MATTERS ARISING

How should we manage fibromyalgia?

We read with interest your leader, “How should we manage fibromyalgia?”.1 We were puzzled by Paul Reilly’s statement that a comprehensive pain management program has the best chances of success, although even rheumatologists can practise amateur cognitive behavioural therapy in the clinic.2 Is Dr Reilly really suggesting that a rheumatologist’s amateur efforts offer the best outcome for people with fibromyalgia? Dr Reilly offers no evidence to support this statement. He does, however, find evidence to raise questions as to the value of patient self help groups. Dr Reilly cites a 1992 paper that reports an association between membership of such a group and worse prognosis in chronic fatigue syndrome.3 As the authors emphasised the caution with which the results should be interpreted, it is surprising that Dr Reilly has used this evidence to inform his clinical practice.

Firstly, this is ancient research. Things have moved on. Although we would agree that some so called self help groups can end up as a circular review of symptoms, self management courses, which we at Arthritis Care espouse, are a very different matter.

Challenging Arthritis is a self management programme—and that title was chosen very deliberately. It is run by people with arthritis for people with arthritis. It gives people the skills to take control of their lives and their arthritis. It is practical and positive, and it works. The effectiveness of similar programmes in the USA is well recorded.4 Experience in the United Kingdom shows similar results, including better understanding of symptoms, improved communication with medical staff, and increased use of exercise and relaxation techniques. Probably most importantly of all, self management programmes significantly decrease pain, fatigue, and anxiety.5 So it is extremely important to differentiate between navel gazing self help systems and courses such as ours, which encourage people to take control for themselves—and which work.

Similar courses run on the Challenging Arthritis model are now available to people with other chronic conditions.

Given Dr Reilly’s desire to disabuse patients of the notion that their fibromyalgia is his problem alone, shouldn’t he also encourage people to take control for themselves be a welcome adjunct to his treatment, even if it is run by a patient self management group?

Author’s reply

I am surprised that Ms Lloyd has chosen to be rather negative about an editorial that was designed to combine optimism with realism. Although one might be optimistic that every patient with fibromyalgia, and similar functional pain syndromes, might have access to professional psychological advice and management, reality dictates that this is not the case, at least not within the health service as it operates in the United Kingdom. As cognitive behavioural therapy sets out to influence the manner in which patients with fibromyalgia think and behave in an attempt to decrease the impact of their disorder, I have merely pointed out that an interested rheumatologist can employ communication and motivational skills, which in many cases will serve the same purpose as formal psychological management.

Ms Lloyd makes much of the “Challenging Arthritis” self management programme run by Arthritis Care. Fibromyalgia, of course, is not a form of arthritis but a form of non-articular rheumatism. I have little doubt that an appropriately run education programme can help people with fibromyalgia cope more effectively with their symptoms. However, self help groups often work to a different agenda than treating clinicians. They function as a lobby to increase recognition and acceptance of a particular disorder, and sometimes such a campaign has financial rewards through litigation and compensation. Not only the objectives but also the objectivity of such a group can be called into question. However, I am delighted to learn from Ms Lloyd that the “Challenging Arthritis” programme is so good and so effective.

Finally, to accuse a paper published in 1992 of being “ancient research” is not only insulting to the authors but also inaccurate. High quality research has a longer shelf life than eight years.

P A REILLY
Frunley Park Hospital,
Portsmouth Road,
Frimley, Camberley,
Surrey GU16 5UP, UK

LETTERS

A “missed” cryoglobulin: the importance of in vitro calcium concentration

Cryoglobulins are immunoglobulins which precipitate at reduced temperature and that redissolve by warming the serum sample to 37 °C. Mixed cryoglobulinaemia may manifest clinically as skin, articular, renal, and peripheral nerve complications.1 To ensure optimal detection, serum samples must be obtained and preserved at 37 °C. We report on a patient whose clinical presentation was suggestive of cryoglobulinaemia. Because cryoglobulins had been either undetectable or found at very low levels for several years despite repeated careful blood sample examinations with conventional assays, we initially thought he had Henoch-Schönlein purpura. The recent use of a modified assay finally led us to diagnose mixed cryoglobulinaemia. Included below is a description of the method used for cryoglobulin detection, emphasising the importance of in vitro calcium concentration.

