Psoriatic spondyloarthritis (PSA) can occasionally be complicated by AA amyloid, and renal amyloidosis should be suspected in patients with PSA who have unexplained proteinuria. The diagnosis of amyloidosis can be made either histologically or by radiolabelled serum amyloid P component (SAP) scintigraphy. Prognosis is determined by the extent of organ involvement and associated impairment of function, and by the degree of response of the underlying disease to anti-inflammatory therapy. A review of the literature identified less than a dozen cases of AA amyloidosis complicating PSA, and the outcome in most cases was poor. We report here the favourable clinical course of a middle-aged Caucasian male patient with severe PSA who developed renal AA amyloidosis, in whom treatment with oral chlorambucil led to stabilization of the amyloid deposits and resolution of the associated nephrotic syndrome. We review the diagnosis and treatment of AA amyloidosis, including the management of patients with underlying inflammatory spondyloarthropathies, and propose the possible role of a therapeutic trial of anti-tumour necrosis factor α in patients with amyloid complicating inflammatory rheumatic diseases.

**KEY WORDS:** Psoriatic spondyloarthritis, AA amyloidosis, Chlorambucil, Anti-TNF.
the full blood count and erythrocyte sedimentation rate were normal. Testing for rheumatoid factor was negative and X-rays of both knees were normal. Non-steroidal anti-inflammatory drugs and an exercise programme were commenced, providing relief until age 43 yr, when his peripheral and axial disease became much more active. He was treated with prednisolone 10 mg daily and sulphasalazine, but failed to respond and his C-reactive protein remained persistently greater than 100 mg\textsuperscript{u}l. He subsequently proved to be refractory to treatment with sodium aurothiomalate (Myocrisin), penicillamine, azathioprine, methotrexate and cyclosporin. By age 48 yr he had fused sacroiliac joints, very restricted spinal mobility and destructive changes in several peripheral joints, and had developed dependent oedema. He was found to have proteinuria 9.87 g per 24 h and proceeded to renal biopsy, which demonstrated amyloidosis. The deposits were confirmed immunohistochemically to be AA type (Fig. 1), and radiolabelled serum amyloid P component (SAP) scintigraphy showed extensive amyloid deposits in the spleen, kidneys and liver. Following counselling on the uncertain risks and benefits, he commenced oral chlorambucil therapy, starting on 2 mg daily and increasing by 2 mg increments every 6–8 weeks to a maximum dose of 8 mg daily. Inflammatory disease activity was monitored by monthly estimation of SAA, and the dose of chlorambucil was tapered after there had been complete serological remission of the spondyloarthropathy for 12 months. The therapy was briefly interrupted due to mild leucopenia and an episode of localized herpes zoster. His inflammatory disease has remained inactive for 1 yr following complete cessation of chlorambucil.

### Table 1. Classification of amyloidosis

<table>
<thead>
<tr>
<th>Type</th>
<th>Fibril precursor protein</th>
<th>Clinical syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>Serum amyloid A protein</td>
<td>Reactive systemic amyloidosis associated with acquired or hereditary chronic inflammatory diseases. Formerly known as secondary amyloidosis.</td>
</tr>
<tr>
<td>AL</td>
<td>Monoclonal immunoglobulin light chains</td>
<td>Systemic amyloidosis associated with myeloma, monoclonal gammopathy, occult B cell dyscrasia. Formerly known as primary amyloidosis.</td>
</tr>
<tr>
<td>ATTR</td>
<td>Normal plasma transthyretin</td>
<td>Senile systemic amyloidosis with prominent cardiac involvement.</td>
</tr>
<tr>
<td>ATTR</td>
<td>Genetically variant transthyretin, e.g. Met30Val and about 80 other point mutations</td>
<td>Familial amyloid polyneuropathy, usually with systemic amyloidosis. Sometimes prominent amyloid cardiomyopathy or nephropathy.</td>
</tr>
<tr>
<td>Aβ₂M</td>
<td>β₂-Microglobulin</td>
<td>Periarticular and, occasionally, systemic amyloidosis associated with renal failure and long-term dialysis.</td>
</tr>
<tr>
<td>AApoAI</td>
<td>Apolipoprotein AI (genetic variants, including Gly26Arg, Trp50Arg, Leu60Arg, Leu90Pro, Arg173Pro, Leu174Ser, Leu178His and several deletion mutations)</td>
<td>Autosomal dominant systemic amyloidosis. Predominantly non-neuropathic with prominent visceral involvement.</td>
</tr>
<tr>
<td>AFib</td>
<td>Fibrinogen α chain (genetic variants, including Glu526Val, Arg554Leu, and frameshift mutations at codons 522 and 524)</td>
<td>Autosomal dominant systemic amyloidosis. Non-neuropathic with prominent visceral involvement.</td>
</tr>
<tr>
<td>ALys</td>
<td>Lysozyme (genetic variants, including Asp67His, Ile56Thr and Trp64Arg)</td>
<td>Autosomal dominant systemic amyloidosis. Non-neuropathic with prominent visceral involvement.</td>
</tr>
<tr>
<td>ACys</td>
<td>Cystatin C (genetic variant Leu68Gln)</td>
<td>Hereditary cerebral haemorrhage with cerebral and systemic amyloidosis.</td>
</tr>
<tr>
<td>AIAPP</td>
<td>Islet amyloid polypeptide</td>
<td>Amyloid in islets of Langerhans in type II diabetes mellitus and insulinoma.</td>
</tr>
</tbody>
</table>

