Serum amyloid P component scintigraphy for diagnosis and monitoring amyloidosis

Philip N. Hawkins

Serum amyloid P component is a normal plasma protein and a universal non-fibrillar constituent of amyloid deposits. Radiolabelled serum amyloid P component scintigraphy is a non-invasive and quantitative method for imaging amyloid deposits *in vivo*, which produces diagnostic images in most patients with systemic amyloidosis, and can be used repeatedly to monitor the course of the disease. The scintigraphy technique and biopsy histology are complementary, providing a detailed microscopic analysis and a quantitative whole body survey respectively. Clinically useful observations provided by the imaging method include different organ distributions of amyloid in different types of the disease, demonstration of amyloid in anatomic sites not available for biopsy, and evidence for rapid progression and sometimes regression of amyloid deposits with different rates in different organs. Labelled serum amyloid P component studies thus make a unique contribution to the diagnosis and management of individual patients with systemic amyloidosis, and to systematic studies of existing and novel therapies. The technique is available routinely for all known or suspected cases of amyloidosis in the NHS National Amyloidosis Centre at the Royal Free Hospital, but it has not been developed commercially.

Curr Opin Nephrol Hypertens 11:649–655.

Department of Medicine, Royal Free and University College Medical School, London, UK

Correspondence to Philip N. Hawkins PhD, FRCP, National Amyloidosis Centre, Royal Free and University College Medical School, Royal Free Hospital, Rowland Hill Street, London NW3 2PF, UK
Tel: +44 20 7433 2815; fax: +44 20 7433 2817; e-mail: p.n.hawkins@rfc.ucl.ac.uk

Current Opinion in Nephrology and Hypertension 2002, 11:649–655

Abbreviation

SAP serum amyloid P component

1062-4821

Introduction

Systemic amyloidosis is the main diagnosis in 2.5% of native renal biopsies [1], and is the cause of death in more than one in 1500 people in the UK. Most forms of amyloidosis are progressive and fatal but better understanding of their pathogenesis has led to rational and often successful treatment strategies. Until recently amyloidosis was exclusively a histological diagnosis, and green birefringence of deposits stained with Congo red and viewed in polarized light remains the histological gold standard; immunohistochemical staining of amyloid-containing tissue is used to aid identification of the amyloid fibril type. However, biopsies provide small samples and therefore can never provide information on the extent, localization, progression or regression of amyloid deposits generally. Radiolabelled serum amyloid P component (SAP) was developed as a specific nuclear medicine tracer for amyloid in order to address these shortcomings [2–4]. SAP is a normal plasma protein which binds specifically by a calcium dependent interaction to a ligand that is present on all types of amyloid fibril [5], but not on amyloid precursor proteins. Quantitative scintigraphic imaging using labelled SAP has yielded new information on the natural history of many different forms of amyloid and their response to treatment [6], and is a core investigation in patients with amyloidosis attending the NHS National Amyloidosis Centre. This review will discuss the background, basis, applications and clinical utility of radiolabelled SAP studies.

Pathogenesis and types of amyloidosis

Amyloid formation involves substantial refolding of the native structures of the various amyloid precursor proteins to generate structures that are rich in β-sheet, and which autoaggregate in a highly ordered manner to form the tissue damaging fibrils [7,8]. All amyloid fibrils share a similar ultrastructure, and associate *in vivo* with a restricted repertoire of glycosaminoglycans and with SAP, both of which contribute to the pathogenesis or stability of the deposits. Monoclonal immunoglobulin light chain, or AL (primary), amyloidosis in association with subtle monoclonal gammopathies is the most common and serious type of systemic amyloidosis, and is the cause of death in about one in 1500 people. AA (secondary) amyloid, derived from the acute phase reactant serum amyloid A protein, has a lifetime incidence of 1–5% among patients with chronic inflammatory disorders. It has lately been shown that hereditary systemic amyloidosis is much more common

DOI: 10.1097/01.mnh.0000040052.33359.6f

than previously recognized, and in one study of 350 patients thought to have acquired AL type, an alternative diagnosis of hereditary amyloid was demonstrated in 10% of cases [9]. β_2-Microglobulin amyloid deposition in the bones, joints, and periarticular structures eventually affects most patients who are on long-term dialysis for endstage renal failure.

