Thrombophilia and thrombosis in systemic lupus erythematosus: a case-control study

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Antiphospholipid/cofactor antibodies are detected in only 60% of patients with systemic lupus erythematosus (SLE) with thrombosis. Therefore, we studied thrombophilia factors and their relation with thrombosis in patients with SLE.

METHODS AND RESULTS
Forty-eight consecutive patients with SLE were included (39 women, 9 men), 15 with and 33 without past thrombosis (Th and NTh group, respectively). Twenty thrombotic events were identified: 17 deep venous and 1 arterial thrombosis, 2 osteonecrosis. Both groups had comparable clinical, biological, therapeutic data, and mean (SD) SLE disease activity index (SLEDAI) (5 (4.6) v 5.3 (4.8)).

Patients were examined at least one month after thrombosis (>3 months in 11 out of 15). The following parameters were determined: protein C, total and free protein S (in 43 patients because five had antivitamin K treatment), antithrombin, activated protein C resistance (APCR), prothrombin gene mutation of the factor V gene and the G20210A allele of the prothrombin gene, lupus anticoagulant (LAC) (activated partial thromboplastin time, tissue thromboplastin inhibition test, and platelet neutralisation procedure), IgG anticardiolipin antibodies (aCL) (>20 GPL), anti-β2-glycoprotein I (anti-β2GPI) antibodies, IgG and IgM antiprothrombin antibodies. Homocysteinaemia (fasting and after oral methionine load (100 mg/kg)) was measured in 38 patients (9 Th, 29 NTh patients). Table 1 gives the main results. LAC and aCL (>30 GPL) were closely associated with thrombosis in SLE.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Thrombophilic factors in patients with SLE with (Th) or without (NTh) thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=48)</td>
<td>Th (n=15)</td>
</tr>
<tr>
<td>LAC, No (%)</td>
<td>15 (31)</td>
</tr>
<tr>
<td>aCL &gt;20 GPL, No (%)</td>
<td>11 (23)</td>
</tr>
<tr>
<td>aCL &gt;30 GPL, No (%)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Anti-β2GPI+, No (%)</td>
<td>9 (19)</td>
</tr>
<tr>
<td>APCT+, No (%)</td>
<td>17 (35)</td>
</tr>
<tr>
<td>Mean (SD) protein C (activity %)</td>
<td>114 (28)</td>
</tr>
<tr>
<td>Mean (SD) free protein S (activity %)</td>
<td>85 (23)</td>
</tr>
<tr>
<td>Mean (SD) antithrombin (activity %)</td>
<td>102.6 (170)</td>
</tr>
<tr>
<td>APCR, No (%)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Prothrombin gene mutation, No (%)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Mean (SD) homocysteinaemia</td>
<td>11.5 (5)</td>
</tr>
<tr>
<td>Fasting (µmol/l)</td>
<td>46 (34.5)</td>
</tr>
</tbody>
</table>

LAC, lupus anticoagulant; aCL, anticardiolipin antibodies; Anti-β2GPI, anti-β2-glycoprotein I; APCR, activated protein C resistance.

DISCUSSION
Our results confirm that LAC and aCL (>30 GPL) are closely associated with thrombosis in SLE. Anti-β2GPI antibodies do not add any information to LAC, and anti-β2GPI and antiprothrombin are not associated with thrombosis. Transiently negative results are unlikely because patients were sampled at least one month after the thrombosis.

As in previous studies, decreased free protein S is common (19%) but not associated with thrombosis. Antiphospholipid/cofactor antibodies are more prevalent in patients with protein S deficiency, suggesting an autoimmune mechanism that might involve antiprotein S antibodies. The negative correlation between free protein S level and SLE activity suggests a link between disease activity and coagulation activation, although we were unable to demonstrate an association between thrombosis and protein S level.

Mild hyperhomocysteinaemia was common (37%) and closely correlated with mild renal function impairment but not with the steroid regimen. Hyperhomocysteinaemia is an arterial thrombosis risk factor in SLE, and it was not associated with the mainly venous thrombosis in our sample.
Genetic thrombophilia was no more prevalent than in the general population.

Finally, we confirm that LAC and aCL >30 GPL units are the main thrombophilic factors associated with thrombosis in SLE. The role of free protein S and homocysteinaemia remains unclear. Prospective studies, with serial sampling, are needed to elucidate which others factors may play a part.


**References**


patients with SLE. We could not detect increased frequencies of the DQβ1*0303 and DQβ1*0502 alleles in our patients with SLE, and our patients with DRB1*1501 positivity exhibited a milder clinical course and a negative correlation with LN.

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**REFERENCES**


**HLA-B27 in patients with a permanent pacemaker**


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In summary, in this observational study patients with a permanent pacemaker were no more likely to be HLA-B27 positive than a group of population controls.

