

Increased IgA antibodies to cytokeratins in the spondyloarthropathies

A A Borg, N B Nixon, P T Dawes, D L Matthey

Abstract

Objectives—Increased levels of IgA antibodies to cytokeratin-18 (CK-18) and epidermal keratins (EpK) in the sera of patients with rheumatoid arthritis (RA) have been demonstrated previously. In the present study investigations were carried out to determine whether levels of these autoantibodies were also raised in the spondyloarthropathies, and whether there was any association with particular disease manifestations.

Methods—Using specific enzyme linked immunosorbent assays (ELISA) measurements were taken of IgA, IgG and IgM antibodies to EpK and to CK-18 in the sera of patients with psoriatic arthropathy, ankylosing spondylitis (AS), Reiter's syndrome, psoriasis and in normal subjects.

Results—IgA antibodies to both EpK and CK-18 were significantly increased in sera from patients with psoriasis and psoriatic arthropathy but not in the sera from the patients with AS or Reiter's syndrome, or in the controls. In psoriatic arthritis, however, these levels were significantly higher only in those patients with peripheral joint disease and not in those with axial arthritis alone. There was no significant increase in antibody levels in patients with AS or Reiter's syndrome. There were no differences in the levels of IgG or IgM antibodies to CK-18 or EpK between the patient groups and controls.

Conclusions—Raised levels of IgA antibodies to CK-18 and EpK in psoriatic arthropathy and psoriasis probably reflect exposure of intracellular cytokeratin antigens to the immune system after damage to cytokeratin containing cells, and suggests a common pathogenic mechanism in these conditions which involves production of cytokeratin autoantibodies. In patients with psoriatic arthropathy, such a mechanism appears only to be operating in patients with peripheral joint involvement and not in those with axial arthritis.

(*Ann Rheum Dis* 1994; 53: 391–395)

Cytokeratins are a constituent of the cytoskeleton, being found mainly in epithelial cells but also in some lymph node associated follicular dendritic cells and in certain endothelial and smooth muscle cells.^{1,2} There are at least 19 different cytokeratins comprised

of two families; an acidic type (Type I, nos 9–19) and a basic or neutral type (Type II, nos 1–8). We and others^{2,3} have demonstrated CK-18 in the endothelial cells of synovial blood vessels, and have recently shown that IgA antibodies to CK-18 and EpK are raised in patients with RA. IgG and IgM antibodies to cytokeratins were not significantly different to the normal group.⁴

We initially proposed that damage to synovial endothelial cells during inflammatory synovitis leads to the production of autoantibodies to CK-18.⁴ However, our finding of a significant difference in IgA, but not IgG or IgM antibodies, may indicate that damage to cells in a mucosal site (for example, in the gut) is involved in the production of such antibodies, such as CK-18 and is one of the major cytokeratins found in the epithelial cells lining the gut. Further studies in our laboratory have shown high levels of these antibodies in patients with coeliac disease and inflammatory bowel disease (unpublished data).

An association between the spondyloarthropathies and abnormalities of the gut and mucosal immune system is well documented.^{5,6} We therefore carried out an investigation of anti-cytokeratin antibody levels in patients with AS, psoriatic arthritis, and in Reiter's syndrome. We also examined a group of patients with psoriasis for comparison with the spondyloarthropathies. In addition, we explored whether there are any associations between anti-cytokeratin antibodies and particular disease manifestations, and whether there are any correlations with serum IgA and laboratory measures of inflammation.

Patients and methods

PATIENTS

Serum specimens were obtained from 20 patients with AS, 42 patients with psoriatic arthropathy (skin involvement varied from mild to severe), 33 patients with severe psoriasis without any arthropathy, and 11 patients with Reiter's syndrome. The demographic data are shown in table 1. Sera was also obtained from 58 healthy control subjects consisting of department staff and blood donors. Local ethical committee approval was obtained for the collection of all samples.

All the patients with arthritis were negative for rheumatoid factor (Latex). The patients with psoriatic arthritis fulfilled the criteria of Moll and Wright,⁷ while the patients with AS fulfilled the 1966 New York Criteria.⁸

Department of Rheumatology, Freeman Hospital, Newcastle upon Tyne, United Kingdom
A A Borg

Staffordshire Rheumatology Centre, Stoke on Trent, United Kingdom
N B Nixon
P T Dawes
D L Matthey

Correspondence to:
Dr A A Borg,
Department of Rheumatology,
Freeman Hospital,
High Heaton,
Newcastle upon Tyne
NE7 7DN,
United Kingdom.

