How should we manage fibromyalgia? We read with interest your leader, “How should we manage fibromyalgia?”

We were puzzled by Paul Reilly’s statement that a comprehensive pain management programme has the best chances of success, although even rheumatologists can practise amateur cognitive behavioural therapy in the clinic. Is Dr Reilly really suggesting that a rheumatology service may not be able to 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
Frimley Park Hospital, Portsmouth Road, Frimley, Camberley, Surrey GU16 5UJ, UK

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.

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P A REILLY
Frimley Park Hospital, Portsmouth Road, Frimley, Camberley, Surrey GU16 5UJ, 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. To ensure optimal detection, 4°C 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 concentrations.

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 subcutaneous cicatricial 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 1.08–3.09). The erythrocyte sedimentation rate was 60 mm/h (normal). Hepatitis B 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 flare up occurred in August 1998, with new skin lesions 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 endocapillary loop fibrinous thrombi (no glomerulus on the sample for immunofluorescence study). The patient temporarily improved with plasmapheresis and methylprednisolone pulses followed by high dose 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


In the case reported by Qi et al.,

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.1 3–8 Firstly, rheumatoid factors bind to immune complexes at reduced temperature because of a cold enhanced affinity. Secondly, 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 determinant factors of precipitation.

Hypocryoglobulins display a quite different property in the way they are isolated from hypotonic serum, though they lead to the other determinants of precipitation.

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>10</td>
</tr>
<tr>
<td>June 1996</td>
<td>25</td>
<td>Oligoclonal IgM</td>
<td>1 / 128</td>
<td>&lt;0.06</td>
<td>25</td>
</tr>
<tr>
<td>August 1996</td>
<td>17</td>
<td>Oligoclonal IgM</td>
<td>ND</td>
<td>&lt;0.06</td>
<td>&lt;20</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>&lt;20</td>
</tr>
<tr>
<td>March 1997</td>
<td>4</td>
<td></td>
<td>1 / 128</td>
<td>0.10</td>
<td>30</td>
</tr>
<tr>
<td>October 1998</td>
<td>63</td>
<td>III, polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>50</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>ND</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>ND</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>ND</td>
</tr>
<tr>
<td>February 1999</td>
<td>103†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>1/128</td>
<td>0.08</td>
<td>60</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>30</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>ND</td>
<td>ND</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>ND</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 specialized centers.

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 measurement of x ray attenuation. This technique is similar to radiographic absorptiometry but provides immediate results; in current radiographic absorptiometry, radiographs are sent to an 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, 16 postmenopausal women with RA, evaluated in the rheumatology outpatient clinic, who fulfilled the inclusion criteria were asked to participate. The inclusion criteria were (a) duration of RA longer than one year, (b) duration of postmenopausal period longer than one year, and (c) no current treatment with bone thinning agents.

Forty five patients fulfilled the inclusion criteria and the consent was obtained from 40 of these. In these patients BMD was assessed by DXA and CDA on the same day. One further patient was not included in the study as she had a severe ulnar deviation that did not allow CDA to be used.

For DXA, BMD (g/cm²) of the lumbar spine and upper femur was assessed using a dual energy x-ray system (Hologic QDR 1000, Hologic Inc, Waltham, Mass); we considered the mean value of the 2 L-spine sites and the value of the femoral neck. For CDA, BMD (g/cm²) of the middle phalanx of the third finger of the non-dominant hand was assessed using a dual energy x-ray system (AccuDEXA, Shick Technologies, Long Island, NY). The x-ray attenuation data was automatically processed and represented as a grey scale image. To assess the in vivo short term precision, 10 serial measurements (with interim repositioning) were performed in seven healthy volunteers. The in vivo precision of AccuDEXA, expressed as a coefficient of variation, was 1.16% (0.74 to 1.56). Data were cross referenced with the T score. According to WHO criteria, osteoporosis is defined as a T score below −2.5.

A Spearman correlation test and linear regression analysis were used to test the relation between the variables; p<0.05 was considered significant. A 2 x 2 table was used to evaluate the positive and negative predictive values for the diagnosis of osteoporosis established by DXA.

Table 1 lists the clinical characteristics of the patients and the mean BMD values obtained.