**Authors’ affiliations**


**REFERENCES**

1 Bottiger LE, Edhag O. Heart block in ankylosing spondylitis and ankyloarthritis. Br Heart J 1972;34:487–92
4 Bergfeldt J, Moller E. Pacemaker treated women with heart block have no increase in the frequency of HLA-B27 and associated rheumatic disorders in contrast to men - a sex linked difference in disease susceptibility. J Rheumatol 1986;13:941–3
Effect of D-penicillamine on pulmonary fibrosis in patients with systemic sclerosis
M Jinnin, H Ihn, Y Asano, K Yamane, N Yazawa, K Tamaki

It has been shown by some researchers that D-penicillamine stabilises or even improves pulmonary fibrosis in systemic sclerosis (SSc), and has a beneficial effect on patient survival, but this has been questioned by others. These controversial results from previous uncontrolled studies were due to short term treatment, absence of control subjects, small number of patients, or the lack of objective criteria for the determination of improvement or deterioration. In this report, we describe a retrospective study of the effect of D-pen treatment in 65 Japanese patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with SSc with pulmonary fibrosis (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex [male:female]</td>
<td>5:20   2.38</td>
</tr>
<tr>
<td>Mean age at onset (years)</td>
<td>41.6 (15.5) 44.3 (12.0)</td>
</tr>
<tr>
<td>Type [diffuse:limited]</td>
<td>18.7 21.19</td>
</tr>
<tr>
<td>Duration of onset—first visit (years)</td>
<td>6.4 (6.3) 9.8 (9.6)</td>
</tr>
<tr>
<td>Follow up duration (years)</td>
<td>3.7 (2.1) 3.1 (1.7)</td>
</tr>
<tr>
<td>Taking corticosteroid (+/-)</td>
<td>5.20 16.24</td>
</tr>
<tr>
<td>%VC</td>
<td>81 (13.7) 89 (21.9)</td>
</tr>
<tr>
<td>%TLCO</td>
<td>89 (20.4) 81 (16.4)</td>
</tr>
</tbody>
</table>

SSc, systemic sclerosis; D-Pen, D-penicillamine; %VC, percentage vital capacity; %TLCO, percentage carbon monooxidase transfer factor.

PATIENTS AND METHODS
Thirty nine patients with diffuse cutaneous SSc (dcSSc) and 26 with limited cutaneous SSc (lcSSc)* with pulmonary fibrosis were randomly enrolled in this study (table 1). None of the patients had received any treatment by their first visit, and had taken no drugs which might affect pulmonary disease, except for D-Pen (100–600 mg/day) and corticosteroid during the follow up period. The percentage predicted vital capacity (%VC) and percentage predicted carbon monoxide transfer factor (%TLCO) were measured by pulmonary function test. Chest computed tomography (CT) or chest x ray examination was used for the evaluation of alveolitis or fibrosis.

The change in pulmonary fibrosis was evaluated for the patients with D-Pen treatment and those without during the follow up period, by measuring six variables; average of the changes in %VC or %TLCO levels of each patient (%VC or %TLCO levels before treatment minus those after treatment), prevalence of patients with over 5% reduction of %VC or %TLCO levels during the follow up period, and prevalence of patients with progression of alveolitis or fibrosis in chest CT or x ray examination during the follow up period. We also evaluated the interaction between D-Pen and each of the following factors: (a) extent of skin involvement (diffuse/limited) (b) duration of disease at the first visit (over/under 10 years); (c) duration of D-Pen treatment (over/under 3 years), and (d) taking corticosteroid treatment (+/-).

Statistical analysis was carried out with a Student’s t test for the comparison of means, and Fisher’s exact probability test for the analysis of frequency. The interaction of two factors

| Table 1 Patients characteristics. Values means (SD) if not indicated |
|-----------------|--------|---------|
| Characteristic  | Patients with SSc with pulmonary fibrosis (n=65) |
|-----------------|--------|---------|
| Sex [male:female] | 5:20   2.38 |
| Mean age at onset (years) | 41.6 (15.5) 44.3 (12.0) |
| Type [diffuse:limited] | 18.7 21.19 |
| Duration of onset—first visit (years) | 6.4 (6.3) 9.8 (9.6) |
| Follow up duration (years) | 3.7 (2.1) 3.1 (1.7) |
| Taking corticosteroid (+/-) | 5.20 16.24 |
| %VC | 81 (13.7) 89 (21.9) |
| %TLCO | 89 (20.4) 81 (16.4) |

SSc, systemic sclerosis; D-Pen, D-penicillamine; %VC, percentage vital capacity; %TLCO, percentage carbon monooxidase transfer factor.

