The NHS National Amyloidosis Centre is the only centre in the UK specialising in amyloidosis and is part of University College London Centre for Amyloidosis and Acute Phase Proteins, one of the world’s leading centres for amyloid research. The Centre has “state of the art” clinical and research facilities, and a team of highly qualified clinical, research and support staff.

We pioneered scintigraphic imaging (scanning) of amyloid as a quantitative diagnostic procedure and provide a comprehensive clinical service for patients with all types of acquired and hereditary systemic amyloidosis. The NHS National Amyloidosis Centre is commissioned by the NHS National Specialised Commissioning team and funded by the Department of Health to provide a diagnostic and management advice service for the UK’s national caseload of patients with amyloidosis and related disorders. The clinical service includes:

- Detailed clinical assessment.
- Diagnosis, quantification and monitoring of amyloidosis with whole body SAP scintigraphy.
- Review of diagnostic biopsies and specialised immunohistochemistry to determine amyloid type.
- Characterisation and exclusion of hereditary amyloidosis by DNA testing; genetic counselling.
- Additional imaging studies when appropriate, which may include DPD scanning and cardiac MRI scanning.
- Recommendations for treatment and monitoring response.
- Measurement and monitoring of specialised biochemical (blood) tests for serum free light chains and serum amyloid A protein.
- 3-12 monthly follow-up to assess response and further treatment requirements. Sometimes follow-up assessment can be performed by telephone if patients live far away.
- Providing information and support to amyloidosis patients, their families and health providers.
- Systematic evaluation of existing and new treatments.
- Diagnosis, monitoring and treatment of inherited fever syndromes.
Index

Amyloidosis ........................................................................................................................................... 3
Diagnostic imaging of amyloidosis: The SAP scan ........................................................... 4
Effectiveness of treatment for amyloidosis ........................................................................ 4
Clinical services provided by the National Amyloidosis Centre ......................................... 4
Overseas and non-NHS entitled patients ........................................................................ 5
Future developments, research and clinical trials ........................................................... 5
Amyloidosis: Some general information and specific questions ..................................... 6
Management and treatment of systemic AL amyloidosis .............................................. 10
Management and treatment of hereditary amyloidosis: general information ............ 14
Management and treatment of ATTR amyloidosis (hereditary and wild-type (non-hereditary)) .................................................................................................................. 15
Management and treatment of non-ATTR hereditary amyloidosis ................................... 19
Outlook for patients with hereditary amyloidosis ............................................................ 20
Management and treatment of systemic AA amyloidosis .............................................. 21
ALECT2 amyloidosis ............................................................................................................. 23
**Amyloidosis**

The term amyloidosis describes a group of disorders caused by abnormal folding, aggregation and accumulation of certain proteins in the tissues, in an abnormal form known as amyloid deposits. These deposits are composed of abnormal protein fibres, the so-called amyloid fibrils that accumulate more quickly than they are cleared away, and which progressively interfere with the structure and function of affected organs throughout the body. Normal healthy proteins are cleared away at about the same rate that they are produced, but proteins that have formed amyloid are broken down only very slowly.

About 30 different proteins have been found to form amyloid in man, but only a few are associated with clinically significant disease. Amyloidosis is classified according to the protein that forms the amyloid fibrils and the clinical picture and symptoms can differ greatly between one amyloid type and another. The proteins that cause two types of systemic amyloidosis (i.e. the types that can affect many parts of the body) are produced in the presence of other disorders. Patients with systemic AL amyloidosis (formerly known as primary amyloidosis) have an underlying bone marrow disorder, and patients with systemic AA amyloidosis (formerly known as secondary amyloidosis) have some form of long-standing inflammatory disorder. Some types of systemic amyloidosis have a genetic basis, most of which can be identified by DNA tests. One relatively common type of amyloidosis, known as wild-type ATTR amyloidosis, is not related to an underlying disease, and does not have a genetic basis.

Amyloid deposits can accumulate virtually anywhere in the body or can remain localised to one particular organ or tissue. Symptoms occur as a result of progressive damage to affected organs and tissues, for example the kidneys or heart, and may vary greatly from patient to patient.

Although various specific anti-amyloid drugs are under development, none as yet has been introduced into routine clinical practice. However, available treatments for the conditions that underlie AL and AA amyloidosis, and new gene silencing therapies to prevent formation of hereditary ATTR amyloidosis can stabilise or improve organ function, and may greatly improve the outlook. Contrary to previous beliefs, we have shown that amyloid deposits often gradually diminish when the formation of new amyloid is prevented.

