A successful renal transplantation in Behçet's syndrome

Renal involvement is not frequent in Behçet's syndrome (BS) and consists of occasional reports of patients having glomerulonephritis, IgA nephropathy and renal amyloidosis. We present the successful outcome of a renal transplantation in a patient who had end stage renal failure secondary to glomerulonephritis. To our knowledge, this is the first patient with BS to receive an organ transplantation.

The detailed history of this patient at the time of the diagnosis of glomerulonephritis was the subject of a case report in 1991. In brief, she was 21 years old when she developed recurrent oral and genital ulcers, bilateral uveitis, erythema nodosum, folliculitis, and intermittent arthritis of the knees. Two years later, she was referred to our centre for further evaluation of eye symptoms. She had no active mucocutaneous lesions at that time, the pathergy reaction was positive and she carried the HLA-B5. It was decided to prescribe only local drops for her mild eye involvement. Three months later she experienced two ocular episodes resulting in a sharp decline of visual acuity and azathioprine 2.5 mg/kg/day was prescribed. Two weeks later she was admitted to the hospital because of microscopic haematuria. She was ANA negative, the anti-DNA and serum complement levels were within the normal range. Her glomerular filtration rate was 67 ml/min. An open renal biopsy showed diffuse proliferative glomerulonephritis and weak focal segmental positivity of IgA and IgM. She was treated with three boluses of 1 g methylprednisolone and was discharged prescribed azathioprine 150 mg/day, aspirin 300 mg/day and prednisone 30 mg/day. She was well except for occasional mucocutaneous symptoms and a mild generalised pruritic rash during the next four years. However her renal function deteriorated progressively despite uninterrupted treatment with azathioprine and changing doses of prednisone and she was put on regular haemodialysis twice a week. In the 14th month of haemodialysis, she received a kidney from her mother. The graft function started immediately and she was prescribed maintenance immunosuppression with azathioprine, cyclosporin A and methylprednisolone. An acute interstitial type reaction on the 11th day of transplantation was treated successfully with pulsed corticosteroids. Now 40 months after transplantation, she has normal renal function and is free of any symptoms of BS except for occasional oral ulcers.

We had some hesitation in performing a renal transplantation on our patient initially because of the lack of any previous experience and particularly because of our concern for the heightened inflammatory response of BS patients to simple penetrating trauma that is best characterised by the pathergy reaction. This reaction, however, is not only limited to the skin and development of aneurysms after vascular punctures and episodes of synovitis after arthrocentesis have been observed. Furthermore, postoperative complications leading to a poor outcome such as occlusions of grafts/anastomoses after the surgical treatment of aneurysms' or paravalvular leakage and suture breakdown after aortic valve replacement have been reported in BS patients. As these complications are probably related to the pathergy phenomenon reaction, you would also reasonably expect problems after an organ transplantation, an operation with arterial and venous anastomoses. On the other hand, we had previously shown that despite the increased inflammation, wound healing after full thickness skin punch biopsies is not changed in BS. We have not experienced any of the feared complications after the transplantation procedure in this instance. One reason for this favourable outcome might be that our patient was female. It is known that BS runs a milder disease course in women compared with men. Additionally, the rather intensive immunosuppressive/anti-inflammatory post-transplant drug use might also have contributed to the diminished disease activity of our patient as well as to the prevention of a reaction at the site of the transplanted renal tissue. Whatever it might be related to, the outcome in our patient suggests that BS patients can undergo renal transplantation with a satisfactory outcome.

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8 VP Vardar-Jashar, Kivitz JL, Pasquali MR. Immunohistological markers on T lymphocyte subpopulations in SSc are not different between SSc patients and control group but in rheumatoid arthritis (RA) CD3+ and CD8+, in Sjögren’s syndrome CD3+, CD4+ and CD8+ levels were significantly decreased compared with those of controls and they suggested that the abnormalities in immune regulatory T cell circuits leading to autoimmunity are different in each connective tissue disease.

Table 1 summarises lymphocyte phenotypes in patients with SSC and healthy controls.