| Table 2 The influence of D-penicillamine on pulmonary fibrosis. Values are means (SD) if not indicated. |
|-------------------------------------------------|--------|---------|
| Changes in %VC levels | Patients with D-Pen Patients without D-Pen p Value |
|-----------------|--------|---------|
| Changes in %TLCO levels | −2.19 (9.30) −1.92 (9.13) 0.45 |
| Patients with over 5% reduction of %VC levels [%] | 25.0 34.2 0.44 |
| Patients with over 5% reduction in %TLCO levels [%] | 57.1 57.1 1.00 |
| Patients with progression of alveolitis or fibrosis in chest CT [%] | 15.4 20.8 0.69 |
| Patients with progression of alveolitis or fibrosis in chest x ray [%] | 14.3 12.0 0.84 |

D-Pen, D-penicillamine; %VC, percentage vital capacity; %TLCO, percentage carbon monooxidase transfer factor; CT, computed tomography.

| Table 3 Interaction between D-penicillamine treatment and extent of skin involvement (diffuse/limited), duration of onset—first visit (over/under 10 years), duration of D-Pen treatment (over/under 3 years), or corticosteroid treatment. Results are p values. |
|-------------------------------------------------|--------|---------|
| Extent of skin involvement | Duration of onset—first visit | Duration of D-Pen treatment | Corticosteroid therapy |
|-----------------|--------|---------|--------|--------|--------|
| Changes in %VC levels | 0.70 0.16 0.56 | 0.61 0.91 0.64 | 0.69 0.77 0.49 | 0.53 0.14 0.39 |
| Changes in %TLCO levels | 0.77 0.06 0.30 | 0.83 0.35 0.95 | 0.69 0.70 0.22 | 0.77 0.40 0.63 |
| Patients with over 5% reduction of %VC levels | 0.17 0.05* 0.64 | 0.38 0.62 0.67 | 0.77 0.90 0.18 | 0.87 0.65 0.53 |
| Patients with over 5% reduction in %TLCO levels | 0.95 0.25 0.18 | 0.69 0.46 0.63 | 0.64 0.28 0.64 | 0.77 0.72 0.56 |
| Patients with progression of alveolitis or fibrosis in chest CT | 0.43 0.63 0.21 | 0.28 0.83 0.61 | 0.94 0.42 0.07 | 0.82 0.25 0.94 |
| Patients with progression of alveolitis or fibrosis in chest x ray | 0.69 0.69 0.22 | 0.56 0.79 0.49 | 0.70 0.20 0.17 | 0.74 0.46 0.27 |

D-Pen, D-penicillamine; I, interaction; %VC, percentage vital capacity; %TLCO, percentage carbon monooxidase transfer factor; CT, computed tomography.

*p<0.05 using Student’s t test.

Statistical analysis was carried out with a Student’s t test for the comparison of means, and Fisher’s exact probability test for the analysis of frequency. The interaction of two factors

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was examined using two factor factorial analysis of variance. Values of p<0.05 were considered significant.

RESULTS AND DISCUSSION

Table 2 shows the correlation between treatment with n-Pen and each of the six variables. No significant differences in the changes of these variables were found between the patients with n-Pen treatment and those without.

Table 3 shows the interaction between n-Pen treatment and four factors described above. For example, table 3 shows that over 5% reduction of %VC was detected significantly more often in the patients with dcSSc than in those with lcSSc, but there was no interaction between n-Pen treatment and extent of skin involvement. This indicates that pulmonary disease in patients with dcSSc has higher tendency to progress than in patients with lcSSc, but the effects of n-Pen treatment did not differ between patients with dcSSc and those with lcSSc. Finally, there was no interaction between n-Pen treatment and each factor.

Furthermore, we analysed 25 patients with n-Pen, to evaluate the association of dose of n-Pen treatment with each variable, but the change in pulmonary fibrosis did not depend on the dose of n-Pen (data not shown). Thus, in our study, we could not show any beneficial effect of n-Pen on pulmonary fibrosis.

But, our results had some limitations. We did not evaluate other manifestations, including the skin or kidney, in this study. And our results were obtained retrospectively. Future controlled trials of this drug should be performed with randomisation in various manifestations of this disease.

**REFERENCES**


**Bone mineral density improvement in spondyloarthropathy after treatment with etanercept**

H Marzo-Ortega, D McGonagle, G Haugeberg, M J Green, S P Stewart, P Emery

New bone formation with spinal fusion is the hallmark of ankylosing spondylitis (AS) and the related spondyloarthropathies (SpA), although concomitant osteoporosis is also a major problem both in early and established disease and correlates with disease activity. We have previously reported the efficacy of etanercept in patients with active and resistant spinal and peripheral SpA. Our aim in this study was to investigate whether suppression of inflammation with etanercept prevents bone loss in patients with AS and SpA.

