of patients with a flare over the median period of follow-up (27 months), 7% per year.

All the patients who had a flare were female (100%), reflecting the cohort generally [48/50 (96%) of those without were also female]. They were slightly younger with a median age of 50.0 yr (range 39–58 yr) compared with 58.5 yr (range 30–84 yr) in those without a flare (P = 0.018). Although the median disease duration (at 31 December 2001) in those with and without a flare was similar [4.0 yr (range 1–15 yr) and 4.5 yr (range 0–31 yr)], the median period of follow-up within the clinic was longer for the flare group [38 months (range 11–58 months) compared with 25 months (range 1–60 months); P = 0.017] (i.e. the detection of flares may be dependent on the duration of follow-up). There was no difference in the frequencies of anti-Ro/La antibody (89% compared with 72%) or rheumatoid factor (RF) positivity (78% compared with 72%), whereas the flare group were slightly more likely to be antinuclear antibody (ANA) positive [8/9 (89%)] compared with those without [26/50 (52%); P = 0.039]. The proportion of patients in this cohort with fibromyalgia was under 5% [4].

Table 1 summarizes the clinical features of the flares. These were predominantly musculoskeletal and consisted of: increased fatigue/malaise, 7/12 (58%); polyarthralgia, 7/12 (58%); polyarthritis, 7/12 (58%); myalgia, 2/12 (17%); alopecia, 1/12 (8%); tenosynovitis, 1/12 (8%) and mononarthritis, 1/12 (8%). In addition, two patients reported worsening Raynaud’s phenomenon [2/12 (17%)] and one worsening livedo reticularis [1/12 (8%)]. In two patients with known osteoarthritis, the features of the flare could not obviously be accounted for by this nor an exacerbation of fibromyalgia.

No clear pattern of changes were observed for the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), immunoglobulin (Ig) G, IgA and IgM levels, or complement C3 or C4 levels in accord with previous studies [5]. Data on anti-Ro and anti-La antibody titres were available in five patients and, similarly, no clear pattern was seen.

Eight flares settled following intramuscular depotmedrone injections. In six patients, hydroxychloroquine therapy was initiated and one patient was started on oral prednisolone. Non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed for two patients. All flares settled within 9 months.

The overall frequency of flares in our cohort at 3–7% per year is much less than that in SLE (62% per year [2]) and the frequency of flares involving the general or musculoskeletal systems also appears substantially lower than in SLE [2].

We did not attempt to assess the severity of the flares in relation to the need for therapy but subjectively they appeared modest in severity and settled over weeks to months with modest therapy. In particular, we did not see any exacerbations involving internal organ systems such as pulmonary or haematological features, although these have been well described in other cohorts [6]. Although the numbers were too small for statistical analysis, two out of three flares that were not treated lasted for over 6 months (Table 1), compared with one out of nine for which treatment was given.

This descriptive study is limited by its retrospective nature and lack of data from comparison groups. It does, however, provide preliminary data to guide the design of standardized activity and damage measures based on the BILAG and SLICC measures used in SLE [7, 8]. These should enable us to characterize the systemic features of PSS and their variation over time in more detail in a prospective study.

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Coombs test was positive and binding of IgG to the red blood cell surface was observed using anti-human globulin monospecific antibodies. Bone marrow aspirate and biopsy demonstrated normal representation of myeloid and megakaryocyte precursors, and high erythroidlastic hyperplasia due to peripheral haemolysis. A nephrotic syndrome with hypoproteinaemia (49 g/l), hypoalbuminaemia (23 g/l) and a high level of urinary albumin (14 g/24 h). Cytobacteriological urinary tests were normal and no Bence-Jones protein was detected. Serum electrophoresis yielded no monoclonal gammapathy, and serum immunoglobulins were diminished for IgG (3.1 g/l, 6.9< normal range <14.0), whereas IgM and IgA were within the normal range. The following blood tests were within the normal range or negative: creatinine clearance, urea and electrolytes, glucose, cholesterol, triglycerides, thyroid function, liver function, creatine kinase, coagulation screening, vitamin B12, red cell folate, cyroglobulins, complement fractions C3/C4/CH50, antinuclear antibodies, anti-DNA and anti-SSA, anti-SSB, anti-RNP, anti-Sm anti-neutrophil cytoplasmic antibodies, peripheral lymphocyte immunophenotyping, serological tests for parvovirus B19, hepatitis B and C, human cytomegalovirus, HIV and Epstein–Barr virus, prostatic specific antigen and carcino-embryonic antigen. Moreover, a search for a hereditary haemolytic anaemia was negative (G6PD, pyruvate kinase, haemoglobin electrophoresis). Chest X-ray, body scan and digestive endoscopies were normal. Renal histology performed 2 weeks after admission showed stage I membranous glomerulonephritis.