Localised forms of amyloidosis can cause significant disease, for example in the airways, skin, bladder, genitals or eye. In the past, almost all patients with end-stage kidney failure who were treated with dialysis for over 5 years developed so-called dialysis related amyloidosis. In this condition, amyloid deposits in the bones and joints are formed from a protein called β2-microglobulin. This type of amyloidosis has become less common due to modern dialysis procedures which have improved the clearance of β2-microglobulin. Localised amyloid deposits composed of a protein called Aβ occur in the brains of patients with Alzheimer’s disease, but it is not known whether they are the cause of the disease. Fortunately, the brain is almost never directly involved in systemic amyloidosis.

The National Amyloidosis Centre offers a clinical service for patients with all types of amyloidosis other than Alzheimer’s disease, although its research programme does include the latter. There are four main types of systemic amyloidosis – AL, ATTR, AA and non-ATTR hereditary – which are described in more detail below. Systemic AL amyloidosis occurs in a small proportion of patients who have either multiple myeloma (a bone marrow cancer) or, much more commonly, a non-malignant disorder of the bone marrow. Systemic AA amyloidosis occurs in up to 5% of patients with chronic inflammatory diseases, most commonly rheumatoid arthritis. ATTR amyloidosis may be hereditary or non-hereditary. In recent years there have been improvements in the understanding of the non-hereditary type, known as wild-type ATTR amyloidosis, which have led to a significant increase in the frequency with which this condition is diagnosed. Unfortunately,
all types of amyloidosis cause rather non-specific symptoms, and diagnosis is often delayed until many investigations, often culminating in a tissue biopsy, have been performed. Systemic AL amyloidosis is currently the most common type in the UK, accounting for about 55% of the patients we see at the National Amyloidosis Centre. Altogether about 1000 new cases of amyloidosis are diagnosed each year.

Diagnostic imaging of amyloidosis: The SAP scan

In 1987 we devised a completely new diagnostic test for systemic amyloidosis comprising a whole body scanning procedure called SAP scintigraphy. This scan can show the distribution and amount of amyloid within the body’s organs without the need for biopsies. SAP scans take about 45 minutes and are performed 6 to 24 hours after an intravenous injection of a small dose of radioactive tracer. The procedure delivers a very small radiation dose similar to a routine X-ray. The scan is specific and is used routinely as part of our clinical assessment. The procedure is safe and painless and can be repeated every 6 to 12 months to monitor the course of the amyloid deposits and therefore help guide the need for on-going treatment. We have performed over 35,000 scans and have obtained a large amount of information that has greatly improved our understanding of amyloidosis and encouraged a much more vigorous approach to its treatment. In particular, we have shown that amyloid deposits often disperse when the underlying disease is controlled, and this is usually accompanied by an improvement in general health.

Effectiveness of treatment for amyloidosis

Although not so many formal clinical trials have been conducted due to the rarity and diversity of amyloidosis, the principles and objectives of treatment are now clear. Until drugs become available that can specifically disperse amyloid deposits, therapy is aimed at suppressing production of the relevant amyloid forming protein, whilst supporting the function of damaged organs. This involves treating the underlying condition, such as bone marrow abnormality (AL amyloidosis) or rheumatoid arthritis (AA amyloidosis), or otherwise suppressing the production of amyloid forming proteins (e.g. hereditary ATTR amyloidosis) as rapidly and completely as possible. Treatment varies depending on the type of amyloid but this typically requires chemotherapy in AL amyloidosis, gene silencing therapies in hereditary ATTR amyloidosis and anti-inflammatory drugs in AA amyloidosis; a majority of patients do derive significant benefit. Dialysis-related amyloidosis can be reversed following renal transplantation. The prognosis depends very much on the degree by which production of new amyloid can be suppressed and on which organs are affected, and how severely.

Clinical services provided by the National Amyloidosis Centre

We provide a comprehensive diagnostic and consultation service for patients with systemic AL, hereditary and wild-type ATTR, systemic AA, non-TTR hereditary amyloidosis and localised amyloidosis (not including Alzheimer’s disease). Our approach to each patient with amyloidosis is tailored individually to the type of amyloid and to patients’ particular problems. Wherever possible, patients are discussed with the referring physician, after which we re-examine any available tissue biopsies. Clinical evaluation of patients can usually be completed over 1-2 days during which hospital or hotel accommodation can be arranged. Investigations include whole body SAP scanning to establish the distribution and quantity of amyloid throughout the body, blood and urine tests, a detailed echocardiogram (ultrasound scan of the heart), and specific additional tests that might include DPD scanning, cardiac MRI, DNA analysis (on a blood sample), fat biopsy and bone marrow examination under local anaesthetic.
Treatment is usually administered at patients’ local hospitals or at other regional centres in conjunction with advice from and reviews at the National Amyloidosis Centre. A small proportion of cases are managed directly by ourselves and our colleagues at the Royal Free Hospital.