Amyloid composed of peptide hormones, prion protein and unknown proteins not included.
Discussion

This is the first detailed report of the response of a patient with an HLA-B27-associated psoriatic spondyloarthropathy to chlorambucil therapy. AA amyloidosis develops during the course of rheumatoid arthritis in up to 20% of patients in certain populations, and probably in 1–5% of cases generally by the time of death [3]. AA amyloid deposits can be distributed widely without causing clinical symptoms, but may nevertheless contribute to morbidity and mortality. The presenting clinical feature in more than 90% of patients is non-selective proteinuria due to glomerular amyloid deposition, and nephrotic syndrome may develop before progression to end-stage renal failure. Haematuria, isolated tubular defects, nephrogenic diabetes insipidus and diffuse renal calcification occur rarely. Although the kidneys may be enlarged, it is usually normal or even (in advanced cases) reduced. Acute and often irreversible renal failure, even in the presence of well-preserved renal function, may be precipitated by hypotension and/or salt and water depletion following surgery, excessive use of diuretics or intercurrent infection. In practice, renal vein thrombosis occurs rarely, and the risk probably does not justify the use of prophylactic anticoagulants. The second most common presentation is with organ enlargement, such as hepatosplenomegaly or occasionally thyroid goitre, with or without overt renal abnormality, but in every case vascular amyloid deposits, at least, are always widespread at the time of presentation. Involvement of the heart rarely causes functional impairment or echocardiographic abnormalities. Gastrointestinal dysfunction is common in advanced disease, and presents most often with bleeding and diarrhoea.

AA amyloidosis may cause clinically evident disease within as little as 1 yr of developing a chronic inflammatory disorder, and the incidence increases with the duration of the underlying condition. The typical duration of chronic inflammatory disease prior to diagnosis of amyloid is about 10 yr, but in about 5% of cases the underlying disorder is covert, for example in patients with cytokine-secreting Castleman’s disease tumours. The prognosis is closely related to the degree of renal dysfunction and the effectiveness of treatment for the underlying inflammatory condition. In the presence of persistent, uncontrolled inflammation, 50% of patients with AA amyloid die within 10 yr of the amyloid being diagnosed, but if the acute-phase response can be kept suppressed proteinuria can resolve, renal function may be retained or improve, and the long-term prognosis is excellent [4]. The availability of chronic haemodialysis and transplantation prevents early death from uraemia per se, but amyloid deposition in extrarenal tissues is responsible for a less favourable prognosis than in other causes of end-stage renal failure. The diagnosis of amyloidosis is traditionally confirmed histologically [5]. The pathognomonic tinctorial property of amyloidotic tissue is apple green/red birefringence when stained with Congo red dye and viewed under intense cross-polarized light, and immunohistochemical staining of amyloid-containing tissue sections is the most accessible method for characterizing the amyloid fibril protein type. However, histology cannot provide information about the overall whole-body load or distribution of amyloid deposits, nor does it permit monitoring of the natural history of amyloidosis or its response to treatment.