We found a higher expression of T cell activation marker CD25+ and NK cell main surface marker CD56+. In lymphocyte phenotypes there was not any difference in disease subsets and CD25+ and CD56+ were not correlated with the disease duration.

Immune system abnormalities have been suspected in the development of SSc because of the presence of autoantibodies, changed cytokine production and evidence of overlap with other autoimmune diseases. It was suggested that immune system changes play the major part in the development of vascular and fibrotic processes. Previous reports on T lymphocyte subpopulations in SSc are partially conflicting. Melendro et al demonstrated that there was no significant difference in the levels of CD4+ and CD8+ in 22 SSc patients and control group but in rheumatoid arthritis (RA) CD3+ and CD8+, in Sjögren’s syndrome CD3+, CD4+ and CD8+ levels were significantly decreased compared with those of controls and they suggested that the abnormalities in immune regulatory T cell circuits leading to autoimmunity are different in each connective tissue disease.

Table 1 Lymphocyte phenotypes in patients with SSC and healthy controls

<table>
<thead>
<tr>
<th>Serum</th>
<th>Systemic sclerosis</th>
<th>Control</th>
<th>t Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3 (%)</td>
<td>71 (9)</td>
<td>69 (9)</td>
<td>0.660 &gt;0.05</td>
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<tr>
<td>CD4 (%)</td>
<td>44 (9)</td>
<td>45 (9)</td>
<td>0.110 &gt;0.05</td>
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<tr>
<td>CD8 (%)</td>
<td>31 (9)</td>
<td>25 (9)</td>
<td>1.914 &gt;0.05</td>
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<tr>
<td>CD3/CD4</td>
<td>1.56 (0.6)</td>
<td>1.84 (0.6)</td>
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<td>CD19 (%)</td>
<td>12 (3)</td>
<td>13 (3)</td>
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<td>CD56 (%)</td>
<td>18 (9)</td>
<td>17 (9)</td>
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<tr>
<td><strong>CD56</strong> (%)</td>
<td>22 (9)</td>
<td>14 (5)</td>
<td>2.691 &gt;0.05</td>
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</table>

* Unpaired Student’s t test. Data shown as mean (SD).
Lymphocyte populations and cytokine concentrations in pericardial fluid from a systemic lupus erythematosus patient with cardiac tamponade

Pericardial involvement is the most common cardiovascular complication in systemic lupus erythematosus (SLE). The clinical picture varies from subclinical pericardial effusion and classic acute pericarditis to cardiac tamponade. In immunological studies of pericardial fluid (PF) have been limited to determination of autoantibodies, complements and immune complexes. To further study the pathogenic mechanisms involved in lupus pericarditis, we examined the lymphocytic populations and cytokine concentration pattern in PF and peripheral blood (PB) from a SLE patient with cardiac tamponade.

We report a case of a 38 year old man with SLE diagnosed in December 1995 when he presented with polyarthralgia, photosensitivity, oral ulcers, nephritis, non-hemolytic anemia, positive ANA, increased anti-dsDNA and hypocomplementemia. The patient improved with corticosteroid and intravenous cyclophosphamide treatment. However, on 18 June 1997 he presented with syncope, hypotension (80/40 mm Hg), a tachycardia, jugular vein distension and cardomegaly. The two dimensional echocardiogram showed a large pericardial effusion with right atria and ventricle collapse in diastole. Pericardiocentesis was performed and 180 ml of an orange fluid was aspirated. Examination of PF showed white blood cell count of 52,800/mm³ (polymorphonuclear cells = 96%). The absolute number of lymphocytes was lower in PF than in PB (211 × 10³/mm³). PF markedly increased reactivity to this cytokine.

