

MATTERS ARISING

Heavy cigarette smoking and RA

Hutchinson *et al* concluded that prolonged heavy cigarette smoking, but not smoking itself, is strongly associated with rheumatoid arthritis (RA), particularly in patients without a positive family history.¹ The authors proposed that increased rheumatoid factor (RF) production resulting from heavy smoking exposures explains, in part, the relation of increasing cumulative pack years smoked and the greater association with RA.¹

No data were presented in that study on the extent of smoking and RF positivity or its titres.¹ The proposal¹ would be strengthened if heavy smoking were associated with RF, either when clinical disease began or when patients were studied at hospital rheumatology clinics. Others have proposed that tobacco smoke exposure triggers RF production, thereby contributing to the onset of RA.^{2,3} However, no significant association was seen between current smoking and IgM RF positivity in the earlier multicase family study,² either among 41 patients with RA or their non-rheumatoid relatives—168 blood and 36 non-blood relatives.⁴

Although heavy cigarette smoking may be associated with RF during clinical disease, it is still relevant to determine whether it is associated with RA, either in the presence or absence of RF positivity. A further question remains as to the sequence of occurrences. Does heavy smoking first induce RF production, which later contributes to RA?¹⁻³ Alternatively, might RA be induced first and RF produced later? Prospective, rather than cross sectional, studies are needed to answer these questions. Prospective data suggest that reported smoking of 30 or more cigarettes daily (CS 30+/day) predisposes to RA risk independently from RF positivity or positive family history.^{5,6}

These complex relationships were investigated in a case-control study nested within a community based cohort (n=21 061 adults)

enrolled in 1974. For each of the 18 male and 36 female unrelated incident patients who satisfied American College of Rheumatology criteria for RA, identified in 1994, four controls from the entry cohort were matched for age, sex, and race (all white subjects).^{5,6} Table 1 shows the number of patients before they developed RA and their respective controls who reported heavy cigarette smoking (CS 30+/day) at baseline. Heavy smoking was not associated with pre-RA RF+ status, but was associated significantly (p=0.001) with patients who were RF- at baseline. The highest observed odds ratio (OR) was in 15 sets in which the patient was RF- at baseline and continued to be RF- after active disease developed (OR 21.5, 95% CI 1.9 to 122.5, p=0.005). The ORs were similar for sets in which the patients had positive or negative FDR status, but was significant (p=0.012) only in the larger FDR- subset (table 1).

The hypothesis that cigarette smoking contributes to RA partly by RF production¹⁻³ is attractive. However, critical substantiation in prospective and cross sectional studies is currently lacking. Available prospective data (table 1)^{5,6} suggest that alternative mechanisms may be more likely. For example, long term cigarette smoking causes general vascular endothelial damage,⁷ and smoking is significantly associated with vasculitis in active RA.^{8,9} Heavy smoking was proposed¹ to contribute to RA risk through its endothelial and microvascular effects, perhaps through nitric oxide pathways,¹⁰ rather than by RF production primarily.¹⁻³

Whether or not heavy smoking differentially associates with RA depending upon family history of disease¹ is as complex as the dilemmas of RF contributions to onset (table 1). Our FDR+ female patients had a significantly (p<0.001) younger mean age at clinical onset (45.6 years) than their counterparts (57.1 years). Might such earlier onset of RA among patients with a positive family history, as also noted by Hutchinson *et al*,¹ have influenced their behaviour to lower cumulative exposures to cigarette smoking compared with their counterparts?²

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Authors' reply

We read the letter of Masi *et al* with interest and are pleased to have an opportunity to discuss the questions they have raised. Our study group was derived from an area of northwest England made up principally of people in a lower socioeconomic class, in contrast with other UK studies.¹ Although we did not record the presence of rheumatoid factor (RF) in our patients for the purpose of this study, seropositivity in our RA patient group was high, approximately 80-90%. This is comparable with Glasgow, an area in Scotland with a similarly high level of social deprivation, where 96% of randomly selected patients with RA were found to be seropositive.² We therefore decided to compare the smoking history of familial and sporadic patients with RA rather than compare seropositive and seronegative patients.

Published reports almost uniformly suggest that cigarette smoking is associated with seropositive rather than seronegative RA. Cigarette smoking is associated with the development of seropositivity in healthy subjects^{3,4} and, furthermore, there is a dose related phenomenon for the development of seropositive RA.⁵ It has also been established that the development of seropositive RA is greatly increased in healthy subjects who are persistently seropositive.⁶ Wolfe noted a significant trend in patients with RA of

Table 1 Numbers of pre-RA cases and matched controls reporting heavy cigarette smoking (CS 30+/day) at baseline by relevant categories and odds ratios (ORs) with 95% confidence intervals (95% CIs) for developing ACR+ rheumatoid arthritis

Categories	Pre-RA cases		Respective matched controls		OR	95% CI
	Number	CS 30+/day (%)	Number	CS 30+/day (%)		
Total subjects	54	13 (24)	216	19 (9)	3.3	1.4 to 7.7
Men	18	8 (44)	72	14 (19)	3.3	1.0 to 11.4
Women	36	5 (14)	144	5 (3)	4.5	1.0 to 19.4
FDR+*	11	5 (45)	44	9 (20)	3.2	0.7 to 16.3
FDR-	43	8 (19)	172	10 (6)	3.7	1.2 to 11.2
Pre-RA RF+	12	2 (17)§	48	7 (15)§	1.2	0.2 to 7.9
Pre-RA RF-	42	11 (26)	168	12 (7)	4.6	1.5 to 10.2
Entry and post-RA RF-	15	4 (27)	60	1 (2)	21.5	1.9 to 122.5
Conversion of pre-RA RF- to RF+†	27	7 (26)	108	7 (6)	5.1	1.4 to 18.5
FDR- and pre-RA RF-	33	7 (21)	132	5 (4)	6.8	1.8 to 27.4
Mild course of RA‡	19	8 (42)	76	11 (14)	4.3	1.2 to 15.1
Non-mild course of RA‡	35	5 (14)	140	8 (6)	2.8	0.7 to 10.2

*FDR+ is a positive history of RA in a first degree relative as determined for patients in 1997, and reported in 6/18 (33%) male patients and 5/36 (14%) female patients.