Principles and problems of histological diagnosis of amyloid

Non-target organ biopsies, for example of rectum or subcutaneous fat, are not diagnostic in 20–50% of patients with systemic amyloidosis in routine practice [10]. Direct biopsy of a clinically affected tissue, such as renal biopsy, is usually diagnostic, but carries a risk of haemorrhage in 1–2% of cases and, rarely, severe organ damage. Various dyes have been used to stain amyloid, but Congo red staining, and its resultant green birefringence when viewed with high intensity cross-polarized light, is the pathognomonic histochemical test for amyloidosis [11]. The stain is unstable and must be freshly prepared every 2 months or less. Thick sections (5–10 μm) are required to optimize birefringence, and appropriate control tissues are critical. AA and β_2-microglobulin amyloid deposits can usually be classified immunohistochemically, but in AL amyloid the deposits typically stain with antisera to κ or λ in less than half of cases. Specificity of immunostaining requires absorption of positive antisera with the respective pure antigens, which is often omitted. The unavoidable problem of sampling means that biopsies may be misleading, and cannot reveal the extent or distribution of amyloid generally. False-positive and false-negative interpretations have previously been made in up to 5% of biopsies reviewed in our centre.

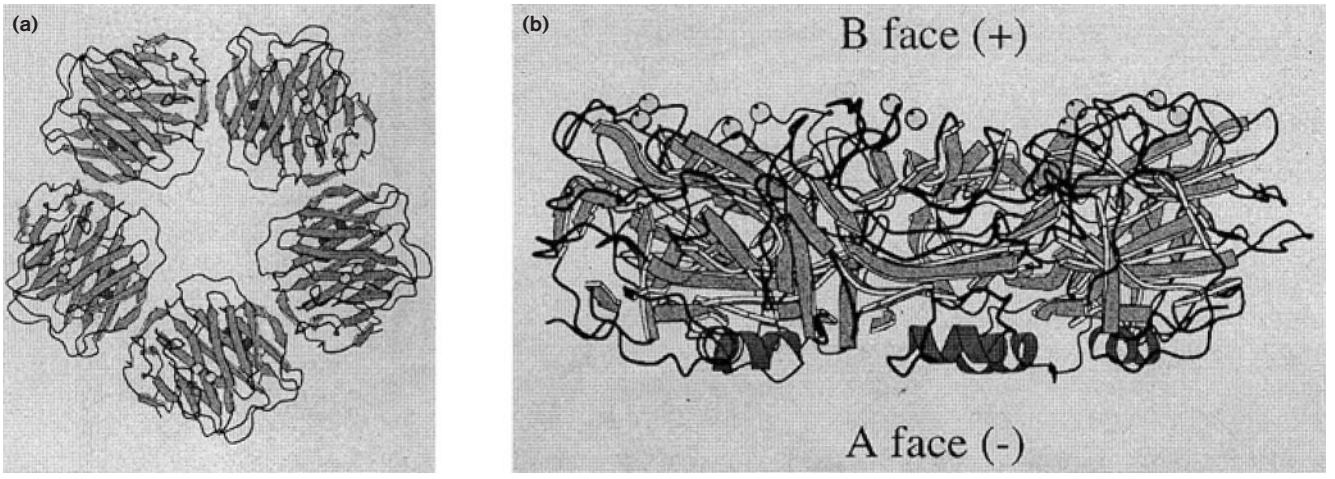
Serum amyloid P component

The normal circulating plasma protein SAP occurs as a non-fibrillar constituent of all amyloid deposits, accounting for up to 15% of their mass. SAP is a member of the pentraxin protein family which includes C-reactive protein. Human SAP is secreted and catabolized [12] only by hepatocytes, and consists of five identical non-covalently associated subunits, each with a molecular mass of 25 kDa, which are non-covalently associated in a pentameric disc-like ring (Fig. 1) [13]. SAP is a calcium-dependent ligand binding protein, which binds to DNA and chromatin [14], and to all known types of amyloid fibrils [5] accounting for its specific accumulation in amyloid deposits. No deficiency or polymorphism of SAP has been described and it has been stably conserved in evolution. Physiological functions of SAP, supported by studies in knockout mice, may include regulation of DNA and chromatin clearance [15] and a contribution to innate host resistance to a range of infections [16]. The SAP molecule is highly resistant to proteolysis and its binding to amyloid fibrils *in vitro* protects them against proteolytic degradation [17]. A contribution of SAP to amyloidogenesis *in vivo* has been confirmed in SAP knockout mice [18].