BMD at the lumbar spine and at the non-dominant hand correlated significantly (r = 0.51, p<0.01). Similarly, BMD at the femoral neck and at the non-dominant hand were significantly correlated (r = 0.51, p<0.01). DXA showed that 13 patients had osteoporosis and CDA that 16 patients had the disease in at least one of the evaluated zones. The positive predictive value of CDA for the diagnosis of osteoporosis was 56%. The negative predictive value for the diagnosis of osteoporosis was 83%.

The correlations found between BMD at the non-dominant hand and at the lumbar spine and femoral neck were moderate. A negative predictive value of 0.91 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>Characteristic</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>61.2 (9.3)</td>
</tr>
<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>23</td>
</tr>
<tr>
<td>Eroosive 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 (0.150)</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. We describe here a case of typical adult onset Still's disease with a seroconversion in the rubella and adult IgM titre to emphasise that it is probably more than a coincidental event.

A 26 year old woman was admitted because of fever with chills, a pruritic rash, myalgia, sore throat and headache. At the time of physical examination the temperature was 40°C and the pulse rate 104 beat/min. The rash consisted of small pruritic macules over back, periorbicular, legs and arms. The liver and spleen were not palpable. Some small cervical lymphadenopaties were detected. The leucocyte count was 42.3 × 10^9/l (93.2% neutrophils) and the haemoglobin concentration was 79 g/l. Liver enzymes were slightly increased, aspartate aminotransferase (AST) 0.80 µkat/l and alanine aminotransferase (ALT) 0.73 µkat/l, but increased to AST 11.77 µkat/l and ALT 7.68 µkat/l after acetylsalicylic acid administration. Lactate dehydrogenase was 17.33 µkat/l. The serum albumin concentration was 26 g/l and the erythrocyte sedimentation rate 60 mm 1st h. The serum ferritin was more than 1500 µg/l (normal value: 20–250 µg/l). Roentenograms of chest and abdomen analysis were normal as well as blood and urine cultures. Abdominal computed tomography showed hepatosplenomegaly. An electromyography study was normal. Tests for antinuclear antibodies and rheumatoid factor were negative. IgM- and IgG-antibodies against rubella virus 1 and 2, Epstein-Barr virus, Mycoplasma, Treponema pallidum, Borrelia burgdorferi, Toxoplasma, Salmonella, Brucella, Legionella, Coxialia burnetti, Chlamydia and Rickettsia were not detected.

The initial rubella IgG antibody titre was 140 000 IU/l. We have tried to relate it to a viral infection, especially viruses, that can be the trigger of the illness in susceptible patients, e.g., echovirus 7, mumps, cytomegalovirus, para-influenza, Epstein-Barr virus, influenza A, parvovirus B19, hepatitis B or C and rubella has been associated.

The relation between rubella virus and adult onset Still's disease has been reported in some series and case reports since the initial description by Bywaters in 1971. Wooters et al performed exhaustive virological studies in patients with adult onset Still's disease in an early phase of the illness and found evidence of viral infection in three cases, two of them corresponding to rubella. The rubella virus genome has also been detected in peripheral blood cell population from patients with adult onset Still's disease. 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.

FRANCISCO JAVIER ESCUDERO OLEG LEM VINCEN FALCO

TOMAS FERNANDEZ DE SEVILLA

Service of Internal Medicine, Hospital General Universitario Vall d'Hebron, Barcelona, Spain

AGUSTI SELLAS

Service of Rheumatology, Hospital General Universitario Vall d'Hebron

Correspondence to: De Escudero, C/ Amapolas, 37 2o Esc 1°, 08906 L'Hospitalet de Llobregat, Spain

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 was present when the pressures of 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 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 and nicardipine hydrochloride (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 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 SSc, PH(−) use-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.

Antiphospholipid syndrome (APLS) is characterised by recurrent arterial or venous thrombosis. Deep veins, such as the femoral vein, are by far the commonest sites of thrombosis. The arterial and venous systems of the mesenteries, liver, kidneys and the adrenal glands are also involved. We report here a 39 year old woman with systemic lupus erythematosus (SLE) and secondary APLS who presented with subacute onset of back pain and was found to have avascular necrosis (AVN) of a single vertebral body at L2, an atypical presentation of this complication.
Vertebral body involvement by APLS is rare. The first case in over 20 years was complicated by the patient who had an unsuccessful pregnancy with previous venous thrombosis and recurrent fetal abortion. Additionally, she had a lupus-dependent manifestation? Lupus 1996;5:323–7.