†Conversion of RF- at baseline to RF+ after clinical onset of RA.

‡Course of RA over 3-20 (median 11) years of clinical disease was determined by the patients' rheumatologist according to predefined criteria.

§No association of CS 30+/day with pre-RA RF+ (p=0.99).

increasing RF titre with pack years smoked.⁷ Yet although the development of rheumatoid joint erosions, nodules, and disability was significantly increased by cigarette smoking, he found that this was independent of RF production.

We suspect that cigarette smoking and RF are strongly interlinked, but other mechanisms, as suggested by Masi, may also be at work. For example, cigarette smoke contains numerous oxidising agents that can inactivate α_1 -proteinase inhibitor (α_1 -PI),⁸ the natural inhibitor of neutrophil elastase (NE), a serine proteinase that can degrade articular cartilage.⁹ Cigarette smoke can also prime neutrophils to degranulate and discharge NE,¹⁰ activate macrophages to produce matrix metalloproteinases,¹¹ up regulate production of interleukin 1 β and interleukin 8¹² and down regulate interleukin 1 receptor antagonist,¹³ and interleukin 10.¹⁴ Furthermore, cigarette smoking induces disease processes in a specific dose dependent fashion (independent of current smoking status), such as pulmonary emphysema, in which there is increased neutrophil priming, increased oxidised α_1 -PI and α_1 -PI-NE complexes (indicative of increased NE activity).⁸ Therefore a heavy smoker may have an otherwise benign short lived inflammatory arthritis modified by the mechanisms outlined above and develop RA.

Whether RA increases or decreases cigarette consumption remains uncertain. Our controls had a pack year total estimated at entry to the study and not at the time of their disease onset. We are, however, unaware of any data to suggest that RA increases cigarette consumption. Indeed, a study by Harrison *et al* observed that 18% of all smokers with polyarthritis stopped smoking within three years of disease onset as opposed to <1% of non-smoking patients who started smoking during this period.¹⁵

Other important questions remain unanswered. For example, does increased cumulative cigarette consumption increase RA susceptibility independently of RF production? (Data presented here by Masi *et al* only consider cigarette consumption at one time point.) If so, do these subjects have an increased prevalence of circulating levels of α_1 -PI-NE complexes, high levels of oxidised and inactivated α_1 -PI complexes, and therefore pulmonary emphysema?

We welcome the heightened interest in the relationship between smoking and RA and look forward to the establishment of new studies designed to answer some of the interesting questions raised by recent studies.

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Rheumatoid arthritis associated with ulcerative colitis

I was interested to read the letter on "Rheumatoid arthritis associated with ulcerative colitis" by Boyer *et al* published recently in the *Annals*,¹ and would like to make the following comments. Studies in patients with established Crohn's disease (CD) have generally supported the predominance of Th1 responses.^{2,3} In ulcerative colitis, although enhanced humoral immunity has been described, evidence for classical Th2 predominance remains to be demonstrated. On the other hand, it has been shown that interleukin 15 is overexpressed in the inflamed mucosa of patients with inflammatory bowel disease at the level of macrophages.⁴ Similar findings have been reported in patients with rheumatoid arthritis (RA).⁵

As shown in this case, it is sometimes quite difficult to distinguish by clinical manifestations alone between two diseases which start almost at the same time. However, the presence of a positive rheumatoid factor and DR1 genotype are arguments for RA. The existence of polymorphisms affecting other genes may take place in such type of arthritis.⁶

Results obtained with anti-tumour necrosis factor monoclonal antibody to prevent mucosal inflammation in CD,⁷ suggest that such an approach may also be of interest in this unusual situation.

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Authors' reply

We thank Dr Mosquera-Martinez for his letter and are happy that our report has stimulated active discussion and suggestions.¹ Indeed, control of disease was difficult even when combining methotrexate 15 mg/week IM, salazopyrine 3 g/day, and prednisone 10 mg/day. The patient still had active arthritis affecting wrists and hands with an erythrocyte sedimentation rate (ESR) of 47 mm/1st h. Furthermore, she also had active colitis, and current treatment prevented surgery for colon anastomosis.

Accordingly, infliximab was started following the now classical rheumatoid arthritis protocol.² Seven months later, steroids could be stopped. Surgery for permanent colon anastomosis could then be performed with success and with no healing delays. When last seen in July 2001, she showed major improvement, with no pain at night and no morning stiffness. She had gained weight and had no sign of active colitis. The ESR was 26 mm/1st h and C reactive protein <4 mg/l.

Such follow up extends the concept of common mechanisms between rheumatoid arthritis and ulcerative colitis. Both diseases appear to depend, at least in part, on the contribution of tumour necrosis factor α .

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Intramuscular methotrexate in inflammatory rheumatic disease

We read with great interest the recent letter entitled "Is parenteral methotrexate worth trying?" by Osman and Mulherin.¹ There has been an increased use of intramuscular methotrexate (IM-MTX) in our department in the past two years, leading to an increased workload in the nurse-led monitoring clinics and in the cost. This has prompted us to review the clinical utility of switching patients to IM-MTX. In addition, we have recorded patients' experiences, focusing chiefly on patient satisfaction, with this treatment.

Medical case notes of 31 patients who had started treatment with IM-MTX, identified from our database, were examined. The clinical diagnosis, previous drug treatment, reason for changing to IM-MTX, efficacy, and side effects were noted. In addition, the patients were asked to complete a questionnaire, looking at patient satisfaction and preferred venue for injections (monitoring clinic or local doctor's surgery/home).