Serum amyloid P component as a specific tracer in amyloidosis

Radioiodinated SAP binds to all types of amyloid fibril in a specific and reversible manner that enables amyloid deposits to be evaluated quantitatively and repeatedly *in vivo* [3,4]. The tracer does not accumulate in healthy subjects or patients with non-amyloid diseases in whom it is rapidly catabolized and the label excreted [19,20]. In patients with amyloidosis, labelled SAP localizes rapidly and specifically to the amyloid deposits, in proportion to

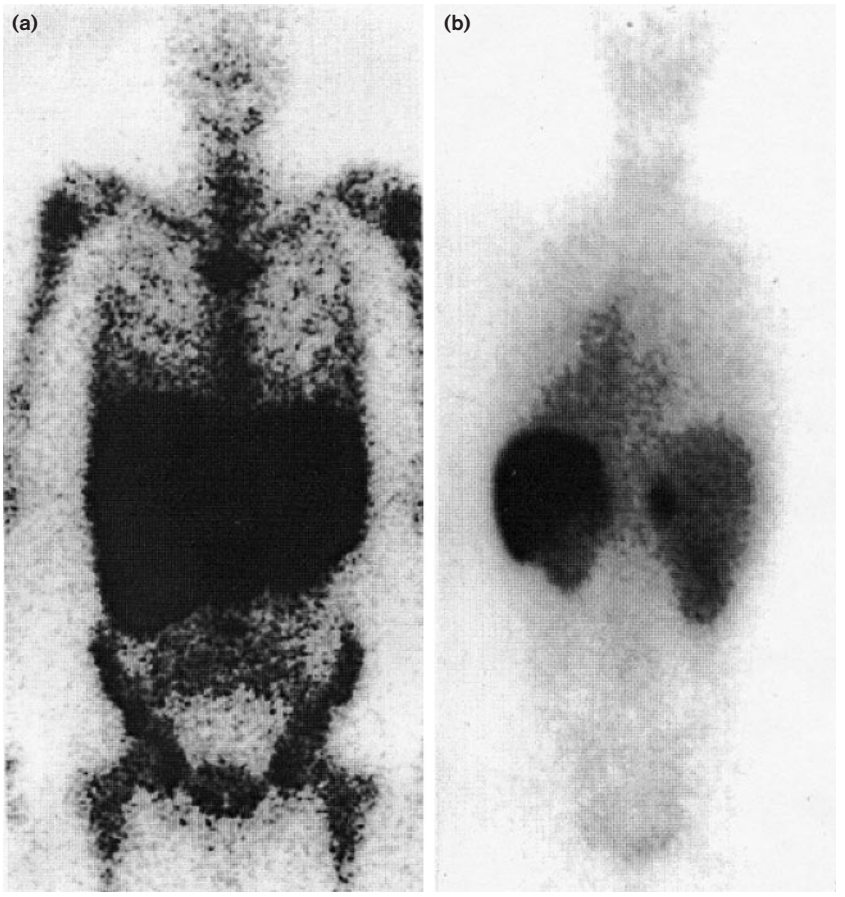
Figure 1. Pentameric disc-like structure of serum amyloid P component



(a) Face-on. (b) Side view. Each of the five subunits has a calcium-dependent binding site, all of which are positioned on the B face of the molecule.

Figure 2. Whole body ^{123}I-serum amyloid P component scintigraphy

(a) A patient with AL amyloidosis.
(b) A patient with AA amyloidosis.
AL amyloid deposits are present in the bones, liver and spleen, and AA amyloid in the spleen, kidneys and adrenal glands. Bone involvement only occurs in AL type.



their quantity, and persists there (Fig. 2). In effect, the localization of labelled SAP to amyloid is a specific dilution phenomenon, due to the constant equilibrium between SAP in the blood and SAP bound to amyloid deposits [19]. When radiolabelled SAP is introduced into the system, it is distributed proportionately between the approximately 100 mg of native SAP present in the plasma and the typically far greater quantity, sometimes exceeding 20 000 mg, which is concentrated within the amyloid deposits. This dynamic equilibrium means that ligands on amyloid fibrils are always available for radiolabelled SAP tracer irrespective of whether amyloid is actually being deposited. Specificity of SAP as a tracer for amyloid has been confirmed in extensive animal studies [2,18], and by studies in many hundreds of patients and disease controls, and healthy volunteers, including comparative histological studies and use of radiolabelled control proteins [6,21].