**Table 1** Demographic and disease characteristics at baseline and at six month follow up in both groups. Unless otherwise indicated, values are the mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Patients with SpA treated with etanercept (n=10)</th>
<th>Patients with SpA treated conventionally (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 Months</td>
</tr>
<tr>
<td>Demographic variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight [kg]</td>
<td>70.1 (19.4)</td>
<td>72.0 (19.1)</td>
</tr>
<tr>
<td>Age [years]</td>
<td>37.6 (8.3)</td>
<td>-</td>
</tr>
<tr>
<td>Body height [cm]</td>
<td>168.3 (8.1)</td>
<td>-</td>
</tr>
<tr>
<td>Men</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>Disease duration [range]</td>
<td>12 years (0.6–34)</td>
<td>-</td>
</tr>
<tr>
<td>Disease variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-B27 positive [n]</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>ESR [mm/1st h]</td>
<td>41.6 (23.3)</td>
<td>10.9 (8.2)</td>
</tr>
<tr>
<td>CRP [mg/l]</td>
<td>48.2 (24.8)</td>
<td>17.0 (20.3)</td>
</tr>
<tr>
<td>Early morning stiffness [min]</td>
<td>120</td>
<td>2.5</td>
</tr>
<tr>
<td>VAS spinal pain during the day [0–100 mm]</td>
<td>53.6 (25.6)</td>
<td>16.3 (19.0)</td>
</tr>
<tr>
<td>VAS spinal pain during the night [0–100 mm]</td>
<td>58.9 (25.6)</td>
<td>13.4 (20.7)</td>
</tr>
<tr>
<td>VAS global disease activity [0–100]</td>
<td>69.6 (19.8)</td>
<td>12.2 (19.1)</td>
</tr>
<tr>
<td>BASFI</td>
<td>7.2 (1.8)</td>
<td>4.0 (3.1)</td>
</tr>
<tr>
<td>BASDAI</td>
<td>6.7 (2.1)</td>
<td>2.3 (2.4)</td>
</tr>
</tbody>
</table>

*Paired two tailed Student’s t test used to test differences between baseline and six month follow up values for both patient groups.

ESR, erythrocyte sedimentation rate (normal value 5–15 mm/1st h); CRP, C reactive protein (normal value <10 mg/l); VAS, visual analogue score; BASFI, Bath Ankylosing Spondylitis Functional Index [0–100]; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index [0–100].
METHODS AND RESULTS

Ten patients with active, resistant spinal and peripheral SpA were treated with a six month course of etanercept 25 mg subcutaneously twice weekly, as previously reported. Diagnoses in this group were: AS (n=7), Crohn's spondylitis (n=2), and undifferentiated SpA (n=1). Results were compared with those for a second group of patients with equivalent disease activity, but shorter disease duration treated conventionally (table 1). The diagnoses of the second group were: undifferentiated SpA (n=6), reactive arthritis (n=3), psoriatic arthritis (n=1). Their treatment during this time was with non-steroidal anti-inflammatory drugs (n=8) and sulphasalazine (n=2). In addition, one patient received an intramuscular injection of corticosteroid at baseline and another patient two intra-articular steroid injections in two peripheral joints (wrist and knee). Hip (femoral neck and total hip) and spine (L2-L4) bone mineral density (BMD) was measured at baseline and after 24 weeks by one technician using the same dual x ray absorptiometry equipment (Lunar Expert, Madison, Wisconsin). Short term in vivo precision was 1.4% at the total hip, 2.9% at the femoral neck, and 2.4% at the spine. The long term spine phantom precision for the whole study period was 0.8%. All analyses were performed with SPSS (Statistical Package for Social Sciences) program 9.0 (SPSS, Chicago, IL). Paired and independent two tailed Student's t test and Pearson's χ² test were used when appropriate.

After six months all measures of disease activity were significantly reduced in the patients treated with etanercept but not in the controls (table 1). Figure 1 shows that the mean BMD increased at the hip and spine during this period in the first group, but decreased in the second (total hip: +1.6% v -1.3% (p=0.03); femoral neck: +0.2% v -1.5% (p=0.34); spine L2-4: +1.1% v -1.4% (p=0.19).

DISCUSSION

Bone loss secondary to active inflammation is a serious long term complication of AS and SpA and can occur early in disease. Here we have shown that disease measurement variables were reduced significantly during the study only in the patients treated with anti-tumour necrosis (anti-TNF) factor, and this was associated with a prompt gain in BMD. Although this is a small and non-homogeneous group we believe that both groups are representative of the wide spectrum encompassed within the SpA. Also, the study was not randomised and the patients in the conventional treatment group had a shorter disease duration but, nevertheless, they were contemporaneous and of similar disease activity. Furthermore, previous studies of longer disease duration have shown an equivalent loss of BMD to that of the patients in this group. These findings suggest that adequate suppression of inflammation in AS and SpA is likely to improve BMD in both early and established disease.