Our patient cohort was made up of 24 patients with rheumatoid arthritis, four with seronegative spondyloarthritis, two with systemic lupus erythematosus, and one with undifferentiated connective tissue disease. Most patients had been receiving a previous disease modifying antirheumatic drug (DMARD), including 24 patients taking oral MTX. Reasons for changing to IM-MTX treatment were as follows: side effects in 11 patients, loss of efficacy in 12, and poor oral compliance in eight. The median starting and maintenance doses were 10 mg weekly (range 5–17.5) and 15 mg weekly (range 10–17.5), respectively. During the study, five patients discontinued IM-MTX: two because of side effects, one developed multiple nodulosis, one did not attend for follow up, and one died from an unrelated cause. Median duration of treatment in the remaining 26 patients was 10 months (range 1–20). Significant improvement in disease activity, as measured by erythrocyte sedimentation rate and C reactive protein, was seen after three months ($p < 0.01$), with improvement maintained after nine months ($p < 0.01$) of IM-MTX treatment. Twenty four of the 26 current patients completed the questionnaire. On a satisfaction scale of 1–5, the average rating was 4.2, indicating that patients were either very or extremely satisfied with their IM-MTX treatment. Fourteen patients preferred their injections in the monitoring clinic, five patients preferred their local doctor's surgery, and five patients expressed no preferences. Only three patients stated that weekly clinic visits were inconvenient.

In conclusion, we found that IM-MTX was effective and well tolerated. In addition, our observations further support the switch to parenteral MTX in those patients previously intolerant or who have failed to respond to oral MTX.² Surprisingly, most patients preferred to have their injections in the monitoring clinic. The reason for this is not clear. Possibly, the patients felt more confident if cytotoxic drugs were given by a trained healthcare professional, although a previous study by Arthur *et al* has found that self injection of DMARDs is safe, convenient, and time and cost saving to the patient.³ We are currently comparing the administration of parenteral MTX in the monitoring clinic with

self administration in the community. Regardless of the outcome, the role of parenteral MTX in rheumatic diseases is likely to expand and the cost and resource implications of continuing with this treatment need to be discussed.

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Author's reply

It is gratifying that Drs Burbage, Gupta, and Lim have also demonstrated efficacy and high levels of patient satisfaction associated with parenteral methotrexate in their study. There remains a surprising dearth of reported information about this useful and widely prescribed development in rheumatology practice. Because of the burgeoning number of patients being treated in this way, it is creating increasing logistical difficulties. It represents an unlicensed use of this drug, which can cause anxiety among less experienced practitioners. Issues related to the appropriate disposal of the residual cytotoxic waste have also caused considerable difficulties. Although weekly oral methotrexate, prescribed and monitored within primary care, is an extremely cheap and effective treatment for rheumatoid arthritis, this is certainly not the case for parenteral methotrexate if it is necessary for it to be prescribed and administered in a costly secondary care setting. As primary care buckles under increasing demands on its resources, cost and logistical issues, rather than issues of efficacy, may curtail the deserved role of parenteral methotrexate in current and future rheumatology practice.

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LETTERS TO THE EDITOR

Epidemiology of vasculitis in Europe

We recently compared the annual incidence of primary systemic vasculitis (PSV) in two different regions of Europe (Norwich, UK (latitude 52°N) and Lugo, Spain (latitude 43°N)).¹ Wegener's granulomatosis (WG) was more common in Norwich (10.6/million) than in Spain (4.9/million), though the overall incidence of PSV was similar. This supports the idea that environmental factors may be important in the aetiopathogenesis of PSV. To extend our observations we have now studied the incidence of PSV in northern Europe (Tromsø, Norway (latitude 70°N)). The same methodology was used as in the previous study.¹ All new patients presenting with PSV between 1 January 1988 and 31 December 1998 were identified in the three centres. WG, Churg-Strauss syndrome (CSS), and polyarteritis nodosa (PAN) were classified by the American College of Rheumatology (1990) criteria,^{2,4} and microscopic polyangiitis (MPA) and classical PAN by the Chapel Hill consensus definition.³ Incidence figures were calculated using the Poisson distribution for the observed number of cases.

Table 1 shows the results obtained. The overall incidence and pattern of vasculitis was similar in the three regions, but there were some differences. MPA was less common in Tromsø than in the other two regions, and there was a trend for WG to be more common in the north. CSS was more common in Norwich than in the other two regions. In all areas and all disease categories the incidence was greater in men than women and showed a peak incidence at age 65–74. Overall, WG is the most common type of PSV and classical PAN the rarest.

These results support the notion suggested by doctors interested in vasculitis that there are geographical differences in the incidence of WG, MPA, and CSS, and, in particular, there is an inverse relation between the incidence of WG and MPA. In clinical practice MPA and WG can be difficult to distinguish. Possibly, despite our best attempts to harmonise the application of classification criteria/definitions, there were still differences in approach. The reason for the apparent excess of CSS in Norwich is unclear

Table 1 Annual incidence of primary systemic vasculitis in three regions of Europe

Criteria/ definition	Tromsø		Norwich		Lugo	
	n	/million (95% CI)	n	/million (95% CI)	n	/million (95% CI)
WG* ACR†	43	10.5 (7.6 to 14.2)	48	10.6 (7.8 to 14.0)	11	4.9 (2.4 to 8.8)
CSS* ACR	2	0.5 (0.06 to 1.8)	14	3.1 (1.7 to 5.2)	2	0.9 (0.1 to 3.2)
MPA* CHCC†	11	2.7 (1.3 to 4.8)	38	8.4 (5.9 to 11.5)	26	11.6 (7.6 to 17.0)
PAN* ACR	18	4.4 (2.6 to 7.0)	44	9.7 (7.0 to 13.0)	14	6.2 (3.4 to 10.5)
PAN CHCC	2	0.5 (0.06 to 1.8)	0	0.0 (0.0 to 0.8)	2	0.9 (0.1 to 3.2)
Total	56	13.7 (10.3 to 17.8)	86	18.9 (15.1 to 23.4)	41	18.3 (13.1 to 24.8)

n = number of patients fulfilling each criteria in each centre, 18 Tromsø patients, 24 Norwich patients, and 12 Lugo patients fulfilled more than one set of classification criteria. Total represents the number of patients seen in each centre.

