### 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 exposes family members, in part, to the increased risk of RA associated with heavy smoking and the greater association with RA.1

No data were presented in that study on the extent of smoking and RF positivity or its titers.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.1 However, no significant association was seen between current smoking and IgM RF positivity in the earlier multicase family study, either among 41 patients with RA or their non-rheumatoid relatives—168 blood and 36 non-blood relatives.2

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? 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.3

These complex relationships were investigated in a case-control study nested within a community based cohort (n=21061 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).4

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 1.2 to 122.9, 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 production is1 attractive. However, critical substantiation in prospective and cross sectional studies is currently lacking. Available prospective data (table 1)5 suggest that alternative mechanisms may be more likely. For example, long term cigarette smoking causes general vascular endothelial damage, and smoking is significantly associated with vasculitis in active RA.6 However, smoking was proposed to contribute to RA risk through its endothelial and microvascular effects, perhaps through nitric oxide pathways,7 rather than by RF production primarily.6

Whether or not heavy smoking differentially associates with RA depending upon family history of disease8 is as complex as the dilemmas of RF contributions to onset (table 1). Our 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 observed by Altman et al,9 have influenced their behaviour to lower cumulative exposures to cigarette smoking compared with their counterparts?10

<table>
<thead>
<tr>
<th>Categories</th>
<th>Pre-RA cases</th>
<th>Respectively matched controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number CS 30+/day (%)</td>
<td>Number CS 30+/day (%)</td>
</tr>
<tr>
<td>Total subjects</td>
<td>54 13 (24)</td>
<td>216 19 (9)</td>
</tr>
<tr>
<td>Men</td>
<td>18 8 (44)</td>
<td>24 12 (19)</td>
</tr>
<tr>
<td>Women</td>
<td>36 5 (14)</td>
<td>144 5 (3)</td>
</tr>
<tr>
<td>FDR+*</td>
<td>11 5 (45)</td>
<td>44 20 (9)</td>
</tr>
<tr>
<td>FDR−</td>
<td>43 8 (19)</td>
<td>172 10 (6)</td>
</tr>
<tr>
<td>Pre-RA RF+</td>
<td>12 2 (17)</td>
<td>48 2 (8.5)</td>
</tr>
<tr>
<td>Pre-RA RF−</td>
<td>42 11 (26)</td>
<td>168 12 (7)</td>
</tr>
<tr>
<td>Entry and post-RA RF−</td>
<td>15 4 (27)</td>
<td>60 1 (2)</td>
</tr>
<tr>
<td>Conversion of pre-RA RF− to RF+</td>
<td>27 7 (26.5)</td>
<td>108 7 (6.5)</td>
</tr>
<tr>
<td>FDR− and pre-RA RF−</td>
<td>33 7 (21)</td>
<td>132 5 (4)</td>
</tr>
<tr>
<td>Mild case of RA</td>
<td>19 8 (42)</td>
<td>76 11 (14)</td>
</tr>
<tr>
<td>Non-mild course of RA</td>
<td>35 5 (14)</td>
<td>140 8 (6)</td>
</tr>
</tbody>
</table>

*FDR+ is a positive history of RA in a first degree relative as determined for patients in 1997, and reported in 1974.1
†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).

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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.4 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.4 We therefore decided to compare cigarette smoking exposure 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 and, furthermore, there is a related phenomenon for the development of seropositive RA.1 It has also been established that the development of seropositive RA is greatly increased in healthy subjects who are persistently seropositive.4 Wolfe noted a significant trend in patients with RA of...
increasing RF titre with pack years smoked. 1
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 mecha-
nisms, as suggested by Masi, may also be at work. For example, cigarette smoke contains numerous oxidizing agents that can activate α-1-proteinase inhibitor (α-1PI), the natural inhibitor of neutrophil elastase (NE), a serine proteinase that can degrade articular carti-
lage. 2 Cigarette smoke can also prime neu-

trophil elastase and discharges E, activate macrophages to produce matrix metalloproteinases, 3 up regulate production of interleukin 1α, and interleukin 1 receptor antagonist, and interleukin 1 receptor activator. 4 Furthermore, cigarette smoking induces disease processes in a specific dose dependent fashion (inde-
pendent of current smoking status), such as pulmonary emphysema, in which there is increased neutrophil priming, in increases oxid-
dised α-1PI and α-1PI-NE complexes (indica-
tive of increased NE activity). 5 Therefore a heavy smoker may have an otherwise benign short lived inflammatory arthritis modified by the organisms outlined above and develop RA.
Whether RA increases or decreases ciga-
ette 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 Harries et al. 6 observed that 18% of all smok-
ers with polyarthritis stopped smoking within three years of disease onset as opposed to <1% of non-smoking patients who started smoking during this period. 7
The important questions remain unan-
swered. For example, does increased cumula-
tive cigarette consumption increase RA sus-
ceptibility independent of RP production? (In studies reviewed by Masi et al. we con-
sider cigarette consumption at one time point.) If so, do these subjects have an increased prevalence of circulating levels of α-1PI-NE complexes, high levels of oxidized and inactivated α-1PI-NE complexes, and there-
fore 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 inter-
esting questions raised by recent studies.

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2 McEntegart A, Capell HA, Crean D, Rumley A, Woodward A, Lowe GD. Cardiovascular risk factors, including thrombosis individuals, in a population with rheumatoid arthritis. Rheu-

6 N Hallordsdottir HD, Jonsson T, Thorsteinsson J, Valdimarsson H, Abo K. A population study on the incidence of rheumatoid arthritis among peo-

gle with persistent increase of rheumatoid fac-

7 Wolfe F. The effect of smoking on clinical, labo-

tion of articular cartilage by alpha 2 macro-
11 Selman M, Montano M, Ramos C, Vanda B, Becerril C, Delgado J, et al. Tobacco smoke-induced lung emphysema in guinea pigs is associated with increased intestinal colla-
13 Hofbauer LC, Mullberg T, Konag A, Heufelder G, Schworm HD, Heufelder AE. Soluble interleukin-1 receptor complexes in serum levels in smokers and nonsmokers with Graves’ oph-

Rheumatoid arthritis associated with ulcerative colitis

I was interested to read the letter on “Rheu-

matoid 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 gener-
ally supported the presence of Th1 responses. 2,3 In ulcerative colitis, although enhanced humoral immunity has been de-
scribed, evidence for classical Th2 predomi-
nance 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 rheuma-
toid arthritis. 5

As shown in this case, it is sometimes quite difficult to distinguish by clinical manifesta-
tions 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 mu-
cosal 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 let-
ter and are happy that our report has stimu-
lated 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 erythro-
cyte 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 follow-
ing the now classical rheumatoid arthritis protocol. 2 Seven months later, steroids could be stopped. Surgery for colon anastomosis could then be performed with success and with no healing delays. When last seen in July 2001, she showed major improve-
ment, 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 con-
tribution of tumour necrosis factor α. 3

4 Liu Z, Geboes K, Colpaert S, D’Haens G, Rut-
geers F, Pauwels C, Peeters J, et al. A short-term study of chimeric monoclonal anti-

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4 Liu Z, Geboes K, Colpaert S, D’Haens G, Rut-
geers F, Pauwels C, Peeters J, et al. A short-term study of chimeric monoclonal anti-
Intramuscular methotrexate in inflammatory rheumatic disease

We read with great interest the recent letter entitled "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 spondyloarthropathy, 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 taking IM-MTX 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. As 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.2 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.