Table 1. Frequency of lymphocyte populations and cytokine concentrations in peripheral blood and pericardial fluid

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Peripheral Blood</th>
<th>Pericardial Fluid</th>
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<tr>
<td>Lymphocyte population (%)</td>
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<tr>
<td>CD8+ T cells</td>
<td>57.8</td>
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<tr>
<td>CD4+ T cells</td>
<td>17.6</td>
<td>25.0</td>
</tr>
<tr>
<td>CD8+ T cells</td>
<td>34.3</td>
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<tr>
<td>B cells</td>
<td>7.8</td>
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<td>NK cells</td>
<td>34.3</td>
<td>41.7</td>
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<tr>
<td>Cytokine concentration (pg/ml)</td>
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<td></td>
</tr>
<tr>
<td>IL1β</td>
<td>&lt;6.0</td>
<td>&gt;2400</td>
</tr>
<tr>
<td>IL4</td>
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<td>IL6</td>
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<td>&gt;2400</td>
</tr>
<tr>
<td>IL10</td>
<td>&lt;5.0</td>
<td>&gt;1300</td>
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<tr>
<td>TNFα</td>
<td>3.8</td>
<td>15.4</td>
</tr>
<tr>
<td>IFNγ</td>
<td>1.5</td>
<td>32.8</td>
</tr>
</tbody>
</table>

* Manufacturer (Genzyme, Boston, MA) detection limits: 3 pg/ml for IL1β, IFNγ and TNFα; 4 pg/ml for IL2; 6 pg/ml for IL4; 18 pg/ml for IL6; and 5 pg/ml for IL10.

level of protein was 4.1 g/dl (serum = 5.3 g/dl), glucose was 53 mg/dl (serum = 110 mg/dl) and LDH was 471 IU/l (serum = 110 IU/l). PF cultures were negative. No malignant cells were seen to rule out particular dose corticosteroids and azathioprine. Predisone was gradually decreased to 10 mg daily over a three month period. After a 22 month follow up, he remained clinically stable without recurrent pericardial involvement or SLE exacerbations.

Before starting immunosuppressive treatment, PF and PB were obtained simultaneously for immunological analysis. Mononuclear cells from both sources were isolated by gradient centrifugation and the frequency of lymphocyte populations was determined by flow cytometry. The cytokine concentrations from plasma and PF were determined by ELISA. Table 1 shows the results. Among lymphocytes, the percentage of CD4+ T cells and NK cells was higher in PF, while the frequency of CD8+ T cells was higher in PB. IL6 concentration was much higher in PF than plasma. Also, IL1β and IL10 concentrations were higher in PF. IL2 was detected in plasma but not in PF.

The considerable increase in pericardial IL1β, with respect to plasma, was particularly interesting. PF concentrations of IL6 in our patient were substantially higher than those observed in PF from patients with inflammatory and non-inflammatory heart conditions. IL6, not only can increase antibody production, but in SLE, B cells have increased reactivity to this cytokine. As in our case, IL6 is usually expressed or increased in the affected organ or system rather than in PB. IL6 has been found to be higher in cerebrospinal fluid and urine than in serum of SLE patients with CNS disease and active nephritis respectively.

The decreased pericardial lymphocyte count and fluid characteristics observed here are in agreement with other studies. The higher frequency of CD4+ T cells and NK cells in PF could be associated with the observed cytokine concentration pattern. For example, CD4+ memory T cells from SLE patients highly secrete IL10 compared with normal controls.

In summary, different patterns of lymphocyte populations and cytokines were found in both sources, with type 2 cytokines predominating in PF and type 1 in PB. Further studies would be required to confirm the results presented here. In addition, immunocytochemical studies of pericardial...
tissue are necessary as the composition of lymphocyte and cytokine profiles may differ between pericardial fluid and tissue.

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HLA-B27+ anterior uveitis with or without associated spondyloarthritis: clinical and immunological features

Anterior uveitis (AU) is the most common form of uveitis,11 and may be produced by different causes. An aetiologic diagnosis is commonly established in approximately half of the patients with AU, being seronegative spondyloarthropathies (SA), and mainly ankylosing spondylitis, the most frequent cause of the disease. Approximately 50% of the patients with AU are HLA-B27 positive; half of them usually present with associated SA,12 the other half are patients with HLA-B27+ but with no associated articular disease (HLA-B27+ AU). Several clinical features have been described to be common in patients with AU associated with HLA-B27, however, these features are similar in either patients with or without associated SA.13 This is why we conducted this clinical and immunological study in patients with AU positive for HLA-B27 with the aim of discovering the differences between patients with and without associated SA.