Accepted for publication
2 March 1994

Table 1 Demographic data

	Psoriasis	Psoriatic arthropathy	Ankylosing spondylitis	Reiter's syndrome	Controls
Number	33	42	20	11	58
Age	47 (16-83)	46 (14-76)	43 (31-60)	31 (18-45)	41 (26-73)
Sex (M:F)	15:18	28:14	16:4	8:3	20:38
Disease duration (months)	195 (2-480)	53 (2-168)	71.4 (5-138)	2 (1.1-2.7)	—

Values for age and disease duration are means with ranges in brackets.

ELISA FOR MEASUREMENT OF ANTIBODIES TO EpK AND CK-18

IgA, IgG and IgM antibodies to EpK and CK-18 were measured using ELISA as described previously.⁴ All results were expressed as arbitrary units (AU) based on a standard serum for each particular antibody. The cytokeratin preparations used to coat the plates had previously been characterised by Western Blotting.⁴

To discover whether antibodies to CK-18 were cross-reactive with epidermal keratins, we carried out a blocking experiment in which we added EpK to 40 sera (20 psoriasis and 20 psoriatic arthritis) before measuring antibodies to CK-18. Each serum sample was diluted 1:80 and divided into two aliquots. One aliquot was preincubated with 50 micrograms/ml of human epidermal keratin overnight at 37°C. The other aliquot was incubated without any EpK. The reactivity of both sets of samples with CK-18 was then measured in a standard ELISA, and the values were compared.

SERUM IgA MEASUREMENT

Serum IgA was measured using a standard ELISA technique. Some samples were also measured by means of a radial immunodiffusion assay to cross-check the ELISA results.

STATISTICAL ANALYSIS

Data were analysed with the Mann-Whitney U test for differences between patient and control groups. Correlations were carried out using Spearman's rank correlation. A value of $p < 0.05$ was considered significant.

Results

ELISA ASSAY FOR CYTOKERATIN ANTIBODIES

A significant difference ($p < 0.0001$) in IgA antibody levels to both CK-18 and epidermal keratin (table 2) was detected in the sera from patients with psoriasis and psoriatic arthropathy compared with sera from the normal controls, and patients with AS or Reiter's syndrome. The upper limit of the normal values for serum IgA anti-CK-18 levels was defined by the upper 95% confidence interval value in the sera for the 58 healthy controls. The same criterion was used for antibodies to EpK.

Using this criterion, only 1.7% of the normal volunteers had elevated serum IgA antibodies to either CK-18 or EpK. In contrast, elevated serum IgA antibodies to CK-18 were found in

75% of the patients with psoriasis and 58% of the patients with psoriatic arthropathy. Raised levels of IgA antibodies to EpK were found in 83% of the patients with psoriasis and 50% of those with psoriatic arthropathy. There was no significant difference in the levels of IgG or IgM antibodies to CK-18 or EpK between the normal sera and those from the patient groups.

A significant correlation was found between the IgA antibody levels to CK-18 and EpK in the patients with psoriatic arthropathy ($r = 0.43$, $p < 0.05$), and in the patients with psoriasis alone ($r = 0.65$, $p < 0.03$). We found that serum IgA levels in psoriasis (mean = 5.55 mg/ml) and psoriatic arthropathy (mean = 5.26 mg/ml) were both significantly higher than in normal controls (mean = 2.4 mg/ml, $p < 0.0001$). There was, however, no correlation between serum IgA levels and IgA antibody levels to CK-18 or EpK in either group of patients.

We investigated whether there was any difference in the levels of IgA antibodies to CK-18 or EpK in patients with psoriatic arthritis with different clinical patterns. The results in table 3 show that IgA antibodies to both CK-18 and EpK are significantly higher in patients with peripheral joint involvement compared with those with axial arthritis alone. Within the group of psoriatic patients with peripheral joint involvement no difference was noted between the various clinical patterns.

Additionally, no relationship was found between antibody levels and a number of acute phase measures including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and serum alkaline phosphatase (table 4).

CROSS-REACTIVITY OF ANTI-CK-18 ANTIBODIES WITH EpK

Twenty psoriatic arthropathy and 20 psoriasis sera were pre-incubated with EpK (50 micrograms/ml), then tested for the ability of IgA antibodies to bind to CK-18 coated plates. Binding was then compared with that of the untreated sera. Only 5% of psoriatic arthropathy sera and 10% of psoriasis sera were inhibited by more than 25% (fig). In 85% of psoriatic arthropathy sera and 75% of psoriasis sera there was no inhibition of binding.