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 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

<table>
<thead>
<tr>
<th>Criterial definition</th>
<th>Tromsø</th>
<th>Norwich</th>
<th>Lugo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n /million (95% CI)</td>
<td>n /million (95% CI)</td>
<td>n /million (95% CI)</td>
<td></td>
</tr>
<tr>
<td>WG* ACR†</td>
<td>43 (10.5 (7.6 to 14.2))</td>
<td>48 (10.6 (7.8 to 14.0))</td>
<td>11 (4.9 (2.4 to 8.8))</td>
</tr>
<tr>
<td>CSS* ACR</td>
<td>2 (0.06 (0.0 to 1.8))</td>
<td>14 (3.1 (1.7 to 5.2))</td>
<td>2 (0.9 (0.1 to 3.2))</td>
</tr>
<tr>
<td>MPA* CHCC‡</td>
<td>11 (2.7 (1.3 to 4.8))</td>
<td>38 (8.1 (5.9 to 11.5))</td>
<td>26 (11.6 (7.6 to 17.0))</td>
</tr>
<tr>
<td>PAN* ACR</td>
<td>18 (4.4 (2.6 to 7.0))</td>
<td>44 (9.7 (7.0 to 13.0))</td>
<td>14 (6.2 (3.4 to 10.5))</td>
</tr>
<tr>
<td>PAN CHCC</td>
<td>2 (0.05 (0.0 to 1.8))</td>
<td>0 (0.0 (0.0 to 0.8))</td>
<td>2 (0.9 (0.1 to 3.2))</td>
</tr>
<tr>
<td>Total</td>
<td>56 (13.7 (10.3 to 17.8))</td>
<td>86 (18.9 (15.1 to 23.4))</td>
<td>41 (18.3 (13.1 to 24.8))</td>
</tr>
</tbody>
</table>

n = number of patients fulfilling each criteria in each centre, 18 Tromso 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.

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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. 1

In our laboratory an indirect immunofluorescence test showed nuclear staining in the serum samples of some patients with LScl. Although autoantibodies to nucleolar antigens have been well described in patients with SSc, 2 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 in LScl using RNA immunoprecipitation, 3 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, 3 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 antinuclear 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 with anti-U3 snRNP antibodies produced bright nucleolar staining with titres >1/640. 4

Taken together, the titres of antinuclear 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 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. 5 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. 6 Okano et al reported that each distinctive serum antibody is associated with its own unique combination of clinical features. 7 In our study anti-U3 snRNP 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 prevalence 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.

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

<table>
<thead>
<tr>
<th>Anti-U3 snRNP antibodies (%)</th>
<th>Patients with LScl</th>
<th>Patients with SSc</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with LScl</td>
<td>2/70 (3)</td>
<td>0/22 (0)</td>
<td>0/40 (0)</td>
</tr>
<tr>
<td>GM</td>
<td>1/28 (4)</td>
<td>1/20 (5)</td>
<td>0/40 (0)</td>
</tr>
<tr>
<td>LS</td>
<td>1/28 (4)</td>
<td>1/20 (5)</td>
<td>0/40 (0)</td>
</tr>
<tr>
<td>M</td>
<td>1/28 (4)</td>
<td>1/20 (5)</td>
<td>0/40 (0)</td>
</tr>
</tbody>
</table>

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

Telomerase activity in peripheral blood mononuclear cells from patients with SLE

Telomerase is a reverse transcriptase that adds the telomeric sequence to the terminal ends of chromosomes, preventing shortening of telomeres, and maintains the complete telomeric structure. It has been recently reported that an increase in telomerase activity is associated with the activation of lymphocytes, 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). They analyzed 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 was obtained, 10 ml of peripheral blood was taken and heparinized. The mononuclear cell fraction was isolated from 10 ml of heparinized peripheral blood by Ficoll-Paque (Sigma Inc, St Louis, USA) density gradient centrifugation. A sample of 1.0×10^6 mononuclear cells was prepared in 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 ladder 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, and 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 used for determining the SLE Disease Activity Index (SLEDAI).

WBC = white blood cell count (µl); Lymph = lymphocyte count (µl); Pts. = platelet count (x10^10/µl); CH₅₀ = serum complement activity (U/ml); IC (C₁q) = serum immune complex level with a C₁q solid phase method (µg/ml); dDNA = anti-double stranded DNA antibody level (U/ml); u-propt. = 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.

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

| Patient No | Age (yr) | Sex | Telomerase activity (WBC) | CH₅₀ (µg/ml) | IC (C₁q) | dDNA | u-propt. | ANA | IgG (g/l) | IgA (g/l) | IgM (g/l) | SLEDAI | Symptom | Treatment (prednisolone) |
|------------|---------|-----|--------------------------|--------------|----------|------|----------|-----|-----------|-----------|-----------|-------|---------|-----------------------|------------------------|
| 1          | 23      | M   | 1.96                     | 2700         | 800      | 158.0| 5        | 640 | 14.69     | 3.05      | 0.53      | 10     | 2,4,5,8 | None                |
| 2          | 36      | F   | 0.76                     | 2900         | 900      | 480.0| 9        | 1280| 12.82     | 1.68      | 0.65      | 12     | 2,4,8   | None                |
| 3          | 28      | F   | 0.82                     | 3700         | 1000     | 243.0| 72       | 640 | 14.89     | 3.89      | 1.90      | 10     | 2,4,5,8 | None                |
| 4          | 61      | F   | 0.47                     | 3600         | 400      | 201.0| 152     | 640 | 13.13     | 2.73      | 0.51      | 16     | 2,3,4,5,8,12 | None                |
| 5          | 19      | F   | 0.85                     | 4520         | 920      | 311.0| 5        | 640 | 14.69     | 3.05      | 2.24      | 21     | 1,2,4,5,8 | None                |
| 6          | 24      | F   | 0.25                     | 8700         | 1400     | 240.0| 92      | 640 | 13.65     | 2.73      | 0.51      | None   | 50 mg/day | None                |
| 7          | 53      | F   | 0.40                     | 5600         | 1200     | 13.0 | 5        | 640 | 14.69     | 3.05      | 2.24      | 21     | 1,2,4,5,8 | None                |
| 8          | 39      | F   | 0.05                     | 6800         | 1300     | 248.0| 5        | 640 | 14.69     | 3.05      | 2.24      | 21     | 1,2,4,5,8 | None                |
| 9          | 41      | F   | 0.18                     | 12400        | 400      | 247.0| 5        | 640 | 14.69     | 3.05      | 2.24      | None   | 50 mg/day | None                |
| 10         | 36      | F   | 0.36                     | 7900         | 1400     | 209.0| 5        | 640 | 14.69     | 3.05      | 2.24      | None   | 50 mg/day | None                |
| 11         | 56      | F   | 0.04                     | 7900         | 1200     | 219.0| 5        | 640 | 14.69     | 3.05      | 2.24      | None   | 50 mg/day | None                |
| 12         | 36      | F   | 0.10                     | 5600         | 1400     | 247.0| 5        | 640 | 14.69     | 3.05      | 2.24      | None   | 50 mg/day | None                |
| 13         | 36      | F   | 0.58                     | 9000         | 1100     | 138.0| 21      | 640 | 16.53     | 3.55      | 1.39      | None   | 30 mg/day | None                |
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.

Conventional radiography showed typical signs of AS. Magnetic resonance imaging (MRI) detected inflammatory activity in the ileosacral joints by contrast enhancement after gadolinium application in the apical 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.

We started treatment with infliximab, a monoclonal antibody (IgG1) directed against tumour necrosis factor α (TNFα), at a dose of 5 mg/kg body weight. Intravenous infusions were given in weeks 0, 2, 6, and 12, 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 1). 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 events. Two mobility variables (cervical rotation and tragus-wall distance) had improved after gadolinium application in the apical portion of the right ileosacral joint in T1 weighted sequences (fig 1). MRI of the ileosacral joints showed no contrast enhancement at weeks 14 and 41 of treatment (fig 1).

