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 suffering from 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 HLA BS. 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 added. 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 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 methylprednisone 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 heightening of an ocular episode 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 rejection 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 perivalvular 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 inflammatory 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 anastomosis. 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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Letters

Lymphocyte phenotypes in systemic sclerosis

Although the pathophysiology of systemic sclerosis (SSc) is not fully clarified, there are considerable data implicating abnormalities of microvascular changes, fibroblast activation and immune system abnormalities. Immune system activation may play a part as a stimulus in both fibrotic and vascular damage. To investigate the immune system abnormalities in the pathogenesis of SSc we evaluated lymphocyte phenotypes in patients with SSc and healthy controls (Epics Profile II) for total T (CD3), T helper (CD4), T suppressor (CD8), B lymphocyte cell surface marker (CD19), activation marker (CD25) and natural (NK) cell surface marker NK1–1 (CD56).

We studied 29 patients (27 women, two men) 16 limited, 12 diffuse and one overlap who fulfilled preliminary criteria for classification of SSc. Anti-nuclear antibody was positive in 25 (86.2%) and anti-Scl70 antibodies was positive in seven (24.1%) patients. The age range of the patients was 20–63 years (mean (SEM) 40 (5)) and the mean (SEM) disease duration was 5.5 (5.5) years. Patients were receiving no medication nor had received any immunosuppressive agent for at least three months. Controls were 12 aged and sex matched healthy volunteers with an age range from 27–51 years.

Data were compared for significance for Student’s unpaired t test.

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 in SSc patients. There was no difference between 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 vasculopathy and fibrosis. 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 CD3, CD8, CD4, CD25, CD28, CD45RA, and CD45RO 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 (n=29)</th>
<th>Healthy Controls (n=29)</th>
<th>t test</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3 (%)</td>
<td>71 (9) 69 (9) 0.660 &gt;0.05</td>
<td>71 (9) 69 (9) 0.660 &gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 (%)</td>
<td>44 (9) 45 (9) 0.110 &gt;0.05</td>
<td>44 (9) 45 (9) 0.110 &gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD8 (%)</td>
<td>31 (9) 25 (8) 1.914 &gt;0.05</td>
<td>31 (9) 25 (8) 1.914 &gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>1.56 (0.6) 1.84 (0.6) 1.339 &gt;0.05</td>
<td>1.56 (0.6) 1.84 (0.6) 1.339 &gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD19 (%)</td>
<td>12 (4) 13 (5) 0.445 &gt;0.05</td>
<td>12 (4) 13 (5) 0.445 &gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD25 (%)</td>
<td>18 (9) 7.1 (3) 4.150 &lt;0.05</td>
<td>18 (9) 7.1 (3) 4.150 &lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD56 (%)</td>
<td>22 (9) 14 (5) 2.691 &lt;0.05</td>
<td>22 (9) 14 (5) 2.691 &lt;0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Unpaired Student’s t test. Data shown as mean (SD).
Whitehead et al. and Barrett et al. by using the indirect immunofluorescence method, reported that CD8+ suppressor/cytotoxic T cells are decreased in SSc group, our findings differ from those of Whitehead and Barrett; we and Degiannis et al. have used the more sensitive flow cytometry method and could not find any differences between the lymphocyte subgroups of SSc patients whereas in the pathogenesis of SSc the role of CD4+ and CD8+ T lymphocytes is still obscure. Presence of autoantibodies and hypergammaglobulinemia support the role of humoral immunity but B lymphocytes were rarely found in the skin biopsy specimens. CD19+ is a cell surface marker of B lymphocytes and we could not observe any CD19+ in the skin biopsy specimens.  


Lympocyte populations and cytokine concentrations in pericardial fluid from a systemic lupus erythematous patient with cardiac tamponade

Pericardial involvement is the most common cardiovascular complication in systemic lupus erythematous (SLE). The clinical picture varies from subclinical pericardial effusion and classic acute pericarditis to cardiac tamponade.  