Etanercept may improve BMD by removing excess cytokine from both osteoclasts and osteoblasts. It has been shown in rheumatoid arthritis that TNFα blockade also reduces interleukin 1 and interleukin 6, both of which are known to be potent pro-resorptive cytokines acting via the osteoprotegerin/RANKL pathway. In addition, it has recently been shown, that the differentiation, activation, and survival of osteoclasts are facilitated by TNFα. TNFα also inhibits the differentiation of osteoblasts from progenitor cells and retards bone formation by differentiated cells. The absence of supportive data on conventional disease modifying antirheumatic drugs in the prevention of osteoporosis in AS and SpA may relate to their inability to adequately suppress TNFα production, although the primary pathogenic pathway of osteoporosis in SpA is still to be determined.

In summary, this report shows that TNF blockade with etanercept may improve BMD in subjects with active and resistant SpA. These findings have implications for the long term treatment of patients with SpA with TNF blocking agents and need to be confirmed in larger cohorts in randomised controlled trials.

ACKNOWLEDGEMENTS

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REFERENCES


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Osteoarthritis (OA) has been variously described as a phenomenon of aging or a mechanically derived process,\textsuperscript{1–3} perhaps a simplification. Animals caught in the wild seldom (about 1%) have any evidence of OA, in contrast with captured animals (be they colony or cage raised).\textsuperscript{4–6} Removal of an animal from its natural habitat is associated with a 10-fold increase in the prevalence of OA, whether the animals were zoo or colony raised.\textsuperscript{4–6} This is clearly not a simple issue of lifespan, as the distribution of affected joints (for example, knee, shoulder), is different in wild-caught and captive samples.\textsuperscript{4–6}

It has been suggested that \textit{Cavia}, the guinea pig, is a possible exception.\textsuperscript{7–9} Analysis in those studies was based on captive guinea pigs. The contribution of an artificial environment to the propensity to develop OA was therefore explored by examination of wild-caught and captive \textit{Cavia} skeletal collections for evidence of OA.

The skeletons of captive and wild-caught \textit{Cavia} (guinea pigs) were examined macroscopically in the collections of the museums and universities of North America: American Museum of Natural History (AMNH), New York City; Cornell University (CU), Ithaca, NY; Field Museum of Natural History (FMNH), Chicago, IL; Kansas University Museum of Natural History (KU), Lawrence; McClung Museum, University of Tennessee (MMNH), Knoxville; Michigan State University (MSU), East Lansing; Museum of Comparative Zoology, Harvard University (MCZ), Boston, MA; National Museum of Natural History (NMNH), Washington, DC; Southern Methodist University (SMU), Dallas, TX; University of Colorado Museum (OS), Boulder; San Noble Oklahoma Museum of Natural History (OMNH), Norman; University of New Mexico, Albuquerque (MSB); and University of Wisconsin Zoological Museum (UWZM), Madison, WI. OA was defined by the presence of distal femoral, proximal tibial, and patellar osteophytes.\textsuperscript{10} Captive versus wild-caught status and sex were obtained from the museum/university specimen acquisition records. $\chi^2$ and Fisher exact tests were used to determine the statistical significance of differences in the prevalence of OA.

There was no evidence of osteophytes in any of 74 \textit{Cavia} (guinea pigs) caught in the wild from Bolivia, Brazil, Uruguay, Paraguay, Argentina, or Venezuela. Tibial osteophytes were found in 41/44 captive specimens (fig 1), independent of cage or colony status. This difference in prevalence of OA was highly significant ($\chi^2=71.83; p<0.00001$; Fisher exact test $p<0.00001$). Sex ratios were 1:1 in both wild-caught and captive specimens.

OA in \textit{Cavia} (guinea pigs) was limited to captive animals. Animals caught in the wild were free of OA. The perspective that OA is common in guinea pigs\textsuperscript{7–9} seems derived from the artificial housing/testing environment of the test subjects, rather than any inherent susceptibility of the species. As the prevalence in captive animals was independent of cage or colony (for example, zoo) status, and zoos have been quite attentive to natural diet, maintaining nutritional balance and assuring appropriate exercise levels, there is little evidence that the propensity to OA could alternatively be blamed on diet, weight, or activity. The similar prevalence of OA in caged and colony raised animals indicates that this is not simply a “cage phenomenon”, but rather a consequence of captivity habitats. Previous genetic attributions in captive guinea pigs\textsuperscript{7–9} are intriguing. Assessment of significant genetic differences between wild-caught and captive guinea pigs is necessary. It seems imperative to determine whether the same loci are present in animals caught in the wild, which do not develop OA, as are found in captive guinea pigs, or whether the latter have different loci owing to artificial environmental factors.

This study confirms previous perspectives\textsuperscript{4–6} that OA is essentially a disease of an artificial environment. As human habitation has removed itself so far from the natural environment, it is perhaps not surprising that OA has become a common problem in humans today.