Methylprednisolone, first at conventional doses (2 mg/kg/day) for 2 weeks, then at high doses (5 mg/kg/day) for 1 week, was administered, and proved to be ineffective on the haemolytic process and nephrotic syndrome. Moreover, a glucocorticoid-induced diabetes was noted.

Several articles about successful treatment with anti-CD20 monoclonal antibody (rituximab) had been published for corticosteroid-dependent autoimmune haemolytic anaemia (AIHA) [1, 2] and idiopathic membranous nephropathy (IMN) [3, 4], thus we reasoned that selective destruction of B cells producing antibodies might be more effective than other immunosuppressive drugs in our case. Moreover, rituximab therapy has been used for treatment of several autoimmune diseases such autoimmune thrombocytopenia, systemic lupus erythematosus, rheumatoid arthritis, cold agglutinin disease, mixed cryoglobulinaemia, neuropathies associated with autoantibodies, myasthenia gravis, Wegener’s granulomatosis and dermatomyositis [5]. Rituximab is well tolerated and has a toxicity profile limited to relatively rare allergic reactions. The infusional protocol for rituximab administration as treatment for autoimmune disorders is not yet consensual. In a study by Zaja et al. [2], patients with autoimmune haemolytic anaemia previously refractory to conventional treatments were successfully treated with weekly infusions of rituximab, 375 mg/m², for 4 weeks. To treat idiopathic membranous nephropathy, Remuzzi et al. [4] gave the patients infusions of rituximab (375 mg/m²) every 4 weeks, for 5 months. Because in our case the aim of rituximab administration was to treat both autoimmune haemolytic anaemia and idiopathic membranous nephropathy, we chose to give rituximab infusions intravenously at a dose of 375 mg/m² as a 4-h infusion, once weekly for a total of four doses then once monthly for a total of five doses. Methylprednisolone was slowly tapered and discontinued. The drug was well tolerated and the patient did not present any adverse reactions or side-effects. Shortly after the first rituximab infusion, the patient showed a rise in haemoglobin level (haemoglobin around 9 g/dl) and in serum total protein level, and a decrease in lactate dehydrogenase level and proteinuria (<1 g/24 h) (Table 1). Bilirubin and haptoglobin levels also normalized. Six months after rituximab therapy the patient had made a complete recovery, and did not need any hypoglycaemic treatment.

We concluded idiopathic AIHA and IMN as there was no evidence for malignancy, infection, vasculitis, systemic autoimmune disorders or other underlying disease. As both conditions improved in a similar way, we assumed that both may have a common immunological basis. An association of AIHA with IMN has not to our knowledge been previously published. Rare cases of membranous glomerulonephritis associated with idiopathic thrombocytopenic purpura, or crescentic glomerulonephritis with positive anti-neutrophil cytoplasmic autoantibody specific for myeloperoxidase associated with autoimmune haemolytic anaemia and thrombocytopenic purpura [6, 7] have, however, been reported.

In view of studies describing effects of rituximab in patients with immune-mediated diseases, and the major side-effects (Cushing’s syndrome, glucocorticoid-induced diabetes, leucopenia, cancer, renal toxicity and opportunistic infections) associated with the use of steroids and/or other aspecific immunosuppressive drugs, rituximab could be a valuable treatment for concomitant autoimmune disorders.

The authors have declared no conflicts of interest.

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Table 1. Follow-up of major laboratory data

<table>
<thead>
<tr>
<th></th>
<th>On admission</th>
<th>After corticosteroid</th>
<th>After 4 weeks of rituximab</th>
<th>After 6 months of rituximab</th>
<th>1 yr after admission</th>
</tr>
</thead>
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<tr>
<td>Haemoglobin (g/dl)</td>
<td>5.6</td>
<td>6</td>
<td>11</td>
<td>12.8</td>
<td>13.1</td>
</tr>
<tr>
<td>Lactate dehydrogenase (&lt;600 U/l)</td>
<td>2345</td>
<td>2011</td>
<td>827</td>
<td>505</td>
<td>540</td>
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<tr>
<td>Haptoglobin (0.55–2.55 g/l)</td>
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<td>&lt;0.07</td>
<td>0.40</td>
<td>0.65</td>
<td>0.70</td>
</tr>
<tr>
<td>Proteinuria (g/24 h)</td>
<td>14</td>
<td>11</td>
<td>4</td>
<td>0.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Rheumatology Vol. 44 No. 3 © British Society for Rheumatology 2005; all rights reserved.
SIR, Two female patients treated with etanercept for extended oligoarticular juvenile idiopathic arthritis (JIA) are presented.