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Peripheral</th>
<th>Pericardial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte population (%)</td>
<td>57.8</td>
<td>50.0</td>
</tr>
<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>
<td>25.0</td>
</tr>
<tr>
<td>B cells</td>
<td>7.8</td>
<td>8.3</td>
</tr>
<tr>
<td>NK cells</td>
<td>34.3</td>
<td>41.7</td>
</tr>
</tbody>
</table>

Cytokine concentration* (pg/ml)  

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IL1ß</th>
<th>IL2</th>
<th>IL4</th>
<th>IL6</th>
<th>IL10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level</td>
<td>3.0</td>
<td>2400</td>
<td>6.0</td>
<td>40</td>
<td>15.4</td>
</tr>
</tbody>
</table>

61 0 7280/mm³ for IL1ß, INFγ and TNFα; 4 pg/ml for IL2; 6 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). CF cultures were negative. No malignant cells were seen to proliferate although dense corticosteroids and azathioprine. Prednisone 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 cultured by gradient centrifugation and the frequency of lymphocyte populations was determined by flow cytometry. The cytokine concentrations from plasma and PB 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, IL1ß and IL10 concentrations were higher in PF. IL2 was detected in plasma but not in PF. The considerable increase in pericardial IL6, with respect to plasma, is 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 anti-body 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 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 periarticular fluid and tissue.

### Table 1: Lymphocyte populations in AU patients and controls

<table>
<thead>
<tr>
<th>Lymphocytes (no/mm³)</th>
<th>AU patients (n=146)</th>
<th>Controls (n=31)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3 (no/mm³) (%)</td>
<td>2425.60 (964.44)</td>
<td>2567.74 (820.72)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4 (no/mm³) (%)</td>
<td>1734.20 (726.67)</td>
<td>1835.64 (586.68)</td>
<td>NS</td>
</tr>
<tr>
<td>CD8 (no/mm³) (%)</td>
<td>71.96 (8.20)</td>
<td>71.27 (4.28)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4/CD8 (%)</td>
<td>1023.91 (489.16)</td>
<td>1161.17 (574.56)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CD4CD8 (%)</td>
<td>42.56 (9.50)</td>
<td>47.00 (6.13)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CD8 (no/mm³) (%)</td>
<td>702.21 (359.67)</td>
<td>675.90 (243.54)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4CD45R (%)</td>
<td>29.25 (8.81)</td>
<td>26.72 (6.81)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4CD45R (%)</td>
<td>1.76 (0.89)</td>
<td>1.57 (0.78)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4CD45R (%)</td>
<td>266.87 (127.44)</td>
<td>335.90 (142.35)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4CD45R (%)</td>
<td>10.81 (5.65)</td>
<td>13.64 (5.09)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CD4CD45R (%)</td>
<td>4067.14 (151.18)</td>
<td>697.70 (301.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4CD45R (%)</td>
<td>16.70 (9.99)</td>
<td>25.20 (7.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4CD45R (%)</td>
<td>661.53 (338.48)</td>
<td>529.41 (219.04)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CD4CD45R (%)</td>
<td>27.70 (7.84)</td>
<td>20.77 (6.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NK (no/mm³) (%)</td>
<td>300.45 (179.63)</td>
<td>323.80 (182.53)</td>
<td>NS</td>
</tr>
<tr>
<td>NK (no/mm³) (%)</td>
<td>13.30 (7.76)</td>
<td>12.81 (5.86)</td>
<td>NS</td>
</tr>
</tbody>
</table>

AU = anterior uveitis, NK = natural killer cells, NS = not significant. Data shown as mean (SEM).

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

Anterior uveitis (AU) is the most common form of uveitis, and may be produced by different causes. An aetiological diagnosis is commonly established in approximately half of the patients with AU by 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 presenting with associated SA.** 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.** 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 to the Department of Internal Medicine, Universidad Central del Caribe School of Medicine, Bayamón, Puerto Rico from April 1988 and October 1995 referred from both the Department of Internal Medicine, Universidad Central del Caribe School of Medicine, Bayamón, Puerto Rico and the Department of Microbiology and Immunology, Universidad Central del Caribe School of Medicine, Bayamón, Puerto Rico.

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diseases. The immunological features studied involved both humoral and cellular, in HLA-B27+ patients without associated SA were similar to those of patients with SA, which suggest a common pathogenetic link between both forms of AU. It is possible that the long term follow up of these patients will clarify whether or not it is the same entity.

We are indebted to Ms E Velasco for assistance in the preparation of the manuscript.

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3 Rosenbaum JT. Uveitis. An internist’s view.

Letters, 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 multicentre study of 27 cases of RS3PE. We included that personal history of polyarthritis rheumataica (two patients), presence of erosions (one patient) and evolution to haematological diseases (two patients concomitantly developed a T lymphoma and one a myelodysplastic syndrome) suggested that RS3PE syndrome might not be a distinct clinical entity. At that moment 12 patients were asymptomatic and 13 required treatment. This was reported elsewhere.2

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 treatment, in contrast none 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 separate serocorticosteroids responsive episodes of bilateral hand oedema and polylymphatic syndromes at different times. Last but not least one patient developed Raynaud’s phenomena, both hands had sclerodactyly. A nailfold capillary microscopy showed a decreased number of capillary loops, which were widened, suggesting systemic sclerosis.