Case report

A 52 year old man with multiple lipoma had a 20 year history of polyarthralgias affecting elbows, wrists, hands, knees, and feet, a 10 year history of Raynaud’s disease affecting the hands and feet, and a seven year history of palpable purpura and coeliac disease. In June 1996 he developed attacks of abdominal pain concomitantly with arthralgias and palpable purpura of both legs. Serum creatinine was 95 μmol/l. Gamma-globulins were low (4.2 g/l) on serum protein electrophoresis. Serum concentrations of immunoglobulins were 4.49 g/l for IgG (normal range 6.42–11.92), 1.84 g/l for IgM (normal range 0.52–1.47), and 2.51 g/l for IgA (normal range 0.10–0.40; Behring Dade, Deerfield, USA) and for CH₅₀ (home method) 25% of the normal range (0.60–1.10) and <0.04 g/l (normal range 0.10–0.80). A set of sero- markers was negative, including antinuclear, and DNA and antineutrophil cytoplasmic antibodies. Complement concentrations were notably down, both for C₄ <0.06 g/l (normal range 0.10–0.40; Behring Dade, Deerfield, USA) and for CH₅₀ (home method) 25% of the normal range (60–120%). C₃c and C₃PA were also decreased at respectively 0.34 g/l (normal range 0.60–1.10) and <0.04 g/l (normal range 0.10–0.80). A complete set of sero- markers was negative, including antinuclear, and DNA and C viruses. Cryoglobulin measurements were initially negative or inconclusive (table 1). Proteinuria was negative. Radiographs of the affected joints were normal. A computed tomographic scan of the abdomen showed a thickened aspect of the duodenal and jejunal loop wall. Skin biopsy was not performed. Prednisone treatment (30 mg/day) was started but, owing to poor response, plasmapheresis was carried out in March 1997; azathioprine (150 mg/day) and colchicine (2 mg/day) were then added and, finally, a marked clinical improvement was obtained. A new flare up occurred in August 1998 with proteinuria including 3 g daily proteinuria of recent onset. The urinary sediment contained 20 red cells per high power field. Renal biopsy showed endocapillary proliferative glomerulonephritis with glomerular crescents and capillary loop fibrinous thrombi (no glomerulus on the sample for immunofluorescence study). The patient temporarily improved with plasmapheresis and methylprednisolone pulses followed by high oral prednisone (50 mg/day). From September 1998 to January 1999, proteinuria increased to 5.4 g daily, and a high serum cryoglobulin concentration was then first detected with the assay described below (table 1). Azathioprine was replaced by monthly intravenous cyclophosphamide (1 g per infusion), associated with subsequent plasmapheresis in January and April 1999. Despite this treatment the patient’s symptoms persisted and renal complications worsened, with a raised proteinuria at 6.28 g/day and a serum creatinine at 192 μmol/l in July 1999. A new evaluation was made. A bone marrow biopsy was normal. The skin biopsy showed leukocytoclastic vasculitis with slight

 deposits of IgM, IgA, and C3 on immunofluorescence study. Renal biopsy showed an endocapillary and extracapillary glomerulonephritis with glomerular crescents in a mean of 30% of glomeruli, and IgG, IgM, and C3 deposits on immunofluorescence study. Prednisone was continued and cyclophosphamide was given orally (150 mg/day). The patient's condition is stabilised at the present time.

A modified assay was developed to detect a possible cryoglobulin. Briefly, a serum sample was obtained and centrifuged at 37 °C, then stored at 4 °C for eight days. The precipitate was separated by centrifugation, then washed each day for three consecutive days with either cold phosphate buffered saline (PBS; conventional assay) or distilled water to enhance the protein solubility (current assay). Indeed, we noted that some of the precipitate was lost in the PBS. Then, a high titre type II cryoglobulin (>1000 µg/ml) was isolated, and subsequently shown to consist of monoclonal IgM and polyclonal IgG, the former being thought to support the previously detected rheumatoid factor activity. Two dimensional polyacrylamide gel electrophoresis confirmed the presence of polyclonal IgG and monoclonal IgM in the cryoprecipitate, and alloimmunisation of an additional monoclonal IgA. Finally, electrophoretic studies of the proteins eluted from protein G columns showed the presence of polyclonal IgG, with only traces of the monoclonal IgM, indicating that the complex dissociated at 37 °C.

This cryoglobulin has unusual properties because it became soluble in PBS, while it precipitated in serum, distilled water, or calcium buffers. Usually, cryoprecipitation is a two step process. 