The patient denied any loss of height. Conventional radiography showed no evidence of new bone formation. The pharmacological basis for TNFα inhibitory treatment in AS is the detection of TNFα-mRNA and TNFα protein in biopsy specimens of ileosacral joints of patients with active AS. In rheumatoid arthritis (RA) and Crohn’s disease (CD), several TNFα inhibitors seem to be successful in significantly reducing inflammatory activity.

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

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.

The case report suggests this is true also for long term treatment, even when constant therapeutic plasma levels are maintained.

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 TNFα 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.

Figure 2 Self assessment of pain on a 1–10 visual analogue scale (A) and CRP and ESR (B).
Retrocalcaneal bursitis in polymyalgia rheumatica

Polymyalgia rheumatica (PMR) is a relatively common disease of the elderly affecting the synovial membrane. Recent studies have emphasised the prominent involvement of the extra-articular synovial structures in both proximal and distal regions of the body. In the distal part of the arms, tenosynovial membrane inflammation is responsible for carpal tunnel syndrome, distal swelling of hands and feet, and with or without pitting oedema, and localised episodes of distal tenosynovitis.

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 spondarthritides.

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

Laboratory examination 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 with a significant sign of Achilles tendinosis 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 peripheral and distal inflammatory processes of PMR has only recently been demonstrated. The distal manifestations of PMR include tenosynovitis in addition to joint synovitis. 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. Tenosynovitis under the transverse carpal ligament may cause carpal tunnel syndrome. The involvement of the long flexor, posterior tibial and peroneal tendons may occur and has been documented with MRI.

To the best of our knowledge retrocalcaneal bursitis has never been reported in patients with PMR. Chiang et al found “bursitis- tendinitis” in 48/96 (50%) patients with PMR. Although they considered these as part of the disease, no mention of the affected bursa 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. The Achilles tendon is the primary site of inflammation. The typical gait and abnormal stance of cerebellar ataxia were also present.

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

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CORRECTION

Comorbidty and lifestyle, reproductive factors, and environmental exposures associated with rheumatoid arthritis
(Reckner Olson 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:
EULAR Executive Secretariat, Witikonerstrasse 15, CH-8032 Zurich, Switzerland
Tel: + 41 1 383 96 90; fax: + 41 1 383 98 10; email: secretariat@eular.org
Heavy cigarette smoking and RA

A T MASI, J C ALDAG and R L MALAMET

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Updated information and services can be found at:
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Supplementary material can be found at:
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MATTERS ARISING

Sciosis and Trendelenburg sign in a painting by P P Rubens

In an article on Rubens’ painting “The Three Graces” Dequeker suggests that hypermobility is a medical explanation of the seeming scoliosis and Trendelenburg sign in the middle figure.1 But the posture of this middle figure should probably be interpreted as an artistic phenomenon without medical reference. Sculptors in classical Greek and Roman periods often used the contrapposto posture. In this, by putting most weight on one leg, the other leg can be shown in a relaxed and semi-flexed position. This undulating between tension and relaxation will animate the figure. A person with normal muscular function and a normal back can perfectly well pose in this way with relaxed hip abductors on the weightbearing side, a descending hip on the opposite side, and a compensating scoliotic posture. This posture is facilitated by support from the arm as in Rubens’ painting. If the person tries to take a forward step, relaxation of the muscles of the weightbearing hip can no longer be maintained, and the positive Trendelenburg sign will disappear.

In the Renaissance period the use of this contrapposto posture was revived. During his stay in Rome Rubens eagerly studied the then recently excavated Laokoon sculpture with its three distorted figures.2 He often used such distorted postures in his paintings to give the impression of vigorous muscular characters capable of performing great tasks. The best example is probably “The Debakation at Marseilles” in the Maria de Medici cycle from 1622 to 1625 for the Luxembourg Palace in Paris.3 Here, three young women, nereides, with curved muscular backs at the bottom of the picture nearly seem to carry the ship of Maria de Medici.

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References

Authors’ response
Dr Hansen’s remarks about our recent article in the *Annals* are pertinent and have to be taken as an alternative explanation for the observed functional scoliosis and positive Trendelenburg sign. I am grateful for this artistic-historical information. However, this does not exclude the possible diagnosis of benign familial hypermobility syndrome. In several other paintings by Rubens, where the three sisters (sisters) of the graces are represented, clinical signs of hypermobility can be seen. In the painting “The Judgement of Paris” (London National Gallery) a positive Trendelenburg sign and scoliosis can be seen in the two blond sisters who are now in a walking position without support. In one of them the right wrist is in 90° hyperflexion. In the painting “Sine Cerere et Baccho friget Venus” (Brussels Koninklijke Musea voor Schone Kunsten), subluxation of the left wrist is seen in the dark blond sister and hyperextension of the distal interphalangeal (DIP) joint of the fourth finger in another sister with brown hair. Hyperextension of a DIP and metacarpophalangeal finger joint and hyperflexion of a wrist joint is also seen in the brown haired sisters of the painting “The Parnasso and Saints” (Antwerp, Sint-Jacobskerk).

1, as well as Sven Hansen, am fully aware that errors of diagnosis are commonly made either by seeing disease where none exists or by interpreting at face value a pathological appearance that is only the expression of an artistic convention. The observations made in P P Rubens’ painting, representing the sitters for “the graces” painting who are Rubens’ second wife Helen Froment and her younger sisters, are very suggestive of the diagnosis of benign familial hypermobility syndrome and not a purely artistic phenomenon.

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Reference

Comparison of WOMAC with SF-36 for OA of the knee or hip

Angst et al compared WOMAC with the SF-36 as tools to assess the outcome of a three to four week inpatient rehabilitation programme for people with osteoarthritis of the knee or hip.1 They concluded that both instruments capture improvement in pain levels, but functional improvement can be better detected by WOMAC. We have reservations about the use of SF-36 in this context.

We too provide residential musculoskeletal rehabilitation of usually three weeks duration and have been searching for a suitable instrument to assess quality of life at the time of discharge from our programme. We have rejected the SF-36 for the following reasons. A large majority of the questions in the SF-36 relate to the subject’s experience over the past four weeks. The condition of most of our patients improves considerably over the three weeks of treatment. It is therefore not appropriate to ask how they have been over the previous four weeks. We note that the period of treatment in the report by Angst et al varies from three to four weeks.

It is not only the length of time which makes the use of the SF-36 inappropriate in this setting, many of the questions assume the subject is living an everyday life. For example, inquiry is made about “both work outside the home and housework”, “other activities at home”, and “normal social activities with family, friends, neighbours, or groups”. Obviously if a person is devoting time and energy to an inpatient musculoskeletal rehabilitation programme they are in no position to be truly engaged in any of these work or social activities.

The while the outcomes of our similar residential rehabilitation programme for people with osteoarthritis are in accordance with those of Angst et al, we do not feel it is appropriate to use the SF-36 to measure improvement at discharge. It is of course quite reasonable to use it before admission and at three or six months’ follow up.

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Authors’ response
In their letter commenting on our article,1 Jones and Leighton deal with two major problems which might arise in the application of the SF-36 to inpatients. We would like to stimulate discussion about this issue by our following response.