For clinical purposes, SAP is isolated from the heat-treated plasma of single accredited donors, and is oxidatively iodinated under conditions that preserve its function intact. The medium-energy, short half-life, pure gamma emitter ^{123}I is used for scintigraphic imaging [4], and the long half-life isotope ^{125}I is used for metabolic studies [19]. ^{124}I-SAP has also been used for positron emission tomography [22]. The dose of radioactivity received by patients (less than 4 mSv) during ^{123}I-SAP scintigraphy is well within accepted safety limits, and is comparable with a plain X-ray of the lumbar spine. More than 3000 studies have been performed without adverse effects. In addition to the scintigraphs, uptake of tracer into various organs can be quantified and, together with metabolic data on the plasma clearance and whole body retention of activity, the progression or regression of amyloid can be monitored serially and quantitatively.

Clinical studies with serum amyloid P component scintigraphy

SAP scintigraphy has been used routinely in our centre since 1990 in known or suspected cases of amyloidosis, including 250 patients with AA, more than 600 with AL and over 250 patients with hereditary types. Follow-up studies are usually performed at 6–12 month intervals. Diagnostic scans have been obtained in 99% of patients with clinically significant AA amyloidosis [23], and more than 90% of those with AL type [6]. The diagnostic yield is thus comparable with target organ biopsies, and better

than screening biopsies, for example of the rectum. Scans reliably demonstrate amyloid deposits in the liver, spleen, kidneys, adrenal glands and bones, but do not have sufficient resolution for hollow, diffuse or small structures, such as the gastrointestinal tract, skin and nerves respectively. It is also unsuitable for evaluating amyloid deposits in the heart due to movement, blood-pool content and because of the frequent, intense uptake of tracer into the adjacent spleen [24]. Although SAP scintigraphy can image articular β_2-microglobulin amyloid deposits in patients who have received long-term haemodialysis [25] and continuous ambulatory peritoneal dialysis [26], interpretation must only be made in light of the full clinical picture because synovial effusions in pathological joints represent an extension of the blood-pool background in nuclear medicine procedures. In addition, β_2-microglobulin amyloid deposits in the spine and hips are unlikely to produce a signal above the relatively intense central blood-pool background level [27]. SAP scintigraphy is therefore best restricted to use as a research tool in β_2-microglobulin amyloidosis.

SAP scintigraphy enables a number of important observations regarding amyloid to be made *in vivo*. The differing distributions of amyloid in different forms of the disease may strongly suggest or be pathognomonic of a particular fibril type, for example, substantial bone uptake only ever occurs in AL amyloidosis, in about one third of cases [4]. The limitations of immunohistochemistry in AL amyloid mean that SAP scintigraphy frequently provides the only definitive confirmation of this fibril type. Extensive amyloid deposits are frequently identified in anatomic sites not available for biopsy (adrenals, spleen), or in organs in which they have not been suspected clinically (bones, liver), but which can contribute to morbidity and mortality during treatment. Functional hyposplenism is common in patients with most forms of systemic amyloidosis, whereas hypoadrenalism is rare, but both are easily overlooked clinically. Although amyloidotic liver and spleens can become massively enlarged, they are not palpable in most cases, and splenomegaly is not due to amyloidosis in most patients with inflammatory diseases such as rheumatoid arthritis. SAP scintigraphy can confirm or refute the possibility of amyloid in all patients with hepatomegaly or splenomegaly. Hepatic involvement is frequent in AL amyloidosis, but its presence in AA type, often in association with normal liver function tests, is a late and ominous feature [28]. Scans show that the distribution of amyloid within individual organs can be very non-homogeneous, contributing to false negative biopsies, and there is a surprisingly poor correlation between the quantity of amyloid present in a particular organ and the severity of organ dysfunction. The rate of accumulation may be an important factor in this latter respect. Measurements of whole body amyloid load correlate with prognosis in AA amyloidosis [28], and the risks during high dose chemotherapy in AL amyloidosis [29].