As a positive control we also tested the binding of EpK treated sera to EpK coated plates and found that 40% of psoriatic arthropathy sera and 60% of psoriasis sera were inhibited by 25% or more. Total inhibition of binding of IgA antibodies to EpK coated plates was never achieved. However, it is likely that competition from IgG and IgM antibodies for binding to the added EpK would probably prevent blocking of all IgA specific EpK antibodies.

Our results suggest that in the majority of patients with psoriatic arthropathy and psoriasis there is little or no cross-reactivity of IgA antibodies to CK-18 with EpK. Only in a small minority (5-10%) is significant cross-reactivity seen.

Table 2 ELISA results

	Psoriasis	Psoriatic arthropathy	Ankylosing spondylitis	Reiter's syndrome	Controls
CK-18 IgA	24.2 (18.1-31.2)***	24.1 (16.3-32.2)***	9.0 (7.6-10.4)	8.2 (3.4-17.9)	9.4 (8.2-10.1)
CK-18 IgG	14.4 (5.1-22.2)	11.3 (8.1-14.3)	15.2 (12.6-17.8)	19.1 (13.7-24.5)	13.0 (7.1-19.3)
CK-18 IgM	12.2 (8.3-15.1)	12.2 (9.1-14.4)	13.1 (10.9-15.1)	13.2 (10.0-16.3)	16.3 (11.1-21.0)
EK IgA	19.3 (15.1-22.4)***	17.2 (14.1-20.3)***	7.1 (6.4-7.8)	6.1 (5.2-7.0)	7.2 (5.1-9.3)
EK IgG	11.9 (4.9-19.8)	12.1 (5.9-18.1)	14.1 (6.0-34.0)	15.1 (8.4-21.7)	14.9 (9.9-19.3)
EK IgM	16.3 (11.8-20.2)	13.4 (8.1-17.8)	21.2 (2.2-40.1)	15.5 (13.2-17.7)	19.2 (13.4-25.9)

*** = $p < 0.0001$.

Values are means with 95% CI in brackets.

All values are in arbitrary units (see text for details).

Table 3 Relationship between clinical patterns of psoriatic arthritis and IgA antibodies to cytokeratins

Pattern	Number	IgA EpK	IgA CK-18
Classical	11	18.2 (16.5-19.8)**	24.0 (14.8-33.2)**
Pauciarticular	14	16.9 (12.0-21.9)**	21.2 (13.2-29.1)**
Symmetrical	11	26.7 (9.9-43.4)**	29.2 (12.5-45.8)**
Spondylitis	6	10.5 (5.03-15.9)	9.9 (1.5-18.3)
Psoriasis	33	19.3 (15.1-22.4)**	24.2 (18.1-31.2)**

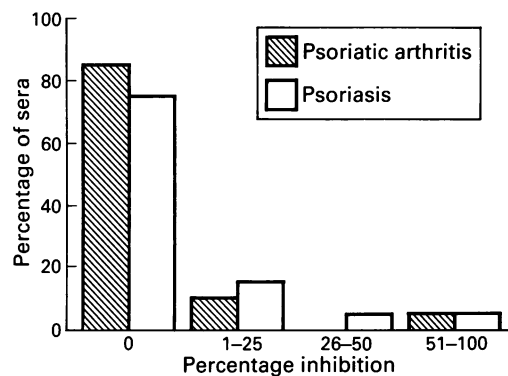
** = $p < 0.001$; values are means with 95% CI in brackets.

Table 4 Relationship between acute phase response and IgA anti-cytokeratin antibody levels in psoriatic arthritis

ELISA value (AU)	IgA Anti-CK-18		IgA Anti-EpK	
	<10	>10	<10	>10
Number	16	21	15	5
ESR (mm/hr)	30	31	29	46
CRP (U/L)	27	29	30	38
Alk Phosph (U/L)	111	98	104	108

AU values represent upper 95% CI in normal control sera.

Rest of values are group means.



Cross-reactivity of IgA anti-CK-18 antibodies with EpK. Sera were preincubated with EpK before incubation with CK-18 coated plates. Binding of IgA antibodies in treated sera was compared with untreated sera and the percentage inhibition was calculated. Little/no inhibition was seen in the majority of sera.