The first problem concerns the fact that many of the SF-36 items ask about subjective health status over the past four weeks at the time of administration of the questionnaire. Jones and Leighton suggest, therefore, that the results at the end of an inpatient rehabilitation (three or four weeks) reflect some kind of an average of the health status during that rehabilitation period in which most of the patients have improved considerably. We agree that this assessment is unlikely to show the maximum of improvement that may be expected at the day of discharge from the clinic or shortly thereafter. However, one can assume that the result overestimates the health status for the time periods close to the day of administration of the questionnaire (for example, at the day of discharge) owing to the fact that the response is based on the patient’s memory. The same problem, but in the opposite direction, would arise if we administered the SF-36 two or four weeks after the day of discharge. Thus we possibly miss the maximal effect, which may last only a few days, but we do obtain an assessment of a certain time period, which is likely to be more valid and more clinically important than that of a single day. To take account of this point, we also reported results.
of the three month follow up (that is, two months after discharge) in our study in order to reflect the course of the effects and whether the different responsiveness of the SF-36 compared with the WOMAC remained consistent. In addition, we will publish further results of three-month evaluations up to the two year follow up of our patients during the next year.

The second issue deals with the fact that some items ask about activities of daily living and social participation which are not demanded or hardly possible to perform during a stay in the clinic. These are mainly the items contained in questions 4 (4a–4d) and five (5a–5c) comprising the role physical and role emotional. For this reason, we report these two scales as part of the SF-36 for the sake of completeness, but we did not include them in the analysis of the comparison of WOMAC and the SF-36. Nevertheless, item 8, which is the bodily pain scale, is also affected by this problem. Müller et al dealt with this issue recently.7 The authors created a modified SF-36m, which was adapted in items 4, 5, and 8 to the situation of a clinic stay. They concluded that bodily pain and role emotional did not show significantly different effects from those obtained by the original SF-36, but that the role physical scale was slightly more responsive in the SF-36m.

We used the SF-36 for three reasons. Firstly, the SF-36 assesses health status comprehensively—that is, not only pain and disease-specific scales as physical function, etc but also psychometric dimensions and dimensions of social participation. As a result, it allows a comparison of the results with those of the SF-36 and with the SF-36m. Secondly, the SF-36 can also be administered to “healthy” people and to patients with different diseases, which allows a comparison of the results with those for other patient groups and the general population. Thirdly, the SF-36 is one of the best tested, best known, and most widely used health measure all over the world.

Is pamidronate effective for acute rheumatic pain?

Parenteral pamidronate is licensed in the United Kingdom for the management of Paget’s disease, tumour related hypercalcaemia, and metastatic bone pain, where it can rapidly relieve symptoms. It is also widely used for the prevention and treatment of osteoporosis, although this represents unlicensed use of the drug, and there is some evidence that it can be rapidly effective for pain relief in patients with osteoporotic vertebral fractures.4,5 It has been used with some effect for the management of ankylosing spondylitis,6 but the full extent of any analgesic properties of the drug has not been fully explored. These properties became apparent to us quite by chance in the three cases described here.

Case reports

Patient A

A 25 year old female nurse with known ankylosing spondylitis was admitted to hospital with worsening back pain uncontrolled by regular opiate analgesia and a variety of potent non-steroidal anti-inflammatory drugs. Parenteral methylprednisolone was prescribed, followed by pamidronate 30 mg for “bone protection”. In the event, pamidronate was given but not methylprednisolone, deferred owing to unexplained pyrexia. Shortly after receiving her pamidronate, her intractable pain was so greatly improved that methylprednisolone was declared and she was discharged three days later. The improvement seen has been sustained for over six months. The unexpected analgesic effect of pamidronate in this case led to its use in two subsequent cases.

Patient B

A 38 year old housewife with chronic low back pain was admitted with a short history of acute back pain and a modestly raised C reactive protein (14 mg/l). Isotope bone scan showed increased uptake in the fifth lumbar intervertebral disc. Magnetic resonance imaging identified abnormal signal of the disc suggestive of discitis. An infective cause was suggested by the presence of an abnormal signal from this disc. The improvement seen has been sustained for two days later.

Patient C

A 33 year old male factory worker with a history of chronic arthritis since early childhood and spondyloarthropathy was admitted with generalised bone pain despite weekly oral methotrexate, phenylbutazone, and oral analgesia. Intercurrent diarrhoea was investigated but remained unexplained. Parenteral pamidronate 30 mg was given, leading to sustained improvement in his rheumatic pains.

Discussion

We believe these cases represent the first time that sustained analgesic efficacy has been attributed to a single dose of parenteral pamidronate in acute rheumatic pain not related to osteoporosis or neoplasia. The mechanism whereby pamidronate provides rapid onset sustained pain relief for metastatic bone disease or osteoporotic fractures is unknown. Many of the known effects of bisphosphonates on bone structure and cell populations are unlikely to be rapidly analgesic.7 However, it has been suggested that bones have complex sensory innervation, with nociception mediated by neuropeptides including substance P, prostaglandin E2, and calcitonin gene related peptide which may be influenced by bisphosphonates.8 There is no reason to believe that such an analgesic effect would be confined to bones affected by osteoporosis or neoplasm and might well extend to bone pain due to inflammation. In the three cases described many other factors might have contributed to the appearance of a parenteral pamidronate, including change. However, the results suggest that the potential role of pamidronate in the control of acute rheumatic pain warrants further evaluation.

References


Antibodies to β, glycoprotein I and cardiolipin in SSc

Systemic sclerosis (SSc) is a multisystem disease in which organ damage is attributed to fibrosis, microvascular occlusion, and proliferation of the vascular intima. The reported prevalence of antiphospholipid antibodies (aCL) in SSc varies from 0 to 25%,1,2 and reports of clinical associations have been variable.3–5 To our knowledge, only one study has examined antibodies to β, glycoprotein I (β,GP-I) in SSc and shown a correlation with pulmonary hypertension and raised mean pulmonary artery pressure.6 In our study we examined the frequency of β,GP-I and aCL in SSc and Raynaud’s phenomenon (RP).

Twenty six patients with SSc (16 diffuse, 10 limited), 23 with RP and 21 healthy volunteers (employees at the research facility) were included in this retrospective study. Informed consent was obtained. All 16 patients with diffuse SSc and one patient with limited SSc patients met American Rheumatism Association (ARA) preliminary criteria for scleroderma.7 The remaining nine with limited SSc had at least three of the following: sclerodactyly, calcinosis, Raynaud’s phenomenon, oesophageal dysmotility, telangiectasia, or positive anticientromere antibodies. The patients with RP had no manifestations of connective tissue disease. Clinical and laboratory assessments were recorded at the initial visit.
αβ2-GPI and aCL were measured by enzyme linked immunosorbent assay (ELISA; INOVA Diagnostics, Inc, San Diego, CA and Hemagen Diagnostics, Inc Waltham, MA, respectively). Commercially obtained HEp-2 slides (Immuno Concepts, Sacramento, CA) were used for indirect immunofluorescence (IIF). Samples were tested for antibodies to topoisomerase 1 (Scl-70), U1 ribonucleoprotein (U1-RNP), and Sjögren’s syndrome antigens A and B (SS-A/SS-B) by double immunodiffusion. Commercially obtained HEp-2 slides (Immunologicals, Inc, San Diego, CA and Hemagen Diagnostics, Inc Waltham, MA, respectively). The sera positive for aCL, which is higher than

Table 1: Demographics and laboratory results in patients with SSc, RP, and normal controls

<table>
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<tr>
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<th>Scleroderma (n=26)</th>
<th>Raynaud’s phenomenon (n=23)</th>
<th>Normal controls (n=21)</th>
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<td>Women</td>
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<td>12</td>
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<td>4</td>
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<td>50+</td>
<td>4</td>
<td>3</td>
<td>4</td>
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<td>Disease duration (months), mean (range)</td>
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<td>89.7 (1–364)</td>
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<td>Anticentromere antibodies</td>
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<td>5 (22%)</td>
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<td>4 (17%)</td>
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<td>Platelets (cells x 10^9/L)</td>
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<td>293 (SD 61)</td>
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<td>CK (µmol/L)</td>
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<td>9.2 (SD 1.0)</td>
<td>N/A</td>
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</table>

BUN, blood urea nitrogen; CK, creatine kinase.