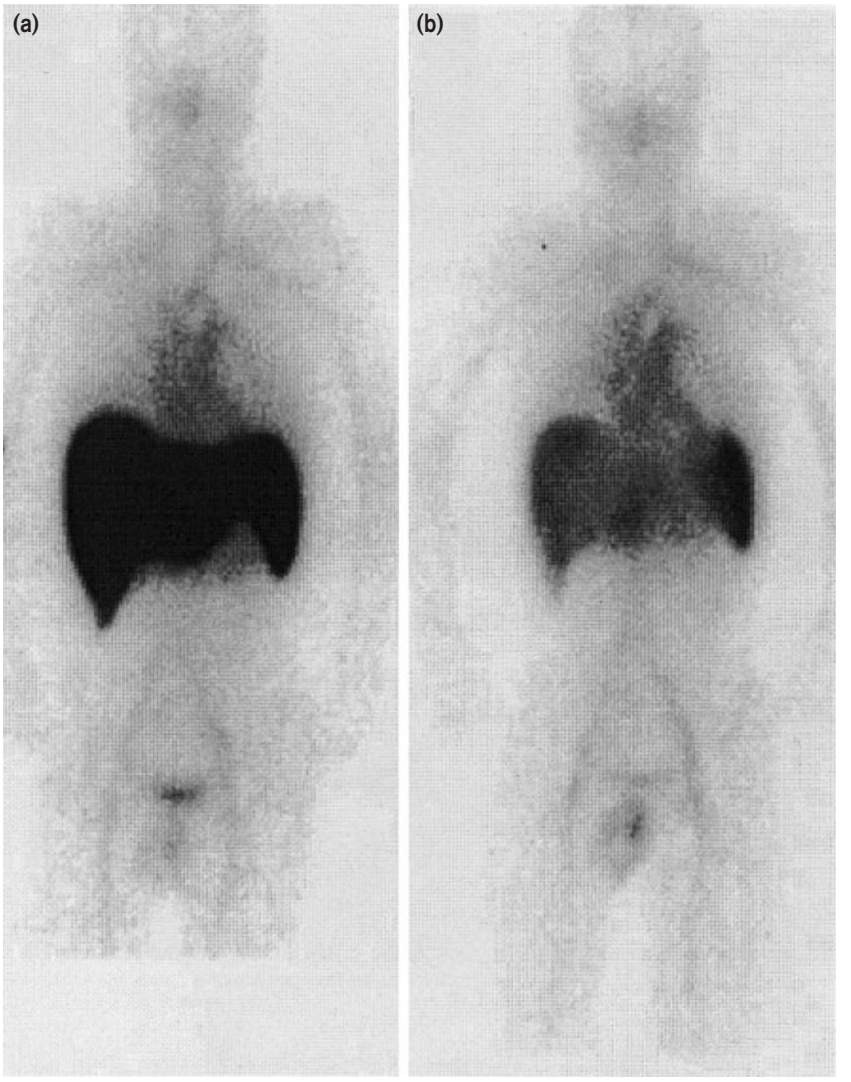
Serial SAP scintigraphy has permitted the natural history of the various acquired and hereditary types of the disease to be studied. The evolution of AA amyloidosis can be explosive and rapid, and AL deposits can be incidental and non-progressive in some patients with multiple myeloma. Scans have systematically demonstrated regression of amyloid deposits in about half of patients in whom it has been possible to reduce or eliminate the supply of fibril precursor (Fig. 3) [6]. This includes patients with AA [23], AL [29], β_2-microglobulin [30] and hereditary transthyretin [31], fibrinogen A alpha chain [32] and apolipoprotein AI [33] types of amyloid. Turnover of amyloid occurs at markedly different rates among different patients with the same type of amyloid, and contributes to the overall course of the disease. Serial SAP scintigraphy and regular measurements of circulating fibril precursor proteins such as serum amyloid A and monoclonal light chains can document the relationship between supply of fibril precursor proteins and the status of amyloid deposits in individual patients, and therefore guide on-going requirements for treatment [23,33]. Studies suggest that slowly progressive amyloid deposition may be tolerated better than rapid accumulation in terms of organ function and survival, and that the rate of amyloid deposition may be an important determinant of outcome generally.

SAP scintigraphy has also been used to evaluate the outcome of renal transplantation in patients with amyloidosis. A study was conducted of 15 patients who had had renal transplants for a median of 73 months [34]. Scans showed no evidence of graft amyloid in all patients in whom the amyloidogenic underlying disorder had remitted and in more than half of those in whom it had not, supporting the use of renal transplantation for end stage renal failure in systemic amyloidosis [34].