Discussion

Our results demonstrate that levels of IgA autoantibodies to CK-18 and EpK are significantly higher in patients with psoriasis or psoriatic arthropathy than in normal controls or patients with AS or Reiter's syndrome. In the psoriatic arthritis group it is only patients with peripheral joint involvement that have elevated antibody levels. This suggests that psoriatic arthritis with peripheral joint disease may share a common pathogenic mechanism with psoriasis which involves production of IgA antibodies to cytokeratins. This mechanism does not appear to be shared with psoriatic arthritis when only axial disease is involved, nor with ankylosing spondylitis. It also appears

that such a mechanism is not operative in Reiter's syndrome where the disease is likely to be of shorter duration and less likely to be associated with chronic synovitis.

Our findings are in contrast to those of Jurik *et al*⁹ who, using an indirect immunofluorescent technique with rat oesophageal keratin as antigen, failed to detect any 'anti-keratin' antibodies in patients with psoriatic arthritis. As discussed previously,⁴ there is considerable doubt as to whether this type of assay is measuring anti-keratin antibodies. Indeed recent evidence indicates that the antigen detected by this technique is flaggrin, a cytokeratin filament aggregating protein.¹⁰

As we initially suggested for patients with RA, damage to cells of the synovial endothelium may explain the presence of increased levels of antibodies to CK-18 in patients with psoriatic arthritis with peripheral joint disease. The reason for an IgA antibody response to CK-18 in psoriasis is not clear, since damage to synovial blood vessels would not be expected in this condition.

The raised levels of antibodies to EpK may be easier to understand in view of the epidermal involvement in this condition. However, CK-18 is not present in normal or psoriatic epidermis,¹¹ although it is expressed in sweat glands, Merkel cells, hair follicles and the nail bed matrix.¹²⁻¹⁴ It does not appear that elevated IgA antibodies to CK-18 can be explained by cross-reactive antibodies to EpK since most patients showed little or no evidence of cross-reactivity. Although there is a significant correlation between levels of IgA antibodies to CK-18 and EpK it appears that these do not represent the same (cross-reactive) antibodies.

There is no direct relationship between levels of IgA antibodies to cytokeratins and levels of serum IgA, even though all of the conditions studied, apart from Reiter's syndrome, are characterised by elevated levels of serum IgA. It has been proposed that elevated levels of serum IgA in patients with AS are related to stimulation of the mucosal compartment,^{15 16} although a recent study has shown that the increase in IgA levels is not due to a significant increase in secretory IgA.¹⁷ We have not investigated levels of secretory IgA in the sera of our patients with psoriasis and psoriatic arthropathy. It is possible that levels of IgA antibodies to cytokeratins are related to secretory IgA levels, but further studies are needed to address this question.

The possibility of a gut-related antigen source for generation of IgA antibodies to CK-

18 cannot be ruled out. Along with CK-8, CK-18 is the major cytokeratin in the epithelial cells of the gut, so any damage to these cells may lead to exposure of the intracellular CK-18 to cells of the immune system. The concept of dermatogenic enteropathy to link skin with gut disorders was introduced by Shuster and Marks in 1965,¹⁸ although they later found that evidence of intestinal changes in small bowel biopsies from patients with psoriasis and eczema were non-specific and similar in controls.¹⁹

However, Barry *et al*²⁰ demonstrated that in patients with severe psoriasis, the jejunal mucosal architecture differed significantly from that in controls and suggested that the mucosal absorptive surface of the small bowel may be decreased. Furthermore, the concept of 'subclinical' bowel inflammation presenting with arthritis is well recognised. Simenon *et al*⁶ with a combination of ileocolonoscopy and biopsy revealed subclinical inflammatory gut lesions in 67% of patients with unclassified seronegative spondyloarthropathies.

Other extra-articular features which occur in the spondyloarthropathies include uveitis, mouth ulcers and urethritis, all of which may involve damage to cytokeratin-containing tissues. If indeed such damage is responsible for increased production of IgA autoantibodies to CK-18, then such a mechanism would appear to occur only in patients with psoriatic arthropathy and peripheral joint disease, and not in those patients with spondylitis or Reiter's syndrome. Thus the grouping together of seronegative spondyloarthropathies on the basis of their negativity for IgM rheumatoid factor, the increased prevalence of HLA-B27 and their spectrum of clinical presentations, may mask some of the differences in their pathogenesis.

A genetic component in both psoriasis and psoriatic arthritis is well recognised. However, psoriatic arthritis only occurs in about 7% of patients with psoriasis,²¹ and there are differences between these groups in their association with various HLA antigens. Many studies have confirmed an increased prevalence of HLA-B27 in psoriatic arthritis,²²⁻²⁴ reflecting the frequent occurrence of sacroiliitis and spondylitis in these patients.