A prospective study was conducted involving 146 patients with active AU seen between April 1988 and October 1995 referred from an ophthalmologist with the syndromic diagnosis of AU of unknown origin. Patients were classified in three aetiological groups: (1) Idiopathic anterior uveitis (IAU), all were HLA-B27−; (2) HLA-B27+ AU without associated SA, and (3) HLA-B27+ AU with associated SA.

Of the 146 patients with AU studied, 98 had IAU (67.1%) and 48 were positive for HLA-B27 of them, 19 (13%) had associated SA (HLA-B27+ AU with SA), and 29 (19.9%) did not (HLA-B27+ AU). No significant differences were found in clinical features of AU between the three study groups. Erythrocyte sedimentation rate, C reactive protein and IgA were found to be lower than those of SA patients (p<0.001). Patients with IAU showed lower percentages (mean (SEM)) of CD4CD45R+ (15.47 (9.49)%) than controls (25.20 (7.76)%) and patients with SA (21.97 (10.16)%) (fig 1). Patients with IAU had higher percentages of CD4CD45R+ (28.46 (7.89)%) than SA patients (23.23 (6.81)%) and the control group (20.77 (6.40)%) (fig 2).

Associated systemic pathology was demonstrated in 13% of the cases (19 patients with seronegative SA) 12 patients (19.9%) were HLA-B27+ without SA; not associated disease was found in the other half of all forms of uveitis, representing 25% of the patients with IAU. In addition, differences found in the values of lymphocytes between patients with IAU and SA suggest a different pathophysiological mechanism in the development of both diseases.
we are indebted to Ms E Velasco for assistance in the preparation of the manuscript.

Francisco rivera-cívico, Juan Jiménez-Alonso, María Martín-Armada, María Teresa Herranz, José Castro, Francisco Pérez-Alvarez, J L del Arbol. Service of Internal Medicine

We are indebted to Dr J Jiménez-Alonso, Jefe del Servicio de Medicina Interna, Hospital General de Especialidades “Virgen de las Nieves” Avda Fuerzas Armadas 2, 18014 Granada, Spain.

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We thank the following rheumatologists for the con-tribution to the study: Jordi del Blanco, Miquel Pons, Isabel Rotés, Raïmon Sannarri, Eduardo Kantarewicz, Miquel Sala, Ivonne Breyese, Rosa Rosello, Javier Arasa, Marta Larrosa, Genomics Cássidès, Jose Fújol, Anna Lafont.

Correspondence to: Dr A Oliva.

MATTERS ARISING

RS3PE: six years later

We read with interest the paper by Cantini et al and would like to comment on it.1

In 1992 we performed a retrospective mul-tilcentre study of 27 RS3PE patients. We con-cluded that personal history of polymyalgia rheumatica (two patients), presence of ero-sions (one patient) and evolution to haemato-logical diseases (two patients concomitantly developed a T lymphoma and one a my- elodysplastic syndrome) suggested that RS3PE syndrome might not be a distinct clinical entity. At that moment 12 patients were asymptomatic and 12 required treatment. This was reported elsewhere.1

Now, six years later, we have reviewed the original cohort of patients with the RS3PE syndrome. A questionnaire was sent to the participating rheumatologists. The survey focused on articular symptoms, treatment and evolution. The current cohort was composed of 22 patients (16 male; 6 female; mean age:77.9; range 64–91). Four patients died (the three with haematological diseases, one stroke) and one was not located. Thirteen patients were asymptomatic and without treat-ment, in contrast nine required treatment, namely corticosteroids (6), gold salts (1), clo-roquine (1) and NSAID (1). Interestingly, two of the patients were identified by their rheumatologist as having a seronegative rheumatoid arthritis, another patient had a chronic disease with specific corticosteroid responsive episodes of bilateral hand oedema and polymyalgic syndromes at different times. Last but not least one patient developed Ray- naud’s phenomena, both hands had sclero-dactyly. A nailfold capillary microscopy showed a decreased number of capillary loops, which were widened, suggesting sys-temic sclerosis.