SAP scintigraphy has a role in patients with localized AL amyloidosis in whom the lack of visceral deposits is helpful in supporting the diagnosis [35]. In one patient with an intracranial mass causing cerebral compression and hemiplegia, which was thought preoperatively to be a tumour, SAP scanning confirmed the presence of amyloid and was considerably more sensitive than computed tomography or magnetic resonance imaging in revealing the extent of residual pathology after craniotomy and resection [36]. The resected tissue consisted of a low grade lymphoma with massive amyloid stroma. Whole body ^{123}I-SAP scans in patients with hereditary gelsolin and cystatin-C amyloid have shown major, but clinically silent, visceral deposits in all cases that have been studied, including patients in whom symptoms have not

Figure 3. Serial ^{123}I-serum amyloid P component scintigraphy in a patient with AA amyloidosis complicating rheumatoid arthritis

Amyloid deposits present in the liver and spleen at diagnosis (a) regressed substantially within 2 years following treatment with oral chlorambucil (b).



yet occurred. The focal intracerebral amyloid deposits in Alzheimer's disease cannot be demonstrated by conventional planar SAP scintigraphy [37].

The technique has a unique role in characterizing genotype–phenotype relationships in hereditary systemic amyloidosis. SAP scintigraphy enables detection of presymptomatic carriers, identification of unaffected family members, assessment of penetrance of causative mutations, and it can document the extent, progression and response to treatment of deposits in the various forms of hereditary amyloid.

Kinetic studies with radiolabelled serum amyloid P component

In health SAP is largely confined to the plasma compartment from which it is cleared with a half-time of about 24 h. The tracer is metabolized exclusively in the liver and associated radioactivity is released rapidly back into the circulation, mainly in the form of iodotyrosine; there is no retention or extravascular accumulation of radioactivity, all of which can be recovered in the urine within 14 days. In amyloidosis labelled SAP is initially cleared from the plasma more rapidly reflecting extravascular localization to the amyloid deposits, where it persists for prolonged periods. These parameters can be measured in plasma turnover studies, by whole body gamma counting and through collection of complete 24 h urine samples. The derived size of the extravascular amyloid compartment has been shown to be of value diagnostically in AL, AA and β_2-microblobulin amyloidosis, and for monitoring therapy [19,20,24,38].

Development of serum amyloid P component scintigraphy and other applications

SAP scintigraphy has been developed in several academic and clinical centres in Europe but the technique has not been developed commercially because the market is perceived to be too small. Another constraint has been the limited availability and expense of ^{123}I. Labelling SAP with ^{99m}Tc, a cheap and widely available metal nuclide, has potential as an alternative, but the radiolabelling technology is challenging [39]. Although ^{99m}Tc-labelled SAP can produce diagnostic scintigraphic images in patients, the specific ligand binding activity of the compound is variably reduced *in vivo*, and a degree of separation of ^{99m}Tc from the SAP occurs in the circulation. Also, Tc-labelled degradation products are cleared incompletely *in vivo*, increasing the non-specific background signal in the liver and kidneys. For these reasons ^{99m}Tc-SAP is less effective than ^{123}I-SAP for diagnosis, and is unsuitable for quantitative monitoring studies. We are developing recombinant human SAP which may be more attractive for commercial development than the present plasma-derived product.

Following our demonstration that SAP contributes to the pathogenesis of amyloidosis and is therefore a valid therapeutic target, in collaboration with F. Hoffmann-La Roche and Co. Ltd. we have developed a potent non-toxic drug that inhibits and reverses binding of SAP to amyloid fibrils *in vivo* [40]. Radiolabelled SAP studies uniquely provided the first indications of this compound's biological effects, and we hope that prolonged administration of this SAP binding inhibitor will lead to the reduction of amyloid deposits in patients.

Conclusion

SAP scintigraphy is a specific quantitative nuclear medicine technique that enables amyloid deposits in solid visceral organs to be imaged serially, and is complementary to biopsy histology. The scans are diagnostic of systemic amyloidosis in most cases, and the pattern of organ involvement may be indicative of the amyloid fibril type. Scintigraphic estimation of whole body amyloid load can provide information on prognosis and risks associated with chemotherapy and organ transplantation. Serial monitoring of the deposits may guide the effects of and need for therapy in individual patients, and contribute to systematic studies of existing and novel treatments.

Acknowledgements

We thank our colleagues for referring patients and supporting our clinical service. This work was supported in part by grants from the Medical Research Council (UK), The Wellcome Trust and by NHS Research and Development Funds.

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