Our results suggest that such patients, together with AS patients, are unlikely to have raised levels of antibodies to cytokeratins. It is known that in patients with psoriasis there is an increased frequency of Cw6,²⁴ while in patients with arthritis as well, there is an increase in A26, B38 and DR7.²⁵⁻²⁷ Further studies are needed to show whether elevated levels of IgA antibodies to cytokeratins are associated with any particular HLA types.

Another possible explanation for an elevated antibody response to cytokeratins may be provided by cross-reactivity of such antibodies with another antigen (for example, a bacterial or viral component). Previous studies^{28, 29} have demonstrated antibodies which are cross-reactive with cytokeratins and the glycine/alanine repeat sequence (P62) of Epstein-Barr nuclear antigen-1 (EBNA-1). Furthermore, we

have previously compared the amino acid sequence of CK-18 with P62 and found two peptides of 13 and 15 amino acids long (numbers 54-68 and 62-74) with 53.8% and 53.3% homologies respectively.⁴ So far, we have failed to detect any IgA antibodies to P62 in psoriasis or psoriatic arthritis and have been unable to demonstrate any differences between IgG antibodies to P62 between both conditions, RA or normal controls (unpublished observations).

We have no evidence at present that anti-cytokeratin antibodies are pathogenic. It has been suggested that the normal role of anti-cytokeratin antibodies is to eliminate cell breakdown products,³⁰ so an increased production of such antibodies might be expected in response to pathological cell damage and/or increased cell turnover. In some conditions the tissue damage may be accompanied by a defect in immune function (for example, polyclonal B cell activation) leading to further enhancement of autoantibody production. It is clear that IgA anti-cytokeratin antibodies are not specific to a particular disease condition, and are most likely to represent an epiphenomenon in diseases such as psoriasis and psoriatic arthropathy. The absence of a significant cytokeratin response in psoriatic arthritis with spondylitis, and in AS and Reiter's syndrome, suggest that there are clear differences in the pathogenetic or immunogenetic mechanisms involved in these conditions.

We thank Dr M Bhavnani for providing the sera from the normal controls and Drs M Wilkinson, D Fitzgerald and A H M Heagerty for providing the sera from the patients with psoriasis.

We also thank Drs T E Hothersall, M F Shadforth and A G Smith, for allowing us to study their patients.

This project was supported by a grant from the Haywood Rheumatism Research Development Foundation (HRRDF).

- 1 Franke W W, Moll R. Cytoskeletal components of lymphoid organs. *Differentiation* 1987; **36**: 145-63.
- 2 Jahn L, Fouquet B, Rohe K, Franke W W. Cytokeratins in certain endothelial cells and smooth muscle cells of two taxonomically distant vertebrate species, *Xenopus laevis* and man. *Differentiation* 1987; **36**: 234-54.
- 3 Matthey D L, Nixon N, Wynn-Jones C, Dawes P T. Demonstration of cytokeratin in endothelial cells of the synovial microvasculature in situ and in vitro. *Br J Rheumatol* 1993; **32**: 676-82.
- 4 Borg A A, Dawes P T, Matthey D L. Antibodies to Cytokeratin-18 in Rheumatoid Arthritis. *Arthritis Rheum* 1992; **36**: 229-33.
- 5 Mielants H, Veys E, Cuvelier C. HLA-B27 related arthritis and bowel inflammation: part 2. Ileocolonoscopy and bowel histology in patients with HLA-B27 related arthritis. *J Rheumatol* 1985; **12**: 293-8.
- 6 Simenon G, Van Gossum A, Adler M, Rickaert F, Appelboom T. Macroscopic and microscopic gut lesions in Seronegative Spondyloarthropathies. *J Rheumatol* 1990; **17**: 1491-4.
- 7 Moll J M H, Wright V. Psoriatic Arthritis. *Sem Arthritis Rheum* 1973; **3**: 55-78.
- 8 Bennett P H, Burch T A. *Population studies of the rheumatic diseases*. Amsterdam, Excerpta Medica Foundation, 1968; 305.
- 9 Jurik A G, Graudal H, Kirstein H. Lack of antikeratin antibodies in patients with palmoplantar pustular eruptions and arthropathy. *Arch Dermatol Res* 1989; **281**: 185-7.
- 10 Simon M, Girbal E, Sebbag M, *et al*. The cytokeratin filament-aggregating protein flaggrin is the target of the so-called "anti-keratin" antibodies, autoantibodies specific for Rheumatoid Arthritis. *J Clin Invest* 1993; **92**: 1387-93.
- 11 Markey A C, Lane E B, Churchill L J, MacDonald D M, Leigh I M. Expression of Simple Epithelial Keratins 8 and 18 in Epidermal Neoplasia. *J Invest Dermatol* 1991; **11**: 763-70.
- 12 Lane E B, Bartek J, Purkis P E, Leigh I M. Keratin antigens in differentiating skin. *Ann New York Acad Sci* 1985; **455**: 241-58.