*WG = Wegener's granulomatosis; CSS = Churg-Strauss syndrome; MPA = microscopic polyangiitis; PAN = polyarteritis nodosa.

†ACR = American College of Rheumatology; CHCC = Chapel Hill Consensus definition.

but might reflect local environmental factors. The aetiopathogenesis of PSV is unknown, but both genetic and environmental factors are likely to be important. The clinically observed differences between MPA and WG may reflect interaction of varying trigger factors on a heterogeneous genetic background. It should therefore not be assumed that the same triggers operate in all regions of Europe.

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Anti-U3 snRNP antibodies in localised scleroderma

Localised scleroderma (LScl) is a connective tissue disorder usually limited to the skin and subcutaneous tissue, but it sometimes affects the muscle beneath the cutaneous lesions. The absence of Raynaud's phenomenon, acrosclerosis, and internal organ involvement differentiates LScl from systemic sclerosis (SSc).¹ LScl has been reported to be accompanied by a variety of abnormal immune reactions, such as the presence of antinuclear antibody, rheumatoid factor, anti-single-stranded DNA antibody (anti-ssDNA), and antihistone antibody.²⁻⁵

In our laboratory an indirect immunofluorescent study showed nucleolar staining in the serum samples of some patients with LScl. Although autoantibodies to nucleolar antigens have been well described in patients with SSc,^{6,7} these antibodies have not been determined in patients with LScl, and the incidence of anti-U3 snRNP antibodies has not been described previously. In this study we investigated the prevalence of anti-U3 snRNP antibodies using RNA immunoprecipitation,⁸ and examined the clinical and

laboratory features of patients with LScl. In addition, we examined the serum samples of patients with SSc and control subjects matched for age and sex with the patients with LScl.

We found anti-U3 snRNP antibodies in 2/70 (3%) serum samples from the patients with LScl (fig 1). One of the 28 patients (4%) with linear scleroderma and one of the 20 patients (5%) with morphea had anti-U3 snRNP antibodies (table 1). This prevalence was smaller than that in patients with SSc,⁹ but there was no significant difference. RNA immunoprecipitation using silver staining of the RNA is not as sensitive as other methods—for example, probing with a labelled U3 snRNP probe. Possibly, some anti-U3 snRNP positive serum samples might have been missed. The three patients with SSc and with anti-U3 snRNP antibodies were diagnosed as having diffuse cutaneous SSc, and they tended to be older and have disease of longer duration than patients with LScl; the difference was not significant. In this study the titres of antinucleolar antibodies in the two patients with LScl with anti-U3 snRNP antibodies were 1/320 and 1/640, respectively. The titres of this antibody did not change in a follow up study. A previous study reported that 43/46 patients with SSc and anti-U3 snRNP antibodies produced bright nucleolar staining with titres >1/640.¹⁰ Taken together, the titres of antinucleolar antibodies in patients with LScl were as high as those in SSc. Patients with LScl and with anti-U3 snRNP antibodies did not have sclerodactyly or nailfold bleeding. Raynaud's phenomenon did not occur at any time in the course of their disease. These results suggest that anti-U3 snRNP antibodies occur in patients with LScl as well as in those with SSc.

The patients with LScl and anti-U3 snRNP antibodies tended to be younger, have shorter disease duration, have fewer sclerotic

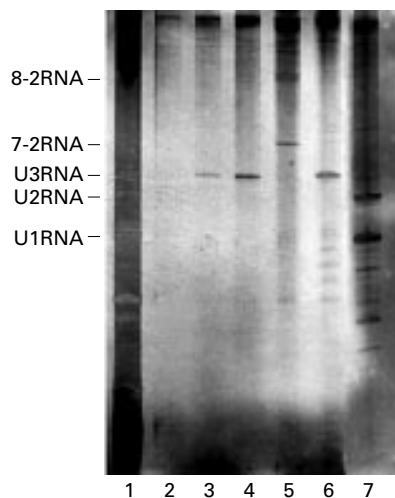


Figure 1 RNA immunoprecipitation. Urea (7 M/10% polyacrylamide gel electrophoresis of phenol-extracted immunoprecipitates from HeLa cell extracts were stained with silver. Total nucleic acids, with 7-2RNA, 8-2RNA, and the U snRNA regions are indicated. Serum samples used for immunoprecipitation included: lane 1, total RNA; lane 2, healthy control serum; lanes 3-4, patients with LScl and with anti-U3 snRNP antibodies; lane 5, patient with SSc and anti-Th/T_o ribonucleoprotein antibodies; lane 6, patient with SSc and anti-U3 snRNP antibodies; lane 7, patient with systemic lupus erythematosus and anti-Sm antibodies.

Table 1 Frequencies of antibodies to U3 small nuclear ribonucleoprotein (snRNP), detected by immunoprecipitation, in patients with localised scleroderma (LScl), systemic sclerosis (SSc), and control subjects

	Anti-U3 snRNP antibodies (%)
Patients with LScl	2/70 (3)
GM	0/22 (0)
LS	1/28 (4)
M	1/20 (5)
Patients with SSc	3/30 (10)
Control subjects	0/40 (0)

LScl = localised scleroderma; GM = generalised morphea; LS = linear scleroderma; M = morphea; SSc = systemic sclerosis.

lesions, and have fewer affected areas than those without, but there was no significant difference. We could not find any correlations with clinical manifestations, probably because of the small number of patients. In earlier investigations of systemic sclerosis, anti-U3 snRNP antibodies did not seem to have any distinctive clinical and laboratory correlation. A large group of patients with SSc was assembled and the clinical features of the patients with anti-U3 snRNP antibodies investigated; various clinical associations were reported.⁹ A large group of patients with LScl might similarly disclose clinical associations of patients with LScl with anti-U3 snRNP antibodies.