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**Figure 1** Osteophytes (arrows) on \textit{Cavia} tibia. (A, B) Large osteophyte in MMNH 349—[A] posterior view; (B) Lateral view. (C) Anterior view of very minimal osteophyte in MMNH 344.
Definition of discontinuation of anti-tumour necrosis factor therapy in rheumatoid arthritis: a preliminary proposal

J Braun, J Sieper, D van der Heijde

Treatment with biological agents is currently inducing dramatic changes in the treatment of the most common inflammatory rheumatic diseases: rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis. Several recent papers have established the efficacy of mainly three different agents directed against tumour necrosis factor α (TNFα)—infliximab, etanercept, and adalimumab—in these rheumatic diseases. Because these treatments may have rare but severe side effects and because they are expensive, guidelines and recommendations have been proposed by expert groups, especially for RA and recently also for AS.

In the AS consensus paper, which was produced by the ASAS working group, recommendations for the discontinuation of anti-TNF therapy in clinical practice have been included. This is in contrast with the RA guidelines, which in St Martin were discussed and updated only recently in April 2003. Although guidelines for the discontinuation of treatment in RA were proposed in the discussions held there, this issue has not been put forward mainly as a result of the argument that this subject is too difficult to deal with. Thus, the arguments and proposals published in this letter may represent a minority statement (in relation to the group that met to update the RA guidelines).

In our opinion, a discussion on discontinuation of anti-TNF therapy in RA is important in clinical practice and in clinical studies because (a) treatment with these agents is costly and healthcare systems do not have unlimited financial resources in most countries. Therefore, unnecessary treatment with these agents should not be performed because other patients who are in definite need of this treatment may be excluded. (b) In an increasing number of studies patients are switched from one biological agent to another. This is generally done because it is the expert’s opinion that this is the right thing to do. This may lead to highly subjective assessments and unnecessary disqualification of treatments which have at least produced some degree of improvement. Usually, a definition of a non-responder as an end point is well defined in each clinical trial (those not fulfilling the criteria for a responder). However, the problem arises when patients “not responding to drug A” are included in a trial to investigate drug B. These are often patients gathered in clinical practice, and for these patients no clear definition is given.

Therefore, we feel that some basic measures should be agreed upon which might represent a starting point for this discussion. We propose to consider the following for both clinical practice and clinical studies:

- Discontinuation of anti-TNF therapy in RA should be considered and possibly performed if the following problems have occurred:
  - Intolerable side effects probably or possibly related to the drug applied
  - Lack of efficacy

The second point deserves further clarification. We think that the treatment with either agent should have lasted for at least two months and include the usual saturation phase in the case of infliximab at weeks 0, 2, and 6. We would like to emphasise that this recommendation says “at least”, which does not imply that one cannot wait one or two months longer, because we are aware that some patients with very severe disease may need longer to experience sufficient clinical benefit.

We realise that the issue of increasing the dosage in selected patients has not been properly assessed to date.

Furthermore we think that it should be recorded that the disease activity has not been substantially decreased. The outcome measures that are most frequently used in RA in clinical trials are ACR20%, ACR50%, and ACR70% and the disease activity score (DAS; reviewed by Verhoven et al.). In clinical practice, the DAS is more widely used, at least in Europe.

We propose that patients with RA who do not fulfil the ACR20% and/or a DAS improvement of 1.2 after at least two months can be formally classified as non-responders. It seems possible that this relatively short period of time can be
extended to three months in certain cases. However, in our clinical experience no major increases of improvement due to anti-TNF agents can be expected if nothing has changed after two months. Most importantly, the definition of non-response as an inclusion criterion should be given in each trial. If the DAS is used the cut off point for non-response is improvement of at least 1.2. Thus, if these levels of response are reached (ACR20% or DAS improvement of at least 1.2), the patient may not be regarded as a non-responder without giving further definitions on this.

There are some differences in these proposals compared with the recommendations given for AS.3 The guidelines for AS recommend assessing disease activity by the Bath AS Disease Activity Index (BASDAI),11 with a value of 4 generally considered to indicate clinically significant disease activity. For assessment of improvement in AS, criteria have been proposed on the basis of trials with non-steroidal anti-inflammatory agents (NSAIDs), in which four domains (pain, function, patient global, and morning stiffness) are defined and three of these must improve by 20%. However, these criteria were recently found not to be suitable for trials with anti-TNF agents because much higher response rates are obtained with these agents. In the consensus statement on anti-TNF therapy in AS, discontinuation of such treatment was proposed to be considered in patients not reaching 50% improvement of BASDAI—an initially rather arbitrary measure,13 which, however, has been used in most of the later trials performed in AS.14–17 In addition to the BASDAI assessment, expert opinion to start or discontinue treatment is essential.