*Comparison of age distribution versus Ssc.

Figure 1: Comparison of αβ2-GPI and aCL antibody levels in patients with SSc, RP, and normal controls. The numbers on the ordinate represent optical density values converted to SMU (standard IgM β2GPI units), MPL (1 MPL unit = the binding of 1 µg/mL IgM aCL), or GPL (1 GPL unit = the binding of 1 µg/ml IgG aCL). The arrows indicate the cut off values for each dataset.

Figure 2: Comparison of αβ2-GPI (IgM) and aCL (IgM) antibody levels in patients with SSc, RP, and normal controls.

αβ2-GPI (IgM) vs aCL (IgM)

αβ2-GPI (IgG) vs aCL (IgG)

References


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Recurrence of reactive arthritis after a booster dose of tetanus toxoid

We report the case of a 24 year old man who developed a recurrence of reactive arthritis after receiving a booster of tetanus toxoid.

Case report

A 24 year old man presented with acute swelling, hand pain, dysthesias and symptoms of ulnar neuritis. Two weeks before presentation, he had been given a booster tetanus toxoid vaccination. Within a few days of the injection, he felt pain and noticed swelling of the right ankle. The swelling and pain worsened, such that at presentation he was walking with a pronounced antalgic gait. There was no preceding history of trauma, infection, or any past history of psoriasis, iritis, inflammatory bowel disease, or inflammatory back pain. There was no family history of ankylosing spondylitis.

Three years previously he had presented to another rheumatologist with acute synovitis of the elbow, ulnar-sided metacarpophalangeal joint of the left big toe, and tenosynovitis of the long flexor of the right middle finger. This was associated with conjunctivitis and chlamydial urethritis, with raised levels of urease. The serology in this specific IgM ELISA was raised at 169 mPa.s; haemoglobin was 139 g/l, rheumatoid factor negative, and HLA-B27 positive. Plain radiographs of the left ankle, foot, and right hand showed no abnormalities. He was treated with indometacin and an intra-articular injection of triamcinolone to the left ankle as well as minocycline for himself and his partner. The conjunctivitis settled within a few days, the ulnar-sided metacarpophalangeal joint improved, and the patient noticed that the swelling of the right middle finger ceased. The patient was discharged to follow up, and was given no further treatment. He was told to avoid vaccination in the future, and was traceable for six months before becoming quiescent.

In the ensuing 23 years, he had attended the hospital a total of 13 times for pain in the right ankle, with tenderness and synovial thickening. The erythrocyte sedimentation rate was raised at 1.69 mPa.s; haemoglobin was 139 g/l, rheumatoid factor negative, and HLA-B27 positive. Physical examination at the second presentation showed swelling of the right ankle joint, with tenderness and synovial thickening. The subtaloid, mid-tarsal, and metatarso-phalangeal joints were fully mobile without pain or swelling. The erythrocyte sedimentation rate was raised at 36 mm/1 h.

Initially, triamcinolone was injected into the right ankle, indometacin 50 mg three times a day was prescribed, and he was given elbow crutches to stop him weight bearing on the right leg. Two weeks later there was partial improvement. Prednisolone (20 mg a day decreasing by 5 mg weekly) and entecort coated sulfasalazine (500 mg twice daily) were added. One month later the ankle synovitis and pain had settled.

Discussion

Several strands of evidence link different vaccine-induced arthritis to the development of a spectrum of arthritides. Often, a close temporal relation between vaccination and the onset of arthritis exists, allowing an inference about the influence of a particular vaccine. On this basis, tetanus toxoid injection has been associated with the development of rheumatoid arthritides, comprising a symmetrical inflammatory polyarthritis and positive rheumatoid factor. Recombinant hepatitis B vaccination has also produced a similar picture. Symmetrical small joint polyarthritis but with negative rheumatoid factor has been described in association with intravesical Bacillus Calmette-Guérin (BCG) vaccine used as immunotherapy for bladder carcinoma.

The spectrum of arthritis associated with vaccination is illustrated by the induction of large joint monarthritis by combined diphteria, poliomyelitis, and tetanus toxoid vaccine.1 In one of these cases, synovectomy was curative until a booster vaccination five years later caused recurrence, and, indeed, it has been suggested that rechallenge with vaccine may be associated with more severe symptoms.2 Further evidence for the role of vaccines in arthritis comes from monitoring of adverse drug reactions, with one survey indicating a causal link between rubella vaccination and acute and chronic arthritis, especially in women.3 The mechanisms underlying arthritis associated with vaccination are not yet fully understood. A cross reaction between bacterial lipopolysaccharide epitopes and synovial antigen, leading to an idiotype-anti-idiotype immunological response enhanced by HLA-B27 expression, may provide one model.4 However, HLA-B27 expression is not a pre-requisite for arthritis linked to vaccines although its presence may predict a more prolonged and severe course.5 Vaccines may also trigger autoimmune responses by binding to critical antigen binding clefts on the major histocompatibility complex class II molecule, thereby triggering T cell proliferation.6 The impact of vaccination associated with vaccination can be severe, with prolonged and significant morbidity lasting many months. Hassan and Oldham reported Reiter’s syndrome with joint pain and monitoring of HLA-B27 lasting many months, whereas Bracci and Zippini additionally reported fevers and lymphadenopathy with the hepatitis B surface antigen vaccine (Engerix B).7 However, as with our case, appropriate treatment, including non-steroidal anti-inflammatory drugs and intra-articular or oral steroids, can be useful in limiting the duration and degree of symptoms.

Vaccination has also been shown to cause necrotising vasculitis. Leucocytoelastic vasculitis has been induced most often, but polyarteritis nodosa-like and systemic vasculitides have also been reported in a few instances.11 In children, two other syndromes may occur after rubella vaccination (and natural infection): (a) the “arm syndrome,” in which brachial radiculoneuropathy causes arm and hand pain, and arterial lesions that are worse at night; (b) “catcher’s crouch,” a lumbar radiculoneuropathy causing pain in the popliteal fossa on arising in the morning, which is exacerbated by knee extension and improves in a “catcher’s crouch” position. Both syndromes occur one to two months after vaccination. Although the initial episode may last up to two months, relapses may occur for up to a year, eventually resolving completely without permanent sequelae.

Our case highlights a relationship between vaccination and arthritis and the ability of vaccine to trigger a reactive arthritis in a susceptible person. Although the mechanisms of vaccination and reactive arthritis are not clear, there is sufficient evidence to suggest that some vaccines may cause joint disease or adversely affect pre-existing joint problems. It would therefore be prudent to warn patients awaiting vaccination about the possible adverse effect on joint symptoms.