Previous studies have shown that anti-U3 snRNP antibodies rarely coexist with other autoantibodies.⁹ Okano *et al* reported that each distinctive serum antibody is associated with its own unique combination of clinical features.⁹ In our study antihistone antibodies or anti-ssDNA did not coexist with anti-U3 snRNP antibodies, and no other autoantibodies were detected by RNA immunoprecipitation. LScl may be a heterogeneous condition with diverse autoantibodies, and these antibodies may have a mutually exclusive status.

In conclusion, we showed for the first time that anti-U3 snRNP antibodies are found in patients with LScl by RNA immunoprecipitation. We found no correlations between clinical and laboratory manifestations in the present study. Our study suggests that the presence of anti-U3 snRNP antibodies is one of the serological abnormalities in LScl. A study of more patients may assist in showing a distinctive association between anti-U3 snRNP antibodies and the clinical and laboratory features of patients with LScl.

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Telomerase activity in peripheral blood mononuclear cells from patients with SLE

Telomerase is a reverse transcriptase that adds the telomeric sequence to the terminal of chromosomes, prevents shortening of telomere, and maintains the complete telomeric structure.¹ It has been recently reported that an increase in telomerase activity is associated with the activation of lymphocytes,²⁻⁷ and, in general, much attention has been paid to the role of telomerase in immunopathology. Katayama *et al* reported the telomerase activity in patients with systemic lupus erythematosus (SLE).⁸ They analysed 17 patients with SLE, and the telomerase activity in peripheral mononuclear cells was increased to 64.7%. Thus, in this study, we divided patients with SLE into treated and untreated groups, and measured the telomerase activity of peripheral mononuclear cells.

Thirteen patients with SLE (1 man, 12 women) with a mean (SD) age of 30.7 (6.5)

years (range 19-61) were enrolled in this study. All patients fulfilled the 1997 revised American Rheumatism Association criteria. As a control group, 10 normal volunteers, six women aged 19-41 and four men aged 30-37, were also included in the study. After informed consent had been obtained, 10 ml of peripheral blood was taken and heparinised. The mononuclear cell fraction was isolated from 10 ml of heparinised peripheral blood by Ficoll-Paque (Sigma Inc, St Louis, USA) density gradient centrifugation. A sample of 1.0×10^6 mononuclear cells was analysed by the TRAP assay method. The TRAP assay was performed with a TRAPeze telomerase detection kit produced by the Intergen Company (Purchase, NY, USA). The level of telomerase activity was expressed by a ratio of the entire TRAP ladders to an internal control band.

Table 1 shows the telomerase activity level data and clinical data used for determining the SLE Disease Activity Index (SLEDAI). Significant differences ($p=0.006$) were detected in the telomerase activity level between the control group, untreated SLE group, and treated SLE group by Kruskal-Wallis test with a significance level of 5%. For multiple comparisons the Mann-Whitney U test was used to evaluate intergroup differences after lowering the significance level using Bonferroni's technique. The p value was 0.002 between the control group and untreated SLE group, 0.005 between the untreated SLE group and treated SLE group, and 0.118 between the control group and treated SLE group. Compared with other groups, telomerase activity was significantly higher in the SLE untreated group. The Spearman rank correlation test with a significance level of 5% showed a significant positive relationship between telomerase activity and SLEDAI in the SLE group with a correlation coefficient of 0.872 and p value of 0.003. The relation between telomerase activity and clinical data in SLEDAI was also analysed using the Spearman rank correlation test with a significance level of 5% in the SLE group. The correlation coefficient and p value were -0.614 and 0.033 between telomerase activity and white blood cell count, -0.715 and 0.013 between telomerase activity and serum complement activity, and 0.637 and 0.027 between telomerase activity and serum IgG level, respectively, with a significance level of

5%. However, the relation between telomerase activity and other clinical data was not significant in the SLE group. Telomerase activity was measured before and after treatment and changes in the activity level were analysed.

SLEDAI decreased in all patients after treatment. Wilcoxon signed rank test with a significance level of 5% showed a significant decrease in telomerase activity ($p=0.043$) after treatment.

The treatment reduced the telomerase activity in peripheral mononuclear cells. We could not confirm whether the cause was due to the steroids or the reduction of disease activity. However, because the telomerase activity of peripheral mononuclear cells was correlated with SLEDAI, the peripheral blood telomerase activity may be useful in the evaluation of disease activity and in judging the therapeutic effects in SLE.