- 13 Heid H W, Moll I, Franke W W. Patterns of expression of trichocytic and epithelial cytokeratins in mammalian tissues. I Human and bovine hair follicles. *Differentiation* 1988; **37**: 137-57.
- 14 Moll R, Moll I, Franke W W. Identification of Merkel cells in human skin by specific cytokeratin antibodies. *Differentiation* 1984; **28**: 136-54.
- 15 Cowling P, Ebringer R, Ebringer A. Association of inflammation with raised serum IgA in ankylosing spondylitis. *Ann Rheum Dis* 1980; **39**: 545-9.
- 16 Calguneri M, Swinburne L, Shinebaum R, Cooke E M, Wright V. Secretory IgA: immune defence pattern in Ankylosing Spondylitis and Klebsiella. *Ann Rheum Dis* 1981; **40**: 600-4.
- 17 Hocini H, Iscaki S, Benlahrache C, Vitalis L, Chevalier X, Larget-Piet B, Bouvet J-P. Increased levels of serum IgA as IgA1 monomers in Ankylosing Spondylitis. *Ann Rheum Dis* 1992; **51**: 790-2.
- 18 Shuster S, Marks J. Dermatogenic enteropathy: a new cause of steatorrhea. *Lancet* 1965; **1**: 1367-8.
- 19 Marks J, Shuster S. Small intestinal mucosal abnormalities in various skin diseases—fact or fancy? *Gut* 1970; **11**: 281-91.
- 20 Barry R E, Salmon P R, Read A E, Warin R P. Mucosal architecture of the small bowel in cases of psoriasis. *Gut* 1971; **21**: 873-7.
- 21 Leczinsky C G. The incidence of arthropathy in a ten year series of psoriasis cases. *Acta Derm Venerol (Stockh)* 1948; **28**: 483-91.
- 22 McClusky O E, Lordon R E, Arnett F C. HL-A27 in Reiter's syndrome and psoriatic arthritis; a genetic factor in disease susceptibility and expression. *J Rheumatol* 1974; **1**: 263-8.
- 23 Metzger A L, Morris R I, Bluestone R, Terasaki P I. HL-A W27 in psoriatic arthropathy. *Arthritis Rheum* 1975; **18**: 111-5.
- 24 Armstrong R D, Panayi G S, Welsh K I. Histocompatibility antigens in psoriasis, psoriatic arthropathy, and ankylosing spondylitis. *Ann Rheum Dis* 1983; **42**: 142-6.
- 25 Roux H, Mercier P, Maestracci D, et al. Psoriatic arthritis and HLA antigens. *J Rheumatol* 1977; **4**: 64-5.
- 26 Espinoza L R, Vasey F B, Oh J M, Wilkinson R, Osterland C K. Association between HLA-B38 and peripheral psoriatic arthritis. *Arthritis Rheum* 1978; **21**: 72-5.
- 27 Murray C, Mann D L, Gerber L N, et al. Histocompatibility alloantigens in psoriasis and psoriatic arthritis. Evidence for the influence of multiple genes in the major histocompatibility complex. *J Clin Invest* 1980; **66**: 670-5.
- 28 Birkenfeld P, Haratz N, Kelin G, Sulitzeanu D. Cross-reactivity between EBNA-1 p107 peptide, collagen and keratin: implications for the pathogenesis of Rheumatoid Arthritis. *Clin Immunol Immunopathol* 1990; **54**: 14-25.
- 29 Baboonian C, Venables P J W, Williams D G, Williams R O, Maini R N. Cross reaction of antibodies to a glycine/alanine repeat sequence of Epstein-Barr virus nuclear antigen-1 with collagen, cytokeratin and actin. *Ann Rheum Dis* 1991; **50**: 772-5.
- 30 Senecal J L, Ichiki S, Girard D, Raymond Y. Autoantibodies to nuclear lamins and intermediate filament proteins: natural, pathologic or pathogenic. *J Rheumatol* 1993; **20**: P 211-219.