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References


Asymptomatic splenic infarction in Wegener’s granulomatosis

Wegener’s granulomatosis (WG) is a necrotising, granulomatous vasculitis that classically involves the clinicopathological triad of upper and lower respiratory tracts and the kidney.1 Less frequently, the disease may affect other organs as well. Serious and occasionally fatal complications within the spleen occur in many autoimmune rheumatic diseases,2,3 and prompt recognition of these complications is important. In a retrospective review of patients with WG, the spleen was commonly affected: 78–100% of patients had splenic lesions with a combination of necrosis, vasculitis, and granuloma formation.4 Clinically apparent splenic disease is rare, however.5 We wish to report briefly the case of a 47 year old woman who presented with manifestations of classical WG and radiological evidence of splenic infarcts.
A 47 year old woman during the past month developed fevers to 38.6°C associated with weight loss, diffuse arthralgias, anaemia, and renal function progressively recovered. A recently collected urinary sediment showed the presence of red blood cell casts. Renal function declined rapidly with a serum creatinine level of 600 µmol/l and the patient was referred to the hospital for further investigation. A positive cANCA titre (1/160) was found using the indirect fluorescence technique and a positive antiproteinase 3 result on enzyme linked immunosorbent assay (ELISA; 66 U/ml). WG was considered on the basis of ANCA analysis results and the multisystemic nature of the disease and a percutaneous renal biopsy was performed under computed tomography (CT) guidance. Evaluation of renal biopsy specimens with light microscopy and immunofluorescence showed an acute necrotising segmental pauci-immune glomerulonephritis with crescent formation in more than 50% of the glomeruli. An impressive and rather unexpected CT finding was the presence of well defined areas of low attenuation within the spleen, consistent with splenic parenchymal arteriolitis and necrosis, dissemi-nated visceral granulomata, and capsulitis. On CT, splenic infarcts classically and more com-monly appear as peripheral, well defined, wedge shaped areas of low attenuation. However, other patterns of infarction have been recognised. These include multiple heterogeneous low attenuation lesions; regions of normal enhancement centrally with peripheral low attenuation; and large, low attenuation hypodense lesions that may have a rim of enhancing tissue peripherally.1 Examination with ultrasound in combination with duplex sonography of splenic blood supply permits assessment of the extent of splenic infarction.2 Splenic involvement in WG may be more prevalent than previously believed.3,4 Pain in the left upper quadrant and left shoulder and fever may be present after splenic infarction, but many patients remain asymptomatic.3 Consequently, cross sectional imaging is not often carried out and the lesion may freq-uently go unrecognised. Unless there are signs of imminent rupture of the spleen or bleeding,3 a conservative approach is justi-fied. In the long term these patients may be more susceptible to pneumococcal infection because of the functionally asplenic condition.2 This possibility provides further help in the diagnosis of this rare condition in vivo.

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References

Two cases of Mycobacterium avium septic arthritis

The “unusual and memorable” case reported by Ter Borg and ‘Tersmette’ serves as a useful reminder that atypical mycobacterial infections, although uncommon, need to be considered in immunocompromised patients. We present here two case reports of patients with pre-existing rheumatic disease receiving immunosuppressive treatment, who developed septic arthritis due to Mycobacterium avium intracellulare.

Case one
A 51 year old woman presented in 1999 with Raynaud’s phenomenon, facial telangiectasia, sclerodactyly, and a positive antinuclear antibody. She complained of exertional dyspnoea, Raynaud’s phenomenon, facial telangiectasia, cervical lymphadenopathy, and Raynaud’s phenomenon. A chest x-ray examination showed a left upper lobe lesion, and her family doctor prescribed oral amoxicillin in combination with clarithromycin, and her family doctor prescribed oral amoxicillin in combination with clarithromycin, without improvement. Ten days before admission gross haematuria was noted and a freshly collected urinary specimen showed the presence of blood cell casts. Renal function was normal. The patient was referred to the hospital for further investigation. A positive cANCA titre (1/160) was found using the indirect fluorescence technique and a positive antiproteinase 3 result on enzyme linked immunosorbent assay (ELISA; 66 U/ml). WG was considered on the basis of ANCA analysis results and the multisystemic nature of the disease and a percutaneous renal biopsy was performed under computed tomography (CT) guidance. Evaluation of renal biopsy specimens with light microscopy and immunofluorescence showed an acute necrotising segmental pauci-immune glomerulonephritis with crescent formation in more than 50% of the glomeruli. An impressive and rather unexpected CT finding was the presence of well defined areas of low attenuation within the spleen, consistent with splenic parenchymal arteriolitis and necrosis, disseminated visceral granulomata, and capsulitis. On CT, splenic infarcts classically and more commonly appear as peripheral, well defined, wedge shaped areas of low attenuation. However, other patterns of infarction have been recognised. These include multiple heterogeneous low attenuation lesions; regions of normal enhancement centrally with peripheral low attenuation; and large, low attenuation hypodense lesions that may have a rim of enhancing tissue peripherally.1 Examination with ultrasound in combination with duplex sonography of splenic blood supply permits non-invasive diagnosis of splenic infarction.2 Splenic involvement in WG may be more prevalent than previously believed.3,4 Pain in the left upper quadrant and left shoulder and fever may be present after splenic infarction, but many patients remain asymptomatic.3 Consequently, cross sectional imaging is not often carried out and the lesion may frequently go unrecognised. Unless there are signs of imminent rupture of the spleen or bleeding,3 a conservative approach is justified. In the long term these patients may be more susceptible to pneumococcal infection because of the functionally asplenic condition.2 This possibility provides further help in the diagnosis of this rare condition in vivo.

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Case two
A 36 year old man presented in 1993 with arthralgia, proximal muscle weakness, and a creatine kinase of 12,000 U/L. Muscle biopsy confirmed the diagnosis of polymyositis. Treatment with prednisolone (initially 60 mg daily) and azathioprine 150 mg was started. In 1997 he developed auxiliary lymphadenopathy, and subsequent biopsy showed M tuberculosis. A good clinical response was achieved with rifampicin, isoniazid, and ethambutol. In 1999 synovitis developed in the left knee and right wrist. Both joints were aspirated and injected with corticosteroids after initial Gram stain, Zielh-Neelsen stain, and bacterial culture were negative. Eight weeks later, M avium was cultured from fluid in the left knee, and treatment with clarithromycin, ethambutol, and rifampicin was started. Histology from a right wrist tenosynovectomy six months later demonstrated granulomas, and culture confirmed the presence of M avium. At present, the patient continues to receive treatment with prednisolone 7.5 mg daily and azathioprine 150 mg daily, together with the antityphus bacterial therapy, but clinical evidence of septic arthritis remains.

Discussion
Infective arthritis due to M avium is rare, mostly commonly occurring in immunocompromised subjects, such as those receiving immunosuppressive drugs, or HIV positive patients. The most commonly affected joint is the knee. Up to 40% of patients with atypical mycobacterial septic arthritis have received prior intra-articular corticosteroid injection in the affected joint. Diagnosis of these infections rests on culture of the synovial fluid (approximately 15%), or culture of surgically obtained specimens, though the often insidious nature of the infection may lead to a delay in diagnosis of many years. Antimycobacterial treatment is given (dependent on sensitivities), with or without surgery (see chapter 8). Prognosis is variable, but most patients can expect to make reasonable or good functional recovery. In summary, we report two cases of septic arthritis due to M avium, in patients with previously diagnosed inflammatory arthritis, who had received azathioprine and systemic and intra-articular corticosteroids. Arthritis with significant synovitis is not a common feature of dermatoysitis or scleroderma and therefore M avium should be considered as a diagnosis in patients receiving these drugs.

Successful radiosynoviorthesis of an olecranon bursitis in psoriatic arthritis
We describe the case of a 45 year old male patient who for more than 10 years had psoriasis with typical manifestations at knees and elbows. The family recalled psoriasis of the grandfather. Without any trauma or special strains, an olecranon bursitis and an arthritis of the left elbow developed in 1999 as the initial manifestation of psoriatic arthritis. Three months after developing the bursitis, the patient came to the rheumatological outpatient clinic for his first visit. The clinical findings showed a patient with good general condition (height 186 cm; weight 93 kg), blood pressure 120/80 mm Hg, rhythmic pulse rate 68 beats/min; psoriatic skin lesions at knees and elbows; no reduction of spine mobility. The left elbow showed an olecranon bursitis with a diameter of 50 mm. The remaining musculoskeletal system was not affected.