Firstly, rheumatoid factors bind to immune complexes at reduced temperature because of a cold enhanced affinity. Secondarily, the large immune complexes precipitate. This requires favourable physicochemical conditions, including suitable pH and ionic strength of the solvent. Usually, the precipitate is stable in saline. Our data suggest that calcium concentration may be crucial for cryoglobulin precipitation, as in the case reported by Qi et al." This property might account for some of the discrepancies observed between the conventional and the current assay. It might also explain the severity of the symptoms in vivo. Further investigation is needed to approach the other determining factors of precipitation. Hypocryoglobulins display a quite different property in the way they are isolated from hypotonic serum, though they lead to the same clinical syndrome.  

Figure 1 Western blot of cryoglobulin. Pattern obtained with anti IgG, IgA, IgM, κ and λ chain labelled with alkaline phosphatase on cryoglobulins transferred onto nitrocellulose sheets: oligoclonal (top) and polyclonal pattern (middle) for cryoglobulin washed with conventional assay, type II pattern IgMx (arrow) and polyclonal IgG, IgA, and IgM for cryoglobulin washed with current assay (bottom).  

Table 1 Evolution of cryoglobulinaemia, rheumatoid factor, and complement levels

<table>
<thead>
<tr>
<th>Date</th>
<th>Cryoglobulinaemia (µg/ml) *</th>
<th>Type</th>
<th>Rheumatoid factor (Rose-Waaler test)</th>
<th>C4 (g/l)</th>
<th>CH50 (%) ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 1994</td>
<td>29</td>
<td>Oligoclonal IgM</td>
<td>0</td>
<td>&lt;0.06</td>
<td></td>
</tr>
<tr>
<td>June 1996</td>
<td>25</td>
<td>Oligoclonal IgM</td>
<td>1 / 128</td>
<td>&lt;0.06</td>
<td></td>
</tr>
<tr>
<td>August 1996</td>
<td>17</td>
<td>Oligoclonal IgM</td>
<td>ND</td>
<td>&lt;0.06</td>
<td></td>
</tr>
<tr>
<td>December 1996</td>
<td>188</td>
<td>III, polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>&lt;0.07</td>
<td></td>
</tr>
<tr>
<td>March 1997</td>
<td>4</td>
<td></td>
<td>1 / 128</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>October 1998</td>
<td>63</td>
<td>III, polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>November 1998</td>
<td>110††</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>December 1998</td>
<td>166††</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>January 1999</td>
<td>1660††</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>February 1999</td>
<td>1031††</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>1/128</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>March 1999</td>
<td>1000††</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>1/128</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>April 1999</td>
<td>273†† (after plasmapheresis)</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>1/128</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>May 1999</td>
<td>848††</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

*Normal <15 µg/ml.
††Determination performed using the method described above since November 1998.
‡Normal range 60–120%.
Computed digital absorptiometry of the hand: screening method of bone loss in postmenopausal women with RA

Dual energy x-ray absorptiometry (DXA) is the most commonly used method of measuring bone mineral density (BMD). It has been shown to be a good predictor of the future risk of fracture. Unfortunately, the generalised use of DXA is limited as it is expensive and time consuming, is not portable, and is available only in large hospitals. Computed digital absorptiometry (CDA) of the hand is a new bone densitometry technique, designed to assess the BMD of the middle phalanx of the third finger using a direct, automated method of x-ray attenuation. This technique is similar to radiographic absorptiometry but provides immediate results; in current radiographic absorptiometry, radiographs are sent to a off-site processing centre and the results are received a few days later. CDA is cheap and quick. Its precision and accuracy seem to be acceptable, but its ability to discriminate between patients with osteoporosis and normal subjects, to predict the risk of future fracture, and to monitor the response to therapeutic intervention has not been established.

Rheumatoid arthritis (RA) is a risk factor for osteoporosis. The available data suggest that there is an increased risk of hip fracture in patients with RA, especially when they are treated with glucocorticoids. DXA is the preferred technique for assessing the presence of bone loss in these patients. However, the prevalence of RA in the general population is high, and it is therefore necessary to use DXA to investigate only those patients at high risk of osteoporosis. Criteria to decide who should be evaluated are currently not available. Recently, in this journal, Lems and Dijkmans presented a proposal from rheumatologists in Amsterdam based on clinical risk factors.

We have undertaken a study to evaluate whether CDA might be a useful screening technique for identifying the patients with RA who should be examined by DXA. Over a period of three months all postmenopausal women with RA, evaluated in the rheumatologists’ clinic, were investigated for osteoporosis established by DXA.