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Table 1 Telomerase activity and clinical laboratory parameters and SLE disease activity index (SLEDAI)

Patient No	Age	Sex	Telomerase activity	WBC	Lymph.	Plt. ($\times 10^9$)	CH ₅₀	IC (C1q)	dsDNA	u-prot.	ANA	IgG	IgA	IgM	SLEDAI	Symptom	Treatment (prednisolone)
1	23	M	1.96	2700	800	158.0	31.2	1.5	5	(-)	640	14.69	3.05	0.53	10	2,4,5,6,8	None
			0.00	6500	1200	211.0	37.0	1.9	5	(-)	1280	—	—	—	2	None	20 mg/day
2	36	F	0.76	2900	900	48.0	23.6	9.3	165	(1+)	1280	12.82	1.68	0.65	12	2,4,8	None
			0.00	5800	1700	243.0	29.2	—	72	(-)	—	—	—	—	2	None	30 mg/day
3	28	F	0.82	3700	1000	226.0	31.6	1.5	77	(±)	640	18.98	3.89	1.98	10	2,5,8	None
			0.78	8000	700	253.0	28.1	1.5	32	(±)	1280	—	—	—	2	None	20 mg/day
4	61	F	0.47	3600	400	201.0	15.0	34.5	83	(±)	5120	31.37	3.44	0.76	16	2,3,4,5,8	None
			0.29	5800	600	200.0	34.8	9.9	12	(-)	5120	—	—	—	0	None	30 mg/day
5	19	F	0.85	4520	920	311.0	27.2	1.9	13	(3+)	320	15.60	3.54	2.24	21	1,2,4,5,8	None
			0.28	16130	1130	327.0	30.0	1.5	5	(1+)	40	6.44	1.84	1.79	0	None	30 mg/day
6	24	F	0.25	8700	1400	149.0	34.2	1.5	185	(2+)	5120	11.34	3.33	0.90	2	None	50 mg/day
7	53	F	0.40	5600	1200	13.0	36.2	1.5	5	(2+)	160	18.24	6.00	0.79	1	None	60 mg/day
8	39	F	0.05	6800	1300	248.0	35.6	1.9	5	(-)	40	9.80	2.09	0.55	0	None	15 mg/day
9	41	F	0.18	12400	400	247.0	47.6	1.6	5	(1+)	640	13.13	2.73	0.51	0	None	20 mg/day
10	36	F	0.06	7900	1400	209.0	41.0	1.5	12	(-)	800	11.89	1.71	0.88	0	None	5 mg/day
11	56	F	0.04	7900	1200	219.0	41.5	1.5	5	(1+)	40	12.19	4.17	0.66	0	None	10 mg/day
12	39	F	0.10	5600	600	134.0	34.2	1.5	7	(3+)	640	7.65	2.32	0.38	0	None	20 mg/day
13	36	F	0.58	9000	1100	138.0	24.0	1.5	21	(2+)	320	16.53	3.55	1.39	4	7	30 mg/day

WBC = white blood cell count (/μl); Lymph. = lymphocyte count (/μl); Plt. = platelet count ($\times 10^9$ /μl); CH₅₀ = serum complement activity (U/ml); IC (C1q) = serum immune complex level with a C1q solid phase method (μg/ml); dsDNA = anti-double stranded DNA antibody level (IU/ml); u-prot. = urine protein analysis with a test paper method; ANA = antinuclear antibody (titre); IgG = immunoglobulin G level (g/l), IgA = immunoglobulin A level (g/l); IgM = immunoglobulin M level (g/l); SLEDAI = SLE disease activity index.

Symptom: 1 = central nervous system lupus; 2 = arthritis; 3 = myositis; 4 = nephritis; 5 = new rash; 6 = alopecia; 7 = serositis; 8 = fever.

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Treatment of ankylosing spondylitis with infliximab

In January 2000 a 35 year old man presented with severe ankylosing spondylitis (AS), diagnosed in 1981. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was 6.0, the Bath Ankylosing Spondylitis Functional Index (BASFI) was 3.0, and on a 1-10 visual analogue scale (VAS) for pain in the previous two months he had a score of 6.

Schober's test was 0 cm (normal 4 cm), Ott's test 1 cm (normal 2 cm), finger-floor distance 16 cm, lateral flexion 3 cm, tragus-wall distance 21 cm, cervical rotation 30°.

C reactive protein (CRP) was 41 mg/l (normal <5), erythrocyte sedimentation rate (ESR) was 25 mm/1st h (normal <15), and HLA-B27 genotype was positive.

Conventional radiography showed typical signs of AS. Magnetic resonance imaging (MRI) detected inflammatory activity in the ileosacral joints¹ by contrast enhancement after gadolinium application in the apical portion of the right ileosacral joint in T₁ weighted sequences (fig 1).

We started treatment with infliximab,² a monoclonal antibody (IgG1) directed against tumour necrosis factor α (TNF α), at a dose of 5 mg/kg body weight. Intravenous infusions were given in weeks 0, 2, 6, and then continued at six weekly intervals for one year without any additional disease modifying drug.

Pain improved within 24 hours of the first infusion. Within six weeks the patient required no ibuprofen and CRP, ESR, BASDAI, BASFI, and VAS improved dramatically (fig 2). With the exception of CRP and ESR, all variables remain normal up to now. CRP and ESR increased mildly at week 12 owing to a mild upper respiratory tract infection. There were no other adverse