The laboratory results were within the normal ranges, HLA-B27 was negative, anti-nuclear antibodies negative, functional tests of liver and kidney were normal. Radiographic findings showed that sacro-iliac joints and the left elbow joint were normal. Sonography showed an olecranon bursitis with a large effusion (fig 1A). Diclofenac 100 mg twice daily was given for the first two weeks but did not produce any effect. After that, the olecranon bursa was punctured aseptically, and a crystal suspension of 10 mg triamcinolone hexacetonide was injected. Two days later, the bursitis relapsed completely. Further therapeutic options were surgical bursectomy or, alternatively, radiation synovectomy. After having received complete information, the patient gave his consent to treatment by radiosynoviorthesis. After aspiration of 9 ml of a serous effusion, 55 Mibi thallium-185 was instilled into the olecranon bursa, and then, to avoid radiosynovitis, 5 mg triamcinolone was injected. Radiosynovectomy was performed immediately after the injection and three days later showed that the radionuclide was distributed uniformly in the bursa. There were no local signs of an infection.

A physical examination three months after radiation synovectomy of the olecranon bursitis showed regular clinical findings. Arthrosonographic results had also normalised (fig 1B). Even six months later the bursitis was not reactivated. Radiation synovectomy is often used as an alternative, or in addition to, surgical synovectomy. Definite indications are chronic persisting synovitis, intermittent hydrops, relapsing synovitis after surgical synovectomy, rheumatoid polyarthritis, and activated osteoarthritis resistant to other treatments. Some studies have reported successful concomitant treatment of Baker’s cysts in the treatment of psoriatic arthritis, but radiosynovectomy has been reported. As far as we know this is one of the first reports on radiosynovectomy in an isolated bursitis. This case gives cause for hope that radiosynoviorthesis represents a successful alternative treatment to operational intervention for chronic inflammation of the bursa.

References

Figure 1 Sonography of the left elbow (A) showing an olecranon bursitis (5.8 1 mm; 17.7 mm; 3 mm; 2.5 mm) and (B) three months after radiation synovectomy.
Multiple sclerosis in the course of systemic sclerosis

We describe the case of a young woman with long-standing systemic sclerosis (SSc), who later developed multiple sclerosis (MS), and discuss the possible explanations for this rare co-occurrence.

A 30 year old white woman was admitted to the department of neurology of our institution with 10 days’ history of vertigo and diplopia. A year earlier the patient had had an episode of paraesthesiae of her right leg, which resolved spontaneously within two to three weeks. Since the age of 22, she had been under the care of the rheumatology service of the same hospital for SSc, and her condition remained stable with treatment with p-penicillamine 500 mg daily and methylprednisolone 2 mg daily.

Clinical examination showed an alert woman with normal vital signs and typical appearance of scleroderma—that is, tightness and atrophy of the skin of her face and hands with contractions of her fingers. Examination of the lungs, heart, and abdomen showed no abnormality. Fundoscopy disclosed temporal pallor bilaterally. There was vertical nystagmus on upward gaze and diplopia on looking to the right, without apparent ophthalmoplegia. Deep tendon reflexes were brisk and abdominal reflexes were absent bilaterally. An extensor plantar response was seen on the right but no muscle weakness or sensory loss was noted. There was no evidence for keratoconjunctivitis sicca, as Schirmer’s I, rose bengal, and break up time eye tests were normal. These had been performed routinely several times previously before the present admission. Furthermore, the patient had never complained of xerostomia.

Routine blood tests were normal. Serology showed positive antinuclear antibodies at a titre of 1:640, of the fine speckled pattern, and positive anti-Scl70 antibodies. Antibodies to cardiolipin and the other extractable nuclear antigens, including Ro(SSA), La(SSB), Sm, and nRNP, were absent, as they had been on several occasions in the past. Visual evoked potentials were abnormal bilaterally. Cerebrospinal fluid (CSF) analysis disclosed increased intrathecal IgG synthesis (IgG index 0.88, normal <0.66) and oligoclonal bands. Magnetic resonance imaging (MRI) studies showed several abnormalities of the brain and the cervical cord (fig 1).

A five day trial of intravenous methylprednisolone 500 mg/day resulted in moderate relief of her symptoms and treatment was started with interferon β to prevent progression of the neurological process. At present, the patient has been receiving interferon β for two years and there is no evidence of any further neurological compromise.

One can suggest three possibilities for the coexistence of the neurological syndrome and the SSc in this patient. Firstly, MS occurring independently from SSc might account for the neurological deficits, given the laboratory findings and the patient’s sex and age, and the prevalence of MS in the general population. However, it is also possible that there is an association between the two conditions, because MS, like SSc, is also believed to be autoimmune in nature, and the pathogenetic role of T cells is crucial in both processes. Furthermore, MS has been increasingly reported in association with other autoimmune diseases not primarily affecting the nervous system. If any of the above possibilities is present, the prognosis and therapeutic approach of our patient should match those of typical MS. The coexistence of SSc and MS is rare and, as far as we know, has been described in only four patients. Rapidly progressive and finally gripping MS developed in their early twenties, whereas SSc appeared later in the course of the MS in all four patients. Interestingly, unlike these cases, our patient presented in her thirties with a mild form of MS, several years after the onset of SSc.

A third possibility exists that, the neurological manifestations of this patient might have been part of her primary disease—that is, SSc. Involvement of the central nervous system (CNS) in this disease is considered uncommon, and secondary to vasculopathic damage. The fact that our patient had prolonged visual evoked potentials, suggestive of optic neuropathy, is rather in favour of MS, although this abnormality has been reported in SSc. On the other hand, a significant percentage of patients with systemic lupus erythematosus may present with optic neuropathy, and some of them with oligoaxial banding in the CSF. Brain or spinal cord disease, or both, with clinical features and laboratory findings indistinguishable from MS has been reported in Sjögren’s syndrome too, although CNS involvement in this syndrome has been a matter of serious debate.

In the absence of guidelines for the management of such patients, we considered our patient as a case of classical MS, and, therefore, she was deprived of the possible benefit of a disease modifying treatment, such as interferon β.

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References
The authors of this letter, in a further analysis of their data, found that four heavy smokers in the control group were incorrectly included in the 168 subjects matched to the 42 pre-RA cases who had baseline negative rheumatoid factor (RF−) status. They should be correctly reassigned to the 48 matched controls for the 12 pre-RA cases who had baseline positive rheumatoid factor (RF+) status.

The correct assignments place 11 (23%) heavy smokers in the 48 controls for the 12 pre-RA RF+ cases. Those 12 cases include two (17%) heavy smokers. The 168 controls for the 42 pre-RA cases who had baseline negative rheumatoid factor (RF−) status should correctly include eight (5%) heavy smokers. Those 42 cases include 11 (26%) heavy smokers. The new correct figures are shown in bold in the table.

The correct assignments strengthen the findings in this prospective, community based study that baseline heavy cigarette smoking was an independent risk factor from baseline positive rheumatoid factor status.

### 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

<table>
<thead>
<tr>
<th>Categories</th>
<th>Pre-RA cases</th>
<th>Respective matched controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>CS 30+/day (%)</td>
</tr>
<tr>
<td>Pre-RA RF+</td>
<td>12</td>
<td>2 (17)*</td>
</tr>
<tr>
<td>Pre-RA RF−</td>
<td>42</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Entry and post-RA RF−</td>
<td>15</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Conversion of pre-RA RF− to RF+†</td>
<td>27</td>
<td>7 (26)</td>
</tr>
</tbody>
</table>

*No association of CS 30+/day with pre-RA RF+ (p=0.99).
†Conversion of RF− at baseline to RF+ after clinical onset of RA.