Our results suggests that RS3PE syndrome has a good prognosis a worse than half of the patients are asymptomatic and without treat-ment six years later. However, there is a sub-set of patients that have other diseases. Although pure RS3PE syndrome does exist the evolution should be carefully monitored.

MONICA GUMÀ ENRIQUE CASADO XAVIER TENA ALEX OLIVE Rheumatology Section, Hospital Universitari Germans Trias i Pujol, C/ de Canyet s/n, Badalona 08016, Spain.

We appreciate the comment by Oliva et al on our article on RS3PE. They reviewed 27 prev-iously described RS3PE patients after a fol-low up of six years.

As we suggested in a previous report, they confirm that RS3PE syndrome should be con-side red a heterogeneous condition associ-ated with different inflammatory rheumatic diseases and also with neoplastic disorders.

In our study none of the 23 patients with RS3PE syndrome developed a T lymphoma or a my- elodysplastic syndrome. The different study design and selec-tion of patients may in part explain the subset of patients with other diseases and with a worse prognosis observed by Oliva et al.

We designed a prospective follow up study excluding patients satisfying the criteria for the diagnosis of polymyalgia rheumatica, rheumatoid arthritis and seronegative spondylarthropathies. Moreover, patients with a clinical history of cancer were excluded from the study. In their original report2 these authors performed a retrospec-tive study including all patients with remit-t ing distal extremity swelling with pitting oedema. They recruited also patients not evaluated for spondylarthropathies, which may be associated with distal extremity swell-ing with pitting oedema.3

However, in their retrospective evaluation Oliva et al found that 13 of 22 (59%) patients were asymptomatic and drug free over a six year follow up period, confirming that RS3PE not associated with other conditions and with a good prognosis does exist.

The problem is how to label this clinical picture. As discussed in our article, the similar-ities of demographic, clinical and MRI findings between patients with “pure” RS3PE syndrome and those with polymyalgia rheumatica and the concurrence of the two syndromes suggest that these conditions may be part of the clinical spectrum of the same disease. In the series of Oliva et al the patient with a clinical course characterised by alturate relapses of HL-A27 associated oedema or polymyalgic symptoms further supports our hypothesis. Even those RS3PE patients successively diagnosed as having seronegative rheumatoid arthritis (elderly onset seronegative arthritis) do not conflict with our conclusions. Healey described pa-tients who developed episodes of polymyalgia rheumatica and seronegative rheumatoid arthritis at different times during follow up.2 Similar clinical characteristics have been recently described in a population based cohort of patients with giant cell arteritis fol-lowed up over a 42 year period. Four of the six patients who fulfilled the criteria for the diagnosis of rheumatoid arthritis during the follow up experienced multiple separate episodes of symmetrical arthritis, proximal symptoms of polymyalgia rheumiatca and distal extremity swelling with pitting oedema.4

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IGNAZIO OLIVIERI Servizio di Reumatologia, Ospedale S Carlo, Potenza, Italy


Authors’ reply
Crysalysts in arthritis: new age nonsense or novel therapeutic target?

Apatite crystals are present in up to 70% of fluids from degenerated joints. Their presence correlates strongly with radiographic evidence of cartilage degeneration and is associated with larger joint effusions when compared with joints without crystals. Whether the presence of apatite crystals is a cause of cartilage damage or an effect of cartilage damage is unclear. Several lines of evidence suggest that apatite crystals cause joint destruction. For example, apatite crystals induce both mitogenic and prostaglandin synthesis in synovial fibroblasts and chondrocytes in vitro. They also induce matrix metalloprotinases (MMP) synthesis and secretion, thus promoting tissue damage. The cellular mechanisms whereby apatite crystals induce such responses are currently under investigation. Like many other growth promoting agents, apatite crystals induce a variety of transcription factors such as nuclear factor-κB (NF-κB) and activator protein 1 (AP-1). They also induce mitogens activated protein kinases (MAPK) and protein kinase C (PKC). Furthermore, such activation is specific as the crystals do not activate protein tyrosine kinases (PTK) or phosphatidylinositol 3-kinases (PI3K). If the crystals were present simply as a consequence of joint destruction, we would expect them to be present in other arthropathies characterised by cartilage dissolution and synovial lining proliferation such as rheumatoid arthritis (RA). However, apatite crystals are rarely found in RA joint fluids. Thus, current data support the possibility of an etiologically specific role of apatite crystals. On the other hand, the clinical significance of apatite crystals in joint degeneration continues to be questioned. Dieppe and Swan doubt that apatite crystals are of pathogenic importance but they fail to refute the suggestion that even if the clinical role of apatite crystals is in doubt, the fact that they are present in synovial fluids may be important, and it costs too much money to search for in the future treatments. However, even if only in the first 10 years of RA, however, this is a major consideration. From previous studies, these patients typically have impaired treatment strategy and that their identification should have no influence on contemporary therapeutic decisions.