Most patients with amyloidosis need long term surveillance, with six-monthly or annual specialist follow up in the shorter term. Follow up SAP scintigraphy and specialist cardiac MRI are the only means of quantitatively monitoring the amyloid deposits. This information, together with the results of certain other tests, such as the free light chain test in patients with AL amyloidosis, helps determine on-going treatment. A careful balance is required in each patient between administering sufficiently ‘strong’ treatment, and minimising adverse effects. Another important role of our unit is to provide patients and their families with counselling and information that may not be available elsewhere.

**Overseas and non-NHS entitled patients**

The Royal Free Hospital and the National Amyloidosis Centre welcome overseas patients. European Union residents may be entitled to an NHS assessment in the UK under EU reciprocal arrangements for medical care that is not available locally (EU S2 form). Non-NHS entitled patients are welcome but are liable to charges.

**Future developments, research and clinical trials**

Teams throughout the world are carrying out research in order to further the understanding of amyloidosis. This research has already identified many helpful treatments, and will undoubtedly lead to discovery of new ones. We hope that specific anti-amyloid drugs will become available in the near future, but these will need to be tested on consenting patients in clinical trials before they can be used generally.

We are actively involved in developing and studying new drugs and studying novel methods of treating amyloid and improving the available supportive treatments. At any given time it is likely that the NAC will be conducting a variety of studies (clinical trials). If you are eligible to participate in a clinical trial, we will provide information during your consultation for you to be able to make an informed decision about taking part in the trial. Should you decide not to participate, this will have absolutely no impact on your clinical care.

**Summary**

The National Amyloidosis Centre is the only centre in the UK dedicated to the needs of patients with amyloidosis. Treatment is now available for most types of amyloidosis, but accurate diagnosis and ‘aggressive’ intervention are essential. Treatment varies a great deal according to the precise type of amyloid and which organs are involved. Follow-up SAP and cardiac MRI scans to measure the amyloid load in the viscera and heart respectively, and other tests that measure organ function and the response to treatment of the underlying amyloid-causing condition, enable the disease to be monitored optimally. Regular and comprehensive assessments guide each patient’s management and their on-going requirement for treatment, as well as minimising toxic side-effects and providing support and information to patients and their families.
Amyloidosis: Some general information and specific questions

What is amyloidosis?

There are various types of amyloidosis, all caused by aggregation and accumulation of specific proteins in tissues and organs throughout the body. These proteins exist in an abnormal fibre-like form (amyloid fibrils, amyloid deposits) that build up and progressively interfere with the structure and function of affected organs throughout the body. Different proteins are implicated in different types of amyloid, and treatment depends on precise identification of the particular amyloid protein. Amyloidosis is a general name for the disease, and amyloid is the name of the abnormal protein deposits that accumulate in the body.

How is amyloid made?

Most amyloid-forming proteins are present in the blood, with some being made in the bone marrow (AL amyloidosis) and others made in the liver (e.g. in ATTR amyloidosis and in AA amyloidosis). In most situations, the process of amyloid formation occurs when these proteins are either being produced in excessive quantity (e.g. in AA amyloidosis) or in abnormal forms (e.g. in AL amyloidosis and in hereditary amyloidosis, such as familial ATTR types of amyloidosis). In-wild type ATTR amyloidosis, ATTR amyloid deposits are formed in older people from deposition of a normal blood protein, called transthyretin (TTR) produced in normal quantities. The particular proteins that form amyloid in patients are able to adopt an abnormal structure that enables them to aggregate in a very stable manner and become lodged in the tissues. It is not known what triggers the initial formation of amyloid but once the process is underway, amyloid tends to build up more quickly than it can be broken down. As a result amyloidosis is usually a progressive disease unless production of the particular amyloid forming protein can be reduced.

Why are the amyloid-forming proteins produced?

