithuania are neighbouring central European countries. During clinical practice we noted that RA was less severe in Lithuanian than in Polish patients. To test this observation we prospectively analysed 24 Polish and 20 Lithuanian randomly recruited patients with recent onset RA diagnosed by modified American Rheumatism Association criteria. The patients had a similar mean (SD) age (53.6 (11.4) *v* 57.0 (14.2) years), mean (SD) age of RA onset (52.2 (11.2) *v* 55.8 (14.4) years), mean (SD) disease duration (16.9 (13.6) *v* 13.9 (9.8) months), rheumatoid factor (RF) seropositivity (50% *v* 40%), and mean (SD) Steinbrocker stage (1.5 (0.5) *v* 1.5 (0.5)), respectively for Polish and Lithuanian cohorts. The only significant difference was higher frequency of women with RA among the Polish group (22/24 (92%) *v* 10/20 (50%), $p<0.01$).

The first assessment of the patients was performed before the start of treatment and then after 2 months and after 1 year. The analysis at baseline indicated significantly more severe disease among Polish than Lithuanian patients (table 1). After 2 months, probably as a result of treatment which was more aggressive in the Poles, disease activity in both groups decreased and most differences present at baseline were no longer seen (table 1). The clinical and laboratory results were similar also after 1 year (table 1), but radiographic analysis performed at that time showed an increase in mean (SD) erosion score and Larsen score in Poles (respectively, 0.7 (1.3) and 4.0 (6.5)), but not in Lithuanians. The difference in Larsen score progression between the two cohorts was significant ($p<0.05$, *t* test).

Because of the relative excess of men among the Lithuanian patients we also performed analysis after adjusting for the sex of the patients. We found that all the differences seen between the cohorts at baseline on univariate analysis (table 1) were also present in the multivariate analysis controlling for sex (not shown).

The participants of the study and some additional patients (in total 49 Poles and 32 Lithuanians) were genomically typed for DRB1* 01 and DRB1*04, and 158 Poles[10] and 134 Lithuanians fully typed for DRB1 (low resolution) constituted ethnically matched controls. When patients were compared with their respective controls a significant increase