The positive predictive value of CDA for the diagnosis of osteoporosis was 56%. The negative predictive value of CDA for the diagnosis of osteoporosis was 83%.

The correlations found between BMD at the non-dominant hand and BMD at the lumbar spine and the femoral neck were moderate. A negative predictive value of 56% was considered acceptable. Our results suggest that CDA could be a screening method used to decide which patients with RA should be investigated for osteoporosis. Further investigations are needed to confirm our findings.

Table 1 Clinical characteristics of the patients with RA and BMD values obtained (n=39). Values are expressed as mean (SD)

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>61.2 (8.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of postmenopausal period (y)</td>
<td>13.3 (7.5)</td>
</tr>
<tr>
<td>Duration of rheumatoid arthritis (y)</td>
<td>9.7 (6.4)</td>
</tr>
<tr>
<td>Rheumatoid factor positive (n)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Eroded RA (n)</td>
<td>16</td>
</tr>
<tr>
<td>Treatment with low dose glucocorticoids (n)</td>
<td>32</td>
</tr>
<tr>
<td>BMD at the lumbar spine (g/cm²)</td>
<td>0.840 (0.105)</td>
</tr>
<tr>
<td>BMD at the femoral neck (g/cm²)</td>
<td>0.560 (0.110)</td>
</tr>
<tr>
<td>BMD at the middle phalanx of the third finger (g/cm²)</td>
<td>0.390 (0.090)</td>
</tr>
</tbody>
</table>

*BMD = bone mineral density.
Rubella infection in adult onset Still's disease

The aetiology of adult onset Still's disease remains unknown although some authors have tried to relate it to a viral infection. In our case we think that rubella was more probably attributable to a reinfection than to a primary infection because the patient had been correctly vaccinated in childhood and this is also supported by the increase in IgG antibody titre without increase in IgM concentration. The seroconversion is not explained by a non-specific polyclonal stimulation after a generalised inflammatory disease because there was no increase in other measured antibody titres.

In summary, we think that the increased rubella IgG antibody titre in our patient should not be considered an anecdotal event and probably rubella virus has been the trigger of the illness. Our case, together with previously published reports, supports the hypothesis about the role of viruses in the aetiopathogenesis of adult onset Still's disease.

References


Raised plasma adrenomedullin in patients with systemic sclerosis complicated by pulmonary hypertension

Adrenomedullin is a hypotensive peptide newly found in human pheochromocytoma tissue. This peptide comprises 52 amino acids with an intramolecular disulfide bond. The mRNA of adrenomedullin has been detected in normal adrenal medulla, heart, kidney, and lung. Adrenomedullin is produced in endothelial cells, vascular smooth muscle cells and other cell types. Adrenomedullin receptors are expressed in both vascular smooth muscle cells and vascular endothelial cells. Adrenomedullin has a vasorelaxant effect, antagonising the vaso- pastic effect of endothelin-1 and seems to be implicated in the physiological and pathologi- cal control of circulation. Through multiple biological effects in the circulatory system, adrenomedullin appears to reduce plasma volume and blood pressure, thus affecting the cardiovascular system. Furthermore, adrenomedullin regulates not only vascular tonus but also vascular function through the autocrine/paracrine system, stimulating cell proliferation and the expression of a thromboplastic manner, and exerting an anti-inflammatory effect by inhibiting the production of a chem- attractant from alveolar macrophages.

Systemic sclerosis (SSc) is a chronic disease of unknown cause characterised by vascular changes and fibrosis of the skin and the visceral organs. Major complications of SSc are renal, myocardial, and pulmonary. Pulmonary hypertension (PH) is a common cause of death in patients with SSc. The plasma of patients with PH the endothelin-1 level is raised. In addition, it was recently reported that the adrenomedullin level is raised also in the plasma of patients with Raynaud's disease or rheumatoid arthritis.

Therefore, we measured the concentrations of adrenomedullin and endothelin-1 in the plasma from patients with SSc, with or without PH, to elucidate the role of adrenomedullin in the pathogenesis of PH.

We obtained plasma from three women with SSc with PH (aged 43–72), 10 patients with SSc without PH (nine women, one man, aged 22–60), and one female patient with primary PH. The diagnosis of SSc was based on accepted criteria. We diagnosed PH in
patients with SSc whose right ventricular systolic pressure was higher than 25 mm Hg measured by echocardiogram. In the three patients with SSc with PH we confirmed PH by catheterisation. The pressures of the pulmonary artery of these three patients were 45, 51, and 54 mm Hg, respectively. All patients with SSc had diffuse-type SSc without interstitial pneumonia, which was diagnosed as interstitial fibrosis by computed tomography. The three patients with PH were taking the following drugs: triclopidine hydrochloride (patient 1), nifedipine and triclopidine hydrochloride (patient 2), and nicardipine hydrochloride and methylprednisolone (patient 3).