The first case was a 12-yr-old girl who was diagnosed at the age of 15 months with oligoarticular JIA with positive ANA. She progressed to extended oligoarticular disease, treated over the years with NSAIDs, salazopyrin, oral methotrexate, prednisolone, intra-articular steroid injections, physiotherapy and finally etanercept. At the age of 8 yr she developed bilateral anterior uveitis, more severe in her right eye, which was treated with topical as well as sub-Tenon’s steroids and oral methotrexate. At the age of 11 she was started on etanercept because of further deterioration in her joint disease. The effect on the joints was excellent, with significant improvement in her daily activities. Two and a half months after commencing etanercept the patient noted deterioration in her vision, with a reduction of visual acuity from 6/12 to 6/60 in the right eye (in which a cataract had developed). Ultrasonography revealed inflammatory cells in the vitreous with a swollen optic disc. Visual evoked potentials (VEP) were reduced in that eye, with prolonged latency. Optic neuritis of the right eye was diagnosed and etanercept was discontinued. She received three intravenous pulses of 1 g methylprednisolone at weekly intervals. At follow-up examination 3 months later vision had improved to 6/24. Follow-up VEP testing revealed improved responses, but latency in the affected eye was still longer than in the other eye. Ultrasound showed a normal appearance of the optic nerve and clearing of the vitreous cells. The child is scheduled for cataract surgery, which will probably improve her vision further.

The second case was a young girl who was diagnosed with ANA-positive oligoarticular JIA at the age of 3 yr. Almost from the onset of her joint disease she also suffered from chronic anterior uveitis of the right eye, which eventually became phthisic. Her joint disease was initially oligoarticular, and then progressed to severe extended polyarthritis. Her treatment regimen included NSAIDs, salazopyrin, systemic and intra-articular corticosteroids and oral methotrexate. At the age of 17, suffering from severe growth retardation, delayed puberty and persistently active joint disease, she started etanercept with striking improvement in her joints, general well-being and growth. The acute-phase proteins returned to normal and ANA became negative for the first time. Eight months after commencement of etanercept, she noted deterioration of vision in her only seeing eye. Fundoscopy revealed optic neuritis. Treatment with etanercept was stopped; she received three pulses of 1 g of intravenous methylprednisolone daily for three consecutive days, followed by oral prednisolone, cyclosporin and topical steroids. Follow-up examination revealed resolution of the optic neuritis and improvement of the visual acuity.

In both cases presented there is an association between etanercept treatment and the appearance of optic neuritis. Initially, only injection site reactions were reported with etanercept [1], but with more widespread use there were reports of other side-effects, such as severe infections as well as eye complications [2, 3]. A recent overview of the drug listed a wide range of side-effects that have been reported in the postmarketing phase of etanercept. These reports include CNS demyelinating disorders, such as multiple sclerosis, transverse myelitis and optic neuritis [4, 5].

The two patients described in this paper developed optic neuritis coinciding with etanercept treatment, which improved upon its discontinuation. In view of this observation and previous reports, there is a high probability that the optic neuritis in these patients was a side-effect of etanercept. Both patients are similar in other aspects of their disease, which started at a young age with oligoarticular JIA and positive ANA and had a persistent, extended oligoarticular course despite aggressive treatment. Both also suffered from severe uveitis, necessitating local and systemic steroids as well as methotrexate. In both patients treatment with etanercept resulted in a striking improvement of their joint disease and general well-being. There is a possibility that children with this type of JIA, and severe eye involvement, are at higher risk of suffering from optic neuritis as a result of etanercept treatment.

In conclusion, patients with JIA, especially those with extended oligoarthritis treated with etanercept, should be closely monitored by an ophthalmologist. Finally, ongoing surveillance for possible side-effects is very important in view of the possibility that there is a subpopulation of JIA patients who are at higher risk of optic neuritis associated with etanercept treatment.

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