### Table 2. Data from a single patient to illustrate acute-phase protein, haemoglobin, urinary protein leak, renal function and amyloid load during treatment with chlorambucil

<table>
<thead>
<tr>
<th>Date</th>
<th>10/12/96</th>
<th>1/10/98</th>
<th>2/12/99</th>
<th>23/11/00</th>
<th>25/01/01</th>
<th>13/10/01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria (g/24 h)</td>
<td>9.72</td>
<td>10.5</td>
<td>5.93</td>
<td>2.55</td>
<td>1.35</td>
<td>0.63</td>
</tr>
<tr>
<td>Albumin (g/day)</td>
<td>20</td>
<td>20</td>
<td>25</td>
<td>31</td>
<td>39</td>
<td>37</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>11.7</td>
<td>15.8</td>
<td>17.6</td>
<td>16.9</td>
<td>17.2</td>
<td>18</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>164</td>
<td>18</td>
<td>6</td>
<td>6</td>
<td>4.6</td>
<td>5</td>
</tr>
<tr>
<td>SAA (mg/l)</td>
<td>190</td>
<td>11</td>
<td>14.7</td>
<td>3.3</td>
<td>6.2</td>
<td>74</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>68</td>
<td>79</td>
<td>82</td>
<td>75</td>
<td>68</td>
<td>74</td>
</tr>
<tr>
<td>Chlorambucil dose (mg)</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Amyloid load</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
treatment. Radiolabelled human SAP is a specific, non-invasive, quantitative \textit{in vivo} tracer for amyloid deposits, and serial studies have shown that the deposits are far from inert but are actually turned over quite rapidly in many patients [4, 6, 7].

The apparent rarity of AA amyloidosis in psoriatic spondyloarthropathy [8] is probably due to the relatively modest acute-phase response that is usually stimulated by this particular disease. However, ‘acute-phase responsiveness’ varies widely among patients whose inflammatory disease activity appears to be similar clinically. AA amyloid fibrils are derived from circulating SAA, and AA amyloidosis occurs in patients who have sustained elevation of their plasma SAA concentration, as part of the acute-phase response to a wide range of diseases (Table 3) [9]. SAA is an apolipoprotein of high-density lipoprotein particles and is the polymorphic product of a set of genes located on the short arm of chromosome 11. It is highly conserved in evolution and is a major acute-phase reactant. Most of the SAA in plasma is produced by hepatocytes, in which its synthesis is under transcriptional regulation by cytokines, especially interleukin (IL)-1, IL-6 and tumour necrosis factor. After secretion, SAA rapidly associates with high-density lipoproteins, from which it displaces apolipoprotein A-I. The circulating concentration can rise from normal levels of up to 3 mg/l to over 1500 mg/l within 24–48 h of an acute stimulus, and with ongoing chronic inflammation can remain persistently high. Although certain isoforms of SAA may be more inherently amyloidogenic than others, the only known prerequisite for the development of AA amyloidosis is a substantially elevated serum SAA concentration. Most patients with AA amyloidosis among the 250 cases evaluated at the National Amyloidosis Centre have had serum SAA concentrations greater than 100 mg/l when their underlying inflammatory diseases have been active.

Once AA amyloidosis has developed, its natural history is generally progressive, leading to organ failure and death within 5–10 yr. Treatment should be focused on attempting to reduce the circulating SAA concentration to healthy baseline levels of less than 10 mg/l [4]. Anti-inflammatory therapy that achieves this prevents further accumulation of amyloid, facilitates regression of existing deposits in many cases, and may promote the functional recovery of amyloidic organs when they are not irreparably damaged. Most patients with AA amyloidosis whose plasma SAA concentration is maintained at less than 10 mg/l have an excellent long-term prognosis [4].