For the comparison group we selected patients with diffuse-type SSc without PH, as all of three patients with SSc with PH had diffuse-type SSc. Six normal volunteers (three women and three men, age 29–40) were also studied. Concentrations of adrenomedullin were measured by radioimmunoassay. Statistical significance was analysed with the Mann-Whitney U test.

Concentrations of adrenomedullin in the plasma were significantly higher in patients with SSc with PH than in those with SSc without PH (p = 0.011) or than in normal volunteers (p = 0.020) (fig 1A). The concentrations of adrenomedullin or endothelin-1 in the plasma from a patient with primary PH were similar to those from patients with SSc without PH (data not shown). The levels of endothelin-1 in patients with SSc with PH were raised compared with those in patients with SSc without PH (p = 0.041) (fig 1B). We did not measure levels of endothelin-1 in normal volunteers (fig 1B).

We recently obtained similar results when measuring the levels of the mature form of adrenomedullin and total adrenomedullin in a different group of patients with SSc with (patients 4, 5, and 6) or without PH, by immunoradiometric assay. The three patients with SSc with PH were women aged 43–54, and two patients with SSc without PH were women aged 47 and 55. The duration of disease was two to seven years. The pulmonary artery pressures of patients 4, 5, and 6 were 46, 59, and 60 mmHg, respectively. The levels of adrenomedullin in the plasma of patients 4, 5, and 6 were 24.9, 58.1, and 27.5, respectively, whereas those of the two patients with SSc without PH were 16.4 and 14.7 pg/ml. These results, however, did not reach statistical significance as the number of patients was small.

Patients 4, 5, and 6 were taking the following drugs: nifedipine, tocopherol acetate, and beraprost sodium (patient 4); nifedipine and triclopidine hydrochloride (patient 5); and nifedipine (patient 6). Levels of adrenomedullin in the plasma were significantly higher in patients with SSc with PH than in healthy volunteers (p = 0.011).

Our results suggest that the amount of adrenomedullin is insufficient to inhibit either the spasm of pulmonary vessels or the proliferation of endothelial cells of the vessels, though the levels of adrenomedullin in plasma increased enough to antagonise the effects of endothelin-1 in patients with SSc. It has been recently reported that chronic infusion of adrenomedullin reduces PH and right ventricular hypertrophy in rats. Thus our results also suggest the possibility that interventions aimed at controlling the balance of adrenomedullin and endothelin-1 might prove fruitful in preventing PH in patients with SSc.

Concentrations of adrenomedullin and endothelin-1 in plasma. Short horizontal lines = 10th and 90th centiles; long horizontal lines = 25th, 50th, and 75th centiles; the circles denote the value outside 10th and 90th centiles in patients with SSc with and without (−) pulmonary hypertension (PH), and normal volunteers. ND = not done.

Figure 1 Concentrations of (A) adrenomedullin and (B) endothelin-1 in plasma. Short horizontal lines = 10th and 90th centiles; long horizontal lines = 25th, 50th, and 75th centiles; the circles denote the value outside 10th and 90th centiles in patients with SSc with and without (−) pulmonary hypertension (PH), and normal volunteers. ND = not done.
The first is the atypical presentation of the more than 20 years was complicated by the all along been normotensive and she has no much improved after the operation. She has involved site showed bone necrosis and features fusion. Histological examination of the in- dic surgery unit for a L1 to L3 vertebral body. She was referred to the orthopaedic spine with increase in signal over the L2 ver-
sce. Bone scan showed no obvious abnormality but magnetic \nlyst. SLE with a positive anti-platelet agent, and atenolol for hyperten-
cy. Her warfarin was stopped in view of polyarthralgia and significant thrombo-
sion that was diagnosed during subsequent follow ups but there was no other evidence of renal involvement. Calcium supplements and vitamin D were started for prophylaxis of AVN. Kienbock’s syndrome is known complication of various systemic conditions including sickle cell disease, prolonged corticosteroids causes AVN. J Rheumatol 1994;21:2376–9.