Corrections printed in the journal also appear on the Annals website www.annrheumdis.com and are linked to the original publication.
FORTHCOMING EVENTS

3rd International Congress on Autoimmunity
20–24 Feb 2002; Geneva, Switzerland
Contact: Professor Yehuda Shoenfeld, 3rd International Congress on Autoimmunity, PO Box 50006, Tel Aviv 61500, Israel
Tel: 9723 514 0018
Fax: 9723 517 5674
Email: autoimm2@kenes.com

22nd European Workshop for Rheumatology Research
28 Feb–3 Mar 2002; Leiden, The Netherlands
Contact: Professor F C Breedveld, Leiden University Medical Centre, Department of Rheumatology, PO Box 9600, 2300 RC Leiden, The Netherlands
Tel: +31 (0)71 526 3598
Fax: +31 (0)71 526 6752
Email: F.C.Breedveld@lumc.nl
Website: www.eurrr.org

Tenth Intensive Applied Epidemiology Course for Rheumatologists
11–15 Mar 2002; Manchester, UK
No previous experience in epidemiology is needed. The course is residential and limited to 25 places.
Contact: Ms Lisa McClair, ARC Epidemiology Unit, University of Manchester, Oxford Road, Manchester M13 9PT, UK
Tel: +44 (0)161 275 5993
Fax: +44 (0)161 275 5043
Email: Lisa@stf1.ser.man.ac.uk

OMERACT VI
11–14 Apr 2002; Bali
Includes two modules: MRI and economics; and four workshops: patients’ perceptions, imaging (healing), progressive systemic sclerosis, minimally important clinical difference and osteoarthritis
Contact: Conference Organisers Q2O, 7 Swann Street, Old Isleworth, Middlesex TW7 6RJ, UK; or Peter Brooks, Faculty of Health Sciences, Level 1, Edith Cavell Building, Royal Brisbane Hospital, Herston 4029, Australia
Fax: +44 208569 9555
Email: tony@q2q.co.uk or p.brooks@mailbox.uq.edu.au

British Society for Rheumatology
XIXth AGM
23–25 Apr 2002; Brighton, UK
Contact: BSR, 41 Eagle Street, London WC1R 4TL, UK
Website: www.rheumatology.org.uk

4th EULAR Sonography Course
25–28 April 2002; Madrid, Spain
The course is entitled “Practical use of musculoskeletal ultrasonography”
Contact: Esperanza Naredo
Email: enaredo@eresmas.com
Website: www.eular.org/courses and www.sameint.it/eular

10th International Vasculitis and ANCA Workshop
29–28 Apr 2002; Cleveland, Ohio, USA
Contact: Deborah J Bork, The Cleveland Clinic Foundation, Desk A50, Center for Vasculitis Care and Research, 9500 Euclid Avenue, Cleveland, OH 44195, USA
Tel: 216 445 8533
Fax: 216 445 7569
Email: borkd@ccf.org
Website for registration and abstract submission: www.clevelandclinicmeded.com/courses/Vasculitis2002.asp

International Congress: New Trends in Osteoarthritis
9–11 May 2002; Milan, Italy
Contact: Organising Secretariat, O.I.C. S.r.l., Via Fatebenefratelli 19, 20121, Milan, Italy
Tel: +39 02 65 71 200
Fax: +39 02 65 71 270
Email: osteoarthritis@oic.it

IOF World Congress on Osteoporosis
10–14 May 2002; Lisbon, Portugal
Contact: IOF Secretariat, 71 cours Albert Thomas, F-69003 Lyon, France
Tel: +33 472 91 41 77
Fax: +33 472 36 90 52
Email: info@ioflyon.org
Website: www.osteofound.org

5th European Conference on Systemic Lupus Erythmatosus
26–30 May 2002, Athens, Greece
Chairman Professor HM Moutsopoulos Secretariat: Amphi-trion Congress Organising Bureau
Email: hmoutsop@med.uoa.gr
Email: congress@amphi-trion.gr

Annual European Congress of Rheumatology
12–15 June 2002; Stockholm, Sweden
Contact: Fred Wiss, Executive Secretary EULAR, Vitikonstrasse 15, CH-8032, Zurich, Switzerland
Tel: +41 1 383 9690
Fax: +41 1 383 9810
Email: eular@bluelca.org
Website: www.eular.org

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27–29 June 2002; Berlin, Germany
Under the auspices of the International Society for Behcet’s Disease
Up to eight young investigator awards, each of $500, will be awarded on the basis of abstracts submitted
Contact: Professor Ch C Zouboulis, Department of Dermatology, University Medical Centre Benjamin Franklin, The Free University of Berlin, Fabrickstrasse 60–62, 14195 Berlin, Germany
Fax: 49 30 84456908
Email: zoubbere@zedat.fu-berlin.de
Website: www.userpages.fu-berlin.de/~zoubbere
ISBD website: www.behcet.ws

29th Scandinavian Congress of Rheumatology
15–18 Aug 2002; Tromso, Norway
Contact: Hans Nossent, Department of Rheumatology, University Hospital Tromso, Norway
Tel: 47 776 27294
Fax: 47 776 27288
Email: 29scrc2002@rito.no or revhan@rito.no

Translational Research in Autoimmunity
21–22 Sep 2002; Pavia, Italy
Contact: Oragnising secretariat: eventi S.R.L., Corso Cavour, 18/20 – 27100 Pavia, Italy
Email: tras@e20pr.com
Website: www.e20pr.com
Congress website: www.medicine.ucsd.edu/albani/2001meeting

OsteoArthritis Research Society International (OARSI) World Congress
22–25 Sep 2002; Sydney, Australia
Contact: OsteoArthritis Research Society International (OARSI), 2025 M Street, NW, Suite 800, Washington DC 20036, USA
Tel: +1 202 367 1177
Fax: +1 202 367 2177
Email: oarsi@oarsi.org
Website: www.oarsi.org

10th International Congress on Antiphospholipid Antibodies
29 Sep–3 Oct 2002; Sicily, Italy
Deadline for abstracts 1 April 2002
Contact: Secretariat, 10th International Congress on Antiphospholipid Antibodies, c/o Kenes International, PO Box 50006, Tel Aviv 61500, Israel
Tel: 972 3 514 0018
Fax: 972 3 514 0077 or 972 3 517 2484
Email: aps@kenes.com
Website: www.kenes.com/aps

7th International Conference on Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation and Related Diseases
14–17 Oct 2002; Nashville, Tennessee, USA
Contact: Lawrence J Marnett, Biochemistry Department, Vanderbilt University, School of Medicine, Nashville TN 37232-0146, USA
Tel: (615) 343 7329
Fax: (615) 343 7534
Website: www.eicosanoids.science.aaync.edu

66th American College of Rheumatology AGM
25–29 Oct 2002; New Orleans, USA
Contact: ACR, Ronald F Olejko, Director of Conferences and Meetings, 1800 Century Place, Suite 230, Atlanta, Georgia 30045-4300, USA
Tel: +1 404 633 3777
Fax: +1 404 633 1870
Email: acr@rheumatology.org
Website: www.rheumatology.org

Third International Meeting on Social and Economic Aspects of Osteoporosis and Osteoarthritis
7–9 November, 2002; Barcelona, Spain
Contact: Yolande Piette Communication, Boulevard Kleyer 108, 4000 Liège, Belgium
Tel: 34 2 254 12 25
Fax: 34 2 254 12 90
Email: ypc@compuserve.com

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18 Nov 2002
Contact: American Board of Pediatrics, 111 Silver Cedar Court, Chapel Hill, NC 27514-1513, USA
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Fax: 919 918 7114 or 919 929 9255
Website: www.abp.org