Although the rationale and objectives of treatment of AA amyloidosis are now clear, the ability to suppress the underlying inflammatory disease adequately is frequently difficult in practice. Most patients who develop AA amyloidosis are, by definition, those whose inflammatory disease activity has been controlled insufficiently by conventional therapies, or are those with diseases for which effective treatment is not available. Chlorambucil was first prescribed to patients with AA amyloidosis over 30 yr ago, for refractory juvenile rheumatoid arthritis. The prognosis of these children has improved dramatically following this approach [10], 80% of those treated with chlorambucil remaining alive 10 yr after diagnosis of amyloid compared with 23.5% of patients who are not treated with this agent. More than half of adult patients with AA amyloidosis complicating RA also respond extremely well to chlorambucil treatment [4]. The protocol for treatment with oral chlorambucil used in our centre comprises a starting dose of 2 mg daily, increasing by 2 mg increments every 6–8 weeks, up to a dose of 6–8 mg daily, until the plasma SAA concentration has fallen substantially or until leucopenia or thrombocytopenia occurs. A response may take up to 6 months, failing which the drug should be discontinued. Among responders, it is reasonable to begin tapering the dose after remission has been maintained for 1 yr. Chlorambucil is remarkably well tolerated on a symptomatic basis, cheap to prescribe, and simple to monitor with monthly full blood counts, but side-effects include myelosuppression, which is much more frequent in older patients, sterility in all males, premature ovarian failure, and, in the longer term, development of myelodysplasia or leukaemia in some cases. Potential recipients of chlorambucil need to be counselled appropriately and informed that chlorambucil is not licensed for this indication in the UK. Sperm banking should be offered. Fewer treatments are known to suppress inflammatory disease activity in the spondyloarthropathies than in rheumatoid arthritis, and, indeed, a therapeutic trial of disease-modifying anti-rheumatic drugs is frequently not even performed in many patients with predominantly spinal disease. The clinical and serological response to chlorambucil in our patient was rapid and sustained, despite his disease having proved refractory to numerous other disease-modifying anti-rheumatic drugs. The

\begin{table}[h]
\centering
\caption{Conditions associated with AA amyloidosis}
\begin{tabular}{l}
\hline
Chronic inflammatory disorders \\
Rheumatoid arthritis \\
Juvenile chronic arthritis \\
Ankylosing spondylitis \\
Familial Mediterranean fever \\
Psoriasis and psoriatic arthropathy \\
Reiter’s syndrome \\
Adult Still’s disease \\
Behçet’s syndrome \\
Crohn’s disease \\
Chronic microbial infections \\
Leprosy \\
Tuberculosis \\
Bronchiectasis \\
Decubitus ulcers \\
Chronic pyelonephritis in paraplegics \\
Osteomyelitis \\
Whipple’s disease \\
Neoplastic disorders \\
Castleman’s disease tumours \\
Hodgkin’s disease \\
Renal carcinoma \\
Carcinoma of gut, lung, urogenital tract \\
\hline
\end{tabular}
\end{table}
potential risks of this therapy were rapidly countered by resolution of his nephrotic syndrome and cessation of amyloid deposition. Although chlorambucil has also proved to be effective in suppressing the inflammatory disease activity in some patients with AA amyloidosis complicating Crohn’s disease, there is no evidence that it has any direct beneficial effect on either the production of SAA or on the amyloid deposits themselves. For example, in our own practice chlorambucil has not been efficacious in patients with AA amyloidosis complicating Castleman’s disease and the Muckle–Wells syndrome.

Treatment with biological agents that neutralize the proinflammatory effects of tumour necrosis factor α (TNF-α) have proven to be highly effective in a substantial proportion of patients with rheumatoid arthritis and juvenile idiopathic arthritis. These agents are lately also emerging as efficacious in patients with spondyloarthropathies [11–14]. The relative freedom from toxicity of anti-TNF-α drugs, their rapid mode of action and the frequency with which they can abolish the acute-phase plasma protein response provides a compelling argument for their application to patients with AA amyloidosis complicating these various inflammatory disorders, and our preliminary experience in this setting has been very favourable. Indeed, the acute-phase response resolves rapidly in some patients following neutralization of TNF-α even when their clinical symptoms fail to improve. It is possible that other biological drugs currently under development, for example agents that neutralize the effects of IL-1 and IL-6, might also reduce SAA production and AA amyloid deposition. Novel treatments that may have a direct effect on the amyloid deposits themselves have lately entered clinical trials. These include low molecular weight polysulphonated compounds that inhibit the association of glycosaminoglycans with amyloid fibrils, and a drug that depletes serum amyloid P component from the amyloid deposits [15].

In conclusion, we have demonstrated the therapeutic efficacy of oral chlorambucil in a patient with AA amyloidosis complicating psoriatic spondyloarthropathy. Treatment strategies in patients with AA amyloidosis should generally be guided by frequent measurement of serum SAA concentration, with the aim of lowering SAA to healthy values. Although chlorambucil therapy achieves this objective in a substantial proportion of patients with inflammatory rheumatic diseases, its potential for producing serious adverse effects restricts its suitability to patients whose disease cannot be suppressed by other agents. The efficacy and rapidity with which anti-TNF-α can suppress the acute-phase response in some patients with rheumatic disease supports consideration of a therapeutic trial of infliximab or etanercept in this group of patients before resorting to chlorambucil.

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References