Although difficult to compare directly, this threshold seems higher than the one proposed for RA. This may possibly represent another indication that anti-TNF therapy is more efficacious in AS than in RA.

We do hope that these proposals contribute to a more scientific approach in future studies including so-called “non-responders” in RA and propose to discuss these proposals in more detail in the next meeting on “Targeted Therapies”.

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REFERENCES
Entrapment neuropathy of the inferior branch of the suprascapular nerve by a ganglion cyst mimicking cervical disk disease

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Ganglia can compress the adjacent structures and in the shoulder they can cause suprascapular neuropathy. We report an unusual case of a ganglion cyst that caused entrapment neuropathy of the inferior branch of the suprascapular nerve mimicking cervical disk disease.

CASE REPORT
A 39 year old man presented to our physical medicine and rehabilitation outpatient clinic with neck and left shoulder pain together with weakness of his left arm. His complaints were of nine months’ duration. A cervical spinal magnetic resonance imaging (MRI) examination showed diffuse bulging of C4-5 and C5-6 disks and flattening of cervical lordosis. Physical examination showed a loss of muscle strength at external rotation and significant atrophy of the infraspinatus muscle. Initial electromyography and nerve conduction studies (EMG/NCS) restricted to the supraspinatus muscle were normal. Later studies inclusive of the inferior branch of the suprascapular nerve and the infraspinatus muscle, however, showed prolonged distal latency (12 msec) and low amplitude (0.2 mV) responses. Moreover, needle-EMG displayed severe subacutheurogenic involvement as well as atrophy of the left infraspinatus muscle and partial denervation findings. The EMG/NCS findings for other muscles and nerves were normal. Because findings suggested entrapment of the inferior branch of the left suprascapular nerve at the level of the spinoglenoid notch, a diagnostic injection of 5 ml lidocaine 2% was made at this location, whereupon the pain of the patient was relieved.

MRI of the left shoulder showed a round cystic mass about 2 cm in diameter and consistent with ganglion posterosuperior to the glenoid portion of the scapula (fig 1). The patient refused surgery upon relief of his pain. Local injections of lidocaine with 40 mg methylprednisolone acetate were made three times, each with an interval of three weeks. In addition, electric stimulation and isometric and isotonic strengthening exercises were given to the infraspinatus muscle. Follow up MRI at two months after the first injection showed no regression of the cystic mass. Persistence of the symptoms three months thereafter and heavy workload of the patient (which he could not dismiss) led to open decompressive surgery with posterior approach. All symptoms of the patient were relieved after the operation and MRI at three months after surgery showed no residual or recurrent cystic mass.

DISCUSSION
The diagnosis of suprascapular nerve entrapment is based on clinical history and physical examination supplemented with EMG/NCS. Patients typically present with longstanding, deep, diffuse posterolateral shoulder pain, which may radiate to the neck, arm, or upper chest wall. In our case, the diagnosis was delayed because of this pain distribution. This sensation of pain is probably referred from the sensory articu lar branches to the glenohumeral and acromioclavicular joints. On physical examination, there is usually weakness of external rotation. Wasting of the infraspinatus would be present in chronic conditions. Pain relief after an injection of lidocaine into the area of entrapment can be used as a confirmatory diagnostic sign. EMG/NCS should be performed to confirm the diagnosis of entrapment neuropathy of the suprascapular nerve. Nevertheless, such an evaluation should not be restricted to the supraspinatus and should encompass the infraspinatus. Assessment of the infraspinatus, along with supraspinatus, can avoid the failure of diagnosing the compression at the spinoglenoid notch, as documented in our case.

Suprascapular nerve entrapment in the suprascapular notch, especially in the spinoglenoid notch, is a rare entity that must be considered in the differential diagnosis of radicular pain, as well as that of shoulder discomfort. Radiological findings of cervical disk degeneration are widely encountered, increasing with age. Extensive use of MRI results in the frequent diagnosis of cervical disk disease. It should be borne in mind, however, that symptoms of a patient need not be wholly attributable to the presence of cervical disk disease, which might be associated with another condition causing similar symptoms, as in our patient.

In conclusion, extensive use of EMG/NCS should be made in patients with shoulder pain with associated atrophy. Ganglion cysts at the spinoglenoid notch should be included in the differential diagnosis of patients presenting with neck and shoulder pain and weakness.

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Ultrasonographic study of painful shoulder

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Painful shoulder is a very common condition in clinical rheumatology. However, knowledge of the lesions responsible for shoulder pain in most patients has been limited to clinical examination and plain radiography in clinical practice. High frequency ultrasonography is an accurate, non-invasive, and cheap imaging technique available in clinical rheumatology for evaluating patients with painful shoulder. However, dependence on the skill of the operator has been considered to be the main disadvantage of ultrasound. Diagnostic results are affected by the quality of the equipment, examination technique, sonographer experience, and sono- graphic diagnostic criteria.