Our results suggest that RS3PE syndrome has a good prognosis a three out of 12 patients are asymptomatic and without treatment six years later. However, there is a subset of patients that have other diseases. Although pure RS3PE syndrome does exist the evolution should be carefully monitored.

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Authors’ reply

We appreciate the comment by Olivé et al on our article on RS3PE. They reviewed 27 previously described RS3PE patients after a follow up of six years.

As we suggested in a previous report,2 they confirm that RS3PE syndrome should be considered a heterogeneous condition associated with different inflammatory rheumatic diseases and also with neoplastic disorders.

In our study3 none of the 23 patients with RS3PE syndrome developed clinical manifestations supporting the diagnosis for another disease. The different study design and selection of patients may in part explain the subset of patients with other diseases and with a worse prognosis observed by Olivé et al.

We designed a prospective follow up study excluding patients satisfying the criteria for the diagnosis of polyarthritis rheumataica, rheumatoid arthritis and seronegative spondylarthropathies. Moreover, two patients with a clinical history of cancer were excluded from the study. In their original report these authors performed a retrospective study including all patients with remitting distal extremity swelling with pitting oedema. They recruited also patients not evaluated for spondylarthropathies, which may be associated with distal extremity swelling with pitting oedema.2

However, in their retrospective evaluation Olivé 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 similarities of demographic, clinical and MRI findings between patients with “pure” RS3PE syndrome and those with polyarthritis rheumataica 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 Olivé et al the patient with a clinical course characterised by distal extremity swelling with pitting oedema or polylymphatic syndromes further supports our hypothesis. Even those RS3PE patients sucessively diagnosed as having seronegative rheumatoid arthritis (elderly onset rheumatoid arthritis) do not conflict with our conclusions. Healey described patients who developed episodes of polyarthritis rheumataica and seronegative rheumatoid arthritis at different times during follow up.4 Similar clinical characteristics have been recently described in a population based cohort of patients with giant cell arteritis followed up for 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 polyarthritis rheumataica and distal extremity swelling with pitting oedema.5

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Cytostatics 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 mitochondrial and proangiogenic synthesis in synovial fibroblasts and chondrocytes in vitro. They also induce matrix metalloprotease (MMP) synthesis and secretion, thus promoting tissue damage. Whether the presence of apatite crystals influence these 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 kappa B (NF-kB), and activator protein 1 (AP-1). They also induce mitogen activated protein kinases (MAPK) and protein kinase C (PKC) signaling. 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 destruction 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 the presence 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 pathogenetic importance but they fail to refute the possibility that they might be involved in osteoarthritic pathophysiology. As with apatite crystals, level of IL1 in OA joints is also interlinked with other cytokines such as tumour necrosis factor alpha (TNF-alpha); the exact role of these cytokines in OA is now considered important. As a consequence of such observation, several laboratories have attempted to inhibit the pathogenic effects of IL1 and TNF-alpha using anti-cytokine agents. However, this approach has not yet been successful.

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 mitochondrial and proangiogenic synthesis in synovial fibroblasts and chondrocytes in vitro. They also induce matrix metalloprotease (MMP) synthesis and secretion, thus promoting tissue damage. Whether the presence of apatite crystals influence these 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 kappa B (NF-kB), and activator protein 1 (AP-1). They also induce mitogen 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 destruction 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 the presence of apatite crystals.

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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.

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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.

ELISABET LINDQVIST
KERSTIN EBERHARDT
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Table 1

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of patients</th>
<th>Expected mortality</th>
<th>Observed mortality</th>
</tr>
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<tbody>
<tr>
<td>15-19</td>
<td>1</td>
<td>0</td>
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</tr>
<tr>
<td>20-24</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25-29</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30-34</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>35-39</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40-44</td>
<td>20</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>45-49</td>
<td>27</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>50-54</td>
<td>34</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>55-59</td>
<td>24</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>60-64</td>
<td>19</td>
<td>3</td>
<td>2</td>
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<td>65-69</td>
<td>16</td>
<td>4</td>
<td>3</td>
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<tr>
<td>70-74</td>
<td>11</td>
<td>4</td>
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</tr>
<tr>
<td>75-79</td>
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<td>2</td>
<td>2</td>
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<tr>
<td>All</td>
<td>183</td>
<td>20</td>
<td>18</td>
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