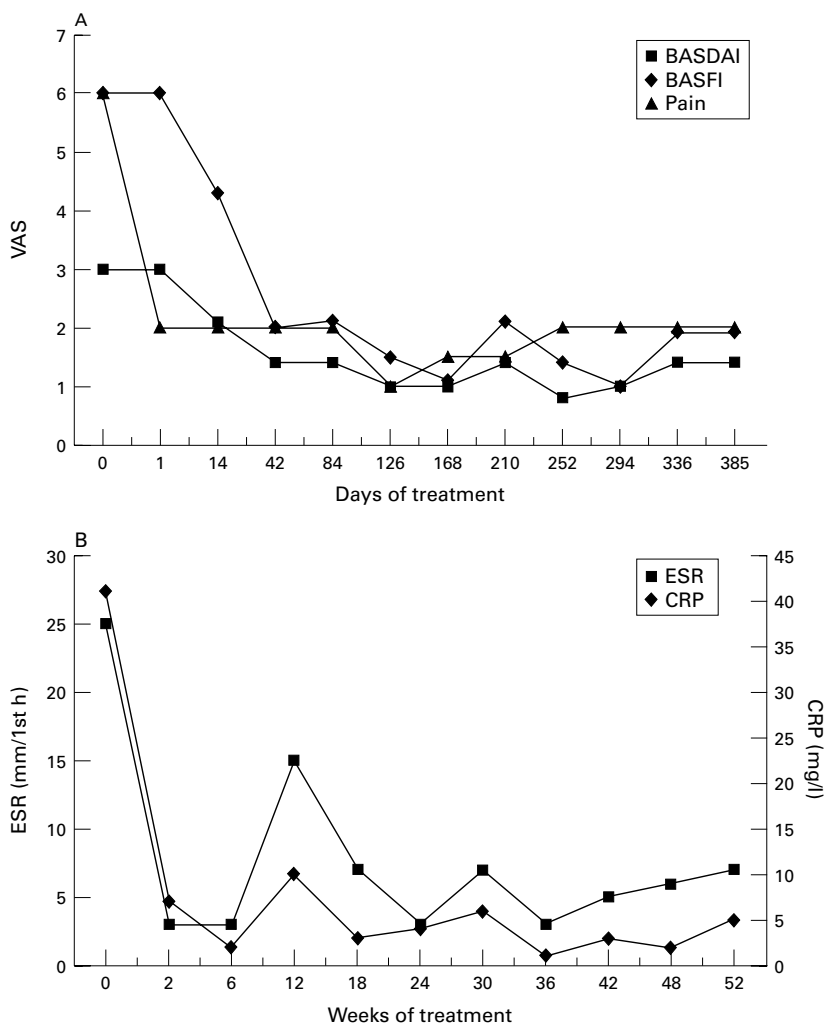


Figure 2 Self assessment of pain on a 1-10 visual analogue scale (A) and CRP and ESR (B).

events. Two mobility variables (cervical rotation and tragus-wall distance) had improved at the end of one year's treatment.

MRI of the ileosacral joints showed no contrast enhancement at weeks 14 and 41 of treatment (fig 1).

The patient denied any loss of effect at the end of the six weekly infusion intervals or after one year of treatment. Except for the mild upper respiratory tract infection, which abated after two weeks without specific treatment, there were no adverse events.

This case report documents the first long term application of infliximab in a patient with AS. Two previous studies reported

effective treatment of a total of 22 patients with AS with three infusions of infliximab at a dose of 5 mg/kg body weight.^{3,4}

The pharmacological basis for TNF α inhibitory treatment in AS is the detection of TNF α -mRNA and TNF α protein in biopsy specimens of ileosacral joints of patients with active AS.⁵ In rheumatoid arthritis (RA) and Crohn's disease (CD), several TNF α inhibitors seem to be successful in significantly reducing inflammatory activity.^{6,7}

Theoretically, up regulation of the TNF α receptors and subsequent tachyphylaxis might be expected upon constant blockade of the agonist. This has not been noted in studies on infliximab, etanercept, and D2E7 in RA, CD, and psoriatic arthritis (PA) during long term treatment, even when constant therapeutic plasma levels are maintained.⁷⁻⁹ This case report suggests this is true also for patients with AS.

In summary, we present the case of a patient with AS effectively and safely treated with infliximab over a period of more than one year. This indicates that treatment of AS with TNF α inhibiting substances may have equal long term safety and long term benefits on peripheral and spinal joint function as does treatment of RA, CD, and PA. Randomised controlled double blind studies are needed to investigate this in further detail.

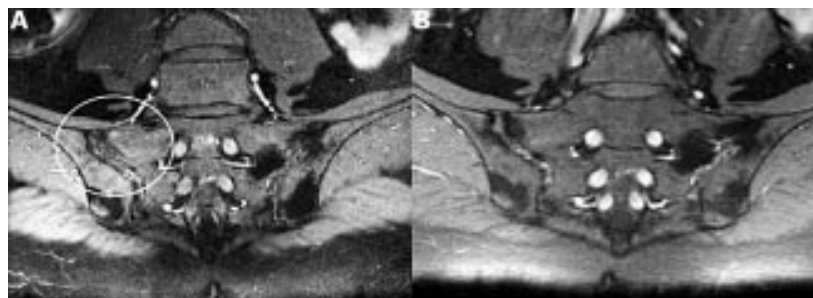


Figure 1 Gadolinium contrast enhanced T₁ weighted magnetic resonance imaging before treatment with infliximab (A) showing contrast enhancement in the right ileosacral joint, and (B) in week 41 of treatment showing no contrast agent uptake.

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Retrocalcaneal bursitis in polymyalgia rheumatica

Polymyalgia rheumatica (PMR) is a relatively common disease of the elderly affecting the synovial membrane.¹

Recent studies have emphasised the prominent involvement of the extra-articular synovial structures in both proximal and distal regions of both the arms and legs.^{1–7} In the distal part of the arms tenosynovial membrane inflammation is responsible for carpal tunnel syndrome, distal swelling of hands and feet with or without pitting oedema, and localised episodes of distal tenosynovitis.^{4–7}

We recently observed the case of a patient with PMR showing retrocalcaneal bursitis, which we describe briefly here.

A 68 year old woman was referred to us for evaluation of a three month history of marked aching and morning stiffness in her neck, shoulder, and hip girdles associated with low

grade fever. Her medical history was otherwise unremarkable except for a hereditary cerebellar cortical degeneration. Her family history was negative for rheumatic diseases, including spondylarthritis.

Physical examination showed tenderness and limitation of cervical and shoulder movement. The typical gait and abnormal stance of cerebellar ataxia were also present.

Laboratory evaluation disclosed an erythrocyte sedimentation rate (ESR) of 72 mm/1st h (Westergren) and a C reactive protein (CRP) concentration of 80 mg/l (normal <5). Tests for rheumatoid factor, antinuclear antibodies, and serum tumour markers were negative, and HLA typing did not show the B27 antigen.

Methylprednisolone at a dose of 16 mg/day was started and symptoms rapidly disappeared. ESR and CRP were normal after one month of treatment.