We compared the ultrasonographic findings in two groups of patients with clinically diagnosed periarticular disorders, with a first flare of shoulder pain—group I: 228 patients (228 shoulders); group II: 110 patients (122 shoulders). Patients with previous trauma or chronic inflammatory arthritis were excluded.

Each group was examined in Italy or in Spain by a different rheumatologist (AI, Rome, Italy and EN, Madrid, Spain) using a different commercially available real time machine (Image Point Hx, Agilent Technologies/HP and Sonoline, Versa, Siemens, Seattle, USA, respectively) with a 7.5 MHz linear phased array transducer. Both rheumatologists used the same scanning technique and the same sonographic diagnostic criteria.

A χ² test was used to compare quantitative variables. A value of p<0.05 was considered significant.

Group I comprised 132 women and 96 men with a mean age of 45.6 years (range 18–64). The mean duration of symptoms was 3.3 months (range 1–8). Group II comprised 81 women and 29 men with a mean age of 54.5 years (range 25–75). The mean duration of symptoms was 8.6 months (range 0.5–36).

The ultrasonographic findings in the painful shoulders were similar for both groups (p>0.05) (table 1). In most patients various different periarticular structures were affected. Supraspinatus tendon lesions were the most common

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**Table 1 Ultrasonographic findings in symptomatic shoulders**

<table>
<thead>
<tr>
<th>Shoulder lesions</th>
<th>Group 1 (228 shoulders) % of shoulders</th>
<th>Group 2 (122 shoulders) % of shoulders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraspinatus lesions</td>
<td>67</td>
<td>66</td>
</tr>
<tr>
<td>Infraspinatus lesions</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Subscapularis lesions</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Biceps tendon lesions</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>Biceps sheath effusion</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>SA-SD bursitis</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>ACRCL involvement</td>
<td>63</td>
<td>61</td>
</tr>
<tr>
<td>RC calcification</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>GH effusion</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

SA-SD, subacromial-subdeltoid; ACRCL, acromioclavicular; RC, rotator cuff; GH, glenohumeral. p>0.05 for all results.
pathological finding (fig 1). Infraspinatus and subscapularis abnormalities were seen less often. Increased fluid within the subacromial-subdeltoit bursa and biceps tendon sheath were also very common, as were degenerative changes in the acromioclavicular joint.

Our results are consistent with those previously reported. Ultrasound provides a valuable method for studying painful shoulders in daily practice and clinical research. The scanning technique and pathological criteria should be standardised to achieve optimum widespread use of ultrasound in rheumatology.

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REFERENCES

Synovial lymphocyte responses if tested fresh not frozen can incriminate microbial intrasynovial DNA and RNA

D K Ford

In a previous issue of the Annals, Sibilia and Limbach reviewed the microbiology of “infectious arthritis” and described various ways in which the agents might be related to the arthritis. One approach, for which there is considerable support, was, however, not discussed.

In 1980 synovial lymphocytes were found to respond maximally to stimulation by either chlamydia or ureaplasma antigens in cases of sexually transmitted reactive arthritis. In 1985 synovial responses were reported in eight cases of enteric and 12 cases of sexually transmitted reactive arthritis. Responses to the relevant antigens of each category differentiated the enteric from the sexually transmitted cases. Additionally, peripheral blood lymphocytes in all eight enteric cases and in eight of the 12 sexually transmitted cases responded negligibly or only minimally to the antigens that initiated the enteric from the sexually transmitted cases.

Responses to the relevant antigens of each category differentiated them from the responses in two hundred consecutive cases. J Bone Joint Surg Am 2000;82:498–504.

Ultrasound provides a valuable method for studying painful shoulders in daily practice and clinical research. The scanning technique and pathological criteria should be standardised to achieve optimum widespread use of ultrasound in rheumatology.

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REFERENCES
evidence, as summarised in 1996.\textsuperscript{14} To be an effective investigative tool however, the synovial lymphocytes should be employed fresh and not frozen, and to validate the significance of findings multiple microbiological antigens should be used for each test so that specific stimulation can be identified. If a micro-organism’s DNA or RNA is associated with a statistical maximal intrasynovial lymphoid response to antigens of that agent, then a presumption of pathogenicity is logical, though not proved.

\textbf{REFERENCES}


\textsuperscript{4} Ford DK. Lymphocytes from the site of disease in reactive arthritis indicate antigen-specific immunopathology. \textit{J Infect Dis} 1991;164:1032–3.


\textsuperscript{10} Ford DK. Lymphocytes from site of disease indicate probable microbiological etiology of “infective-immune” diseases such as rheumatoid arthritis. \textit{Infect Agents Dis} 1996;5:223–30.
HLA-B27 in patients with a permanent pacemaker


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