Immunoglobulin and lymphocyte decrease concurrent with adverse reactions induced by methotrexate for RA

The limiting factor in low dose pulse methotrexate treatment for rheumatoid arthritis (RA) has been its toxicity. We recently treated a female patient with RA, in whom pneumonitis and granulocytopenia developed during methotrexate treatment; her white blood cell count was 1.10×10^11/l and Pao, was 37 mm Hg. Before treatment, at the time of development of adverse reactions, and after recovery after methotrexate was withdrawn, her IgG levels were 17.99, 10.15, 16.75 g/l, IgA 5.14, 3.69, 4.33 g/l; IgM 1.73, 1.04, 3.36 g/l; and CRP 0.42, 1.56×10^11/l, respectively. We then investig-ated whether immunoglobulin levels and lymphocyte count decrease when adverse reactions to methotrexate develop.

One hundred consecutive patients with RA (80 women and 20 men, mean (SD) age 57.5 (9.2) years) receiving between 2.5 and 15 mg of methotrexate weekly in Tokyo Metropoli-
tan Komagome Hospital were followed up from 1991 to 1998. When the patients did not respond and had no adverse reactions, the dose was increased by 1.25 to 2.5 mg/week. Response to treatment, assessed by the patient’s impression of improvement, a decrease in swelling and pain of more than two joints, a decrease of >20 mg/l in the C reactive protein (CRP) level, adverse reactions to methotrexate treatment associated with ischemic necrosis of bone in systemic lupus erythematosus. Am J Med 1985;79:596–604.


Figure 1 Plain radiograph of the lumbosacral spine (AP view) of the patient.

Figure 2 T2 weighted magnetic resonance scan sagittal image of the lumbosacral spine of the patient.

CRP from 63 (36) to 32 (55) mg/l, whereas all 22 non-responders who had no adverse events showed a decrease in CRP from 46 (39) to 41 (34) mg/l. A significant relation was found between a good response to treatment and the appearance of adverse reactions. The patients with adverse reactions had a higher creatinine level, and more frequent use of steroid at high dose (7.9 (7.8) v 2.8 (3.5) mg/day prednisolone). The patients with the higher creatinine level were older.

The albumin level increased more in responders. The rheumatoid factor titre decreased in responders and in patients without adverse reactions. The eosinophil count did not correlate either with response or adverse reactions.

After treatment the levels of IgG, IgA, and IgM, γ fractions, and lymphocyte count in the 15 patients who had adverse reactions were significantly reduced compared with the values before treatment. The reductions and reduction ratios compared with pretreatment values were significantly greater in patients with adverse reactions than in those without. Table 1 gives the results obtained and the threshold values that could differentiate between patients with and without adverse reactions. When the patients were grouped according to therapeutic response, significant reductions were seen only in the levels of immunoglobulins and γ fractions, but no reduction was seen in lymphocyte counts, in 78 responders. The greater decreases in responders than in non-responders were seen only in IgG and IgA levels. The reductions and reduction ratios of immunoglobulins were greater in patients with adverse reactions, grouped according to toxicity (30–35%, table 1), than in those with therapeutic response grouped according to efficacy (13–14%, data not shown).

Our study shows that when a patient’s immunoglobulin levels and lymphocyte count decrease globally by as much as 25% or more from the pretreatment level, this decrease is suggestive of toxicity. Conversely, in patients without adverse reactions, the decreases were less than 20%. The clinical improvement contributed only partially to the reductions; steroid treatment was not likely to have been the cause either, as they had been given for a long time without a significant change in the dose.

Recently, we reported that the immunoglobulin level decreases with adverse reactions, during a disease modifying antirheumatic drug, bucillamine, treatment. A reduction in interleukin 6 level was reported to parallel an improvement during methotrexate treatment. The reduction in lymphocyte numbers is controversial. Immuno-modulation might relate mainly to adverse reactions, whereas the effect might appear owing to anti-inflammatory mechanisms. It can only be speculated whether consumption or leakage of immunoglobulin plays a part in the previously supposed mechanism of acute hypersensitivity or cytotoxicity, or in an independent epi-


The authors thank Dr Victoria Elegant and Ms Keiko Miyahara for their help.

SHIGEGO INOKUMA
HIJME KONO
HISANORI NAKAYAMA
JUNIE YAMAZAKI

Department of Allergy and Immunological Diseases, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Dr Shigeko Inokuma, Tokyo Metropolitan Komagome Hospital, 3-18-2 Komagome, Bunkyo-ku, Tokyo, 113-8677, Japan

Email: inokuma-ko@komagome-hospital.bunkyo.tokyo.jp