Nine months after starting treatment, when the dose of methylprednisolone was 6 mg/day, the patient experienced pain in her shoulder girdle and right foot. Physical examination showed an enlarged and painful right retrocalcaneal bursa. There was no pain and swelling along her right Achilles tendon and at its calcaneal insertion. Magnetic resonance imaging (MRI) showed an enlarged retrocalcaneal bursa without any sign of Achilles tendonitis or enthesitis (fig 1). An anteroposterior view of her pelvis showed normal sacroiliac joints. Both shoulder girdle symptoms and retrocalcaneal bursitis disappeared promptly when the dose of methylprednisolone was increased and have not reappeared so far, 12 months after discontinuation of treatment.

Our patient had PMR and showed retrocalcaneal bursitis as a distal manifestation of the disease.

The prominent involvement of the extra-articular synovial structures in both the



Figure 1 Sagittal T₁ (A) and axial T₁ (B) weighted images of the left Achilles tendon showing the distension of the retrocalcaneal bursa by fluid collection (arrows) together with normal Achilles tendon and enthesitis.

peripheral and distal inflammatory processes of PMR has only recently been demonstrated.^{2–7} The distal manifestations of PMR include tenosynovitis in addition to joint synovitis.^{1–4,7} Extensor tenosynovial sheath involvement, which may give swelling with pitting oedema over the dorsum of the hands and feet, is common and has been recorded by MRI.^{4,7} Tenosynovitis under the transverse carpal ligament may cause carpal tunnel syndrome.⁷ The involvement of hand flexor, posterior tibial and peroneal tendons may occur and has been documented with MRI.^{1,4,5,7}

To the best of our knowledge retrocalcaneal bursitis has never been reported in patients with PMR. Chuang *et al* found “bursitis-tendinitis” in 48/96 (50%) patients with PMR.⁸ Although they considered these as part of the disease, no mention of the affected bursae was made in their article. Possibly, some of the 48 patients developed retrocalcaneal bursitis. The retrocalcaneal bursa differs from other deep bursae, such as the subacromial and subdeltoid bursa and the gastrocnemius-semimembranosus bursa.⁹ The synovial membrane is present only at its roof while its anterior wall is fibrocartilage layered onto the calcaneus and its posterior wall sesamoid fibrocartilage differentiated in the Achilles tendon. This anatomical arrangement makes the bursa an integral part of the Achilles enthesitis. In spondylarthritis, which is a disease of the entheses, retrocalcaneal bursitis often occurs in association with Achilles enthesitis.¹⁰ In contrast, retrocalcaneal bursitis tends to occur in isolation in rheumatoid arthritis, suggesting that the synovial membrane at the top is the primary site of inflammation.⁹ The same may be valid for PMR. Our patient had no clinical sign of Achilles tendon involvement and MRI showed no sign of enthesitis, that is to say, tendon swelling and bone oedema.

In conclusion our report suggests that the synovial membrane of distal bursae may also be affected in PMR.

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CORRECTION

Comorbidity and lifestyle, reproductive factors, and environmental exposures

associated with rheumatoid arthritis (Reckner Olsson Å, Skogh T, Wingren G. *Ann Rheum Dis* 2001;60:934-9.)

The authors regret that an error is present in the fourth paragraph of the "Results" section. The first sentence should read: "A non-significant increased risk of RA was seen in both men and women who consumed at least 75 ml of alcohol per drinking session at the age of 25 compared with total abstainers" and not "750 ml" as stated.

(Note: Corrections printed in the journal also appear on the *Annals* web page (www.annrheumdis.com) and are linked to the original publication.)

EULAR training bursaries

Up to 10 scholarships for clinical or laboratory work (3-6 months) in a foreign unit will be made available for applicants from countries where there is a clear educational need.

The value of each bursary is 7000 euros. Candidates should be under 35 years of age and the grant will not be made if the applicant is already abroad in training.

A curriculum vitae, a statement of qualification, a project outline, and a written confirmation from the host hospital that training is possible must be received at the EULAR Secretariat no later than 28 February 2002.

EULAR prize

The prize, to the value of 30 000 euros, is awarded by EULAR for an outstanding contribution in the field of rheumatology in recent years.

The competition is open to both scientists and clinicians working in the field of rheumatology. The prize will be awarded for the work of a group and not to an individual person.

The documents submitted in support of an entry may take the form of an essay or a description of the project. The prize will not be awarded for a publication or an abstract.

The essay with the CV of the head of the group and a publication list must be received at the EULAR Secretariat in Zurich no later than 28 February 2002.

EULAR young investigator awards

Three awards for a scientific (clinical or basic) research project of 30 000 euros each, will be made available for laboratory/research work in the field of rheumatology.

Candidates must submit a project outline, a CV, and expense budget and should be under 35 years of age.

Entries for the Young Investigator Awards must be received at the EULAR Secretariat in Zurich no later than 28 February 2002.

AMGEN/EULAR young investigator award

AMGEN (Europe) will make an award of 30 000 euros for a scientific (clinical or basic) research project in the area of rheumatoid arthritis. The prize money is intended to support laboratory/research work.

Candidates must submit a project outline, a CV, and expense budget and should be under 35 years of age.

Entries for the award must be received at the EULAR Secretariat in Zurich no later than 28 February 2002.

Endowment of the awards

The EULAR prize, the EULAR young investigator awards, and the AMGEN/EULAR young investigator award will be endowed at the opening ceremony of the Annual European Congress of Rheumatology to be held in Stockholm, Sweden, on 12 June 2002.

www.eular.org

Bursaries, the EULAR prize, and the Young Investigator Awards are also announced on www.eular.org

Applications should be forwarded to:

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Tel: + 41 1 383 96 90; fax: + 41 1 383 98 10; email: secretariat@eular.org