Author’s reply

We agree with all the points made by Dr McCarthy. Basic calcium phosphates (BCPs) in synovial fluids may be important, and it may be that their identification will be valuable in relation to future treatments. However, she seems to agree with the two points made about BCPs in our article (which is about the identification of urate and pyrophosphate crystals): that, on the basis of current evidence, their presence is doubtful significance, and that their identification should have no influence on contemporary therapeutic decisions.

PAUL DIEPPE
MRC Health Services Research Collaboration, University of Bristol

Mortality in rheumatoid arthritis patients

The paper “Mortality in rheumatoid arthritis patients with disease onset in the 1980s” is of considerable interest. A decrease in mortality risk for rheumatoid arthritis (RA) patients in more recent years would be important, even if only in the first 10 years of RA. However, this is a major consideration.

Yet, even at first perusal, there are a lot of deaths in this series of relatively young people. In the 10 years after a mean age of 51, 18 patients (10%) had died. Over 20 deaths were said to be “expected”. However, using US mortality rates for a population mean aged the same, projected over 10 years, two thirds women, and white, one would expect only 11 deaths using 1996 mortality rates, and 12 deaths using 1985 rates, over the 1710 patients years of follow up. While we did not have the age distribution of this RA cohort to calculate precise expectations, these figures should be conservative. Female mortality rates in the US white female popula-
tion, at 3.4 per 1000 per year at age 51 and 9.0 per 1000 per year at age 61 are presumably higher than those in long lived Malmöhus County, Sweden.

Of interest, in our own larger study with meticulously computed “expected” values in four different populations we also had an “expected” death rate of about 10% to 15% over 10 years. But, these were not inception cohorts and their age at start of follow up was 60.4, 62.6, 59.8, and 69.1 years. Thus, they were much older cohorts. Given the expected doubling of mortality rates each eight years (Gompertz’s law), expected deaths should have been two to three times more in our cohorts than in a cohort beginning at age 51.

Finally, recent studies have not suggested that “rheumatoid” deaths in themselves are the cause of the increased mortality in RA. The observed “excess” deaths are spread around in multiple disease categories, with accelerated atherosclerosis numerically the largest problem and only a slight relative increase in systemic RA complications, gastrointestinal haemorrhage, and infections.

JAMES F FRIES
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Authors’ reply

We were pleased to notice the interest in our paper shown by Drs Fries and Bloch. In reply to their comments we do not consider the death rate of 10% in the cohort as an excessive one compared with the age and sex matched general population. It is not possible to calculate more precise figures of expected deaths knowing the mean age of the cohort only. To clarify this and make comparison possible we enclose a table of the age distribution in our cohort in five year intervals giving the number of observed and expected deaths for each age interval separately.

Women do live longer in Malmöhus County, Sweden than in the US. Female mortality rates in Malmöhus County were 3.76 per 1000 at age 51 and 7.32 per 1000 at age 61 in 1985. In 1996 the corresponding figures were 2.03 per 1000 at age 51 and 3.39 per 1000 at age 61.

We agree that the main cause of death in RA patients very seldom is the rheumatoid disease in itself. This was true also for our study where no certain connection between RA and death was found in any of the cases.

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KERSTIN EBERHARDT
Department of Rheumatology, Lund University Hospital, Sweden

Table 1

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of patients</th>
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<th>Observed mortality</th>
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