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 1.10×10^9/l and Pao, was 87 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, 1.08, 3.56 g/l, and lymphocyte count decrease of 40% (9.2) years) receiving between 2.5 and 15 mg of methotrexate weekly in Tokyo Metropolitan 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, was classified as 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, lymphocyte and eosinophil counts, serum concentrations of immunoglobulins, fraction, rheumatoid factor, and albumin were studied.

Sixteen adverse reactions occurred in 15 patients; the reactions affected the liver (six patients), the lung (three), the skin (three), the bone marrow (three), and the oral mucosa (one). They recovered after methotrexate was discontinued or reduced, without steroid treatment. Thirty-three of these 15 patients showed a mean (SD) decrease in

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

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

The lunate bone is another unusual site of involvement by AVN. Kienbock’s disease (AVN of lunate bone) was reported in a patient with primary APLS and two others with antiphospholipid (APL) antibodies. The disease was associated with the lunate bone necrosis. J Rheumatol 1994;21:2376–9.


Table 1  Pretreatment value, decrease, decrease ratio, and threshold value of immunoglobulin levels and lymphocyte count in patients used to differentiate between patients with and without adverse reactions. Values are shown as mean (SD) 

<table>
<thead>
<tr>
<th></th>
<th>With adverse reaction (n)</th>
<th>Without adverse reaction (n)</th>
<th>p Value</th>
<th>Threshold value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>20.87 (7.34)(15)</td>
<td>20.12 (5.50)(83)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post−pre (g/d)</td>
<td>−6.23 (3.53)(15)</td>
<td>−1.47 (3.73)(81)</td>
<td>****</td>
<td>4.62</td>
<td>***</td>
</tr>
<tr>
<td>IgA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>4.50 (2.17)(15)</td>
<td>4.13 (1.61)(93)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post−pre (g/d)</td>
<td>−1.35 (0.87)(15)</td>
<td>−0.21 (0.65)(81)</td>
<td>****</td>
<td>0.83</td>
<td>***</td>
</tr>
<tr>
<td>IgM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.03 (0.86)(15)</td>
<td>2.04 (0.84)(83)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post−pre (g/d)</td>
<td>−0.35 (0.17)(15)</td>
<td>−0.07 (0.17)(81)</td>
<td>****</td>
<td>0.26</td>
<td>***</td>
</tr>
<tr>
<td>γ Globulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>15.64 (7.00)(15)</td>
<td>15.54 (4.69)(74)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post−pre (g/d)</td>
<td>−5.07 (3.61)(12)</td>
<td>−1.30 (3.22)(67)</td>
<td>****</td>
<td>2.38</td>
<td>***</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1.82 (0.80)(15)</td>
<td>1.38 (0.61)(81)</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post−pre (10³/l)</td>
<td>−0.6 (0.55)(14)</td>
<td>−0.01 (0.58)(80)</td>
<td>****</td>
<td>0.18</td>
<td>***</td>
</tr>
<tr>
<td>(Post−pre)/pre</td>
<td>−0.35 (0.31)(14)</td>
<td>0.12 (0.71)(92)</td>
<td>*</td>
<td>0.267</td>
<td>***</td>
</tr>
</tbody>
</table>

NS = p<0.05; *p<0.05; ***p<0.005; ****p<0.0001.
†Comparison of patients with and without adverse reactions.
¶To differentiate between patients with and without adverse reactions.

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 occurrence or leakage of immunoglobulin might relate mainly to adverse reactions, whereas the ejection of circulating soluble tumor necrosis factor receptor, interleukin-2 receptors, tumor necrosis factor-α, and interleukin-6 levels in rheumatoid arthritis. Arthritis Rheum 1993;36:34–42.

To differentiate between patients with and without adverse reactions, the eosinophil count decreased in responders and in patients without adverse reactions. The ephrin-p1, a gene involved in lymphocyte depletion, was found to be upregulated in 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, 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 episodic event.
Immunoglobulin and lymphocyte decrease concurrent with adverse reactions induced by methotrexate for RA

SHIGEKO INOKUMA, HAJIME KONO, HISANORI NAKAYAMA and JUNKO YAMAZAKI

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