This differs with the type of amyloid. The amyloid-forming protein in AL amyloidosis is known as monoclonal immunoglobulin light chains, or light chains for short; the abnormal light chain protein is produced by an abnormal growth of ‘clonal’ plasma cells in the bone marrow, which do not usually cause symptoms in their own right. Hereditary types of amyloid occur when a gene is inherited from one or other parent that causes a blood protein to be made life-long in a slightly abnormal form. DNA tests are usually very helpful in excluding or corroborating a diagnosis of inherited amyloidosis, although many individuals with potentially amyloid causing genes never actually develop the disease, and among those who do, it can sometimes worsen very slowly. In non-hereditary ATTR amyloidosis, the amyloid forming protein is the genetically normal (‘wild-type’) form of transthyretin (TTR), which is naturally able to be converted into amyloid in the bodies of some older people for reasons that are not clear. The amyloid-forming protein in AA amyloidosis is called serum amyloid A protein (SAA); the concentration of SAA in the blood is greatly elevated in many inflammatory diseases, for example rheumatoid arthritis, and SAA is converted into AA amyloid in about 1-5% of patients who have persistently high levels. In the past, patients with kidney failure often developed dialysis-related amyloidosis as a consequence of accumulation of a blood protein called β2-microglobulin which is normally cleared away by the kidneys. Current dialysis systems have improved the clearance of β2-microglobulin, and this type of amyloidosis has therefore become less common.

What types of amyloidosis are there?

There are actually over thirty types of amyloid in man, many of which are extremely rare or do not cause significant disease. Some types of amyloid cause problems purely or mainly in just one part of the body. Among patients with systemic amyloidosis, i.e. amyloid deposits distributed to some extent throughout the body, AL type is most common, followed by ATTR type (including both
hereditary ATTR amyloidosis and wild-type ATTR amyloidosis); AA amyloidosis has become far less common in recent years due to effective new treatments for many inflammatory conditions. It now accounts for only about 5% of cases seen at the NAC. Non-ATTR hereditary amyloidosis is very rare.

How does amyloid affect the body and cause symptoms?
The build-up of amyloid in various organs gradually interferes with their function. Amyloid commonly affects the kidneys and may cause them to leak healthy blood proteins into the urine (proteinuria or nephrotic syndrome), or to lose their ability to purify the blood effectively (renal failure). Amyloid in the intestine can cause poor appetite, diarrhoea or weight loss. Amyloid in the skin can cause easy bruising. Amyloid in the heart muscle causes it to become unusually stiff, leading to fatigue, shortness of breath and fluid retention. Amyloid in the nerves can cause abnormal sensation and weakness, or interfere with the body’s automatic functions such as bladder, bowel and blood pressure control. Amyloid in and around the wrist joints can cause carpal tunnel syndrome. There is often some amyloid in blood vessel walls which can increase the risk of bleeding or bruising.

What symptoms does amyloidosis cause?
Symptoms are often very non-specific and include tiredness, weight loss, weakness and loss of appetite. More specific symptoms related to particular organs include, for example, swollen ankles (oedema) due to kidney or heart involvement, tingling in the fingers or toes (paraesthesiae) due to nerve involvement, or breathlessness due to amyloid in the heart.

How is amyloidosis diagnosed?
The diagnosis is often made at quite a late stage because the build-up of amyloid protein may not give rise to any symptoms at all for many years, and the signs and symptoms that it does cause are often not specific and vary greatly from patient to patient. No blood or urine test is diagnostic of amyloidosis, but certain specialist blood tests can provide support for (or in some situations effectively exclude) the possible diagnosis. Ultimately the diagnosis is usually made when a tissue biopsy (small tissue sample) is taken, processed and examined under the microscope. Biopsies can be taken from almost any organ, and are performed either because a particular organ is not functioning properly (for example, the kidneys), or because the possibility of amyloidosis has been considered. In the latter situation, a small biopsy may be taken from the fat under the skin in the stomach area (abdominal fat biopsy). These procedures are quick and safe, with the hope that the sample will contain at least some traces of amyloid. Biopsies are usually retained by hospitals in a preserved state for many years; we often find it valuable to re-examine them in our own laboratory and to perform additional specialised tests to try to determine the precise type of amyloid.

What is an amyloid scan (SAP scan)?
In 1987 Professor Mark Pepys invented a new approach to diagnosis and monitoring of amyloidosis which avoids tissue biopsy, and with Professor Philip Hawkins this method was developed for routine clinical use. The whole body scan (known as the SAP scan, SAP scintigraphy or amyloid scan) is diagnostic in most cases of AA and AL amyloidosis, and many hereditary forms. SAP scans can show the location and quantity of amyloid deposits in organs throughout the body. SAP (full name serum amyloid P component) is a normal blood protein that binds to all kinds of amyloid, which we purify from healthy subjects and tag with a trace of radioactive iodine enabling SAP to be imaged throughout the body by a gamma camera scanner. Most patients with systemic amyloidosis have at least some amyloid in sites other than that which may have been biopsied, even when such organs appear to be functioning normally. Unlike biopsies which can show traces of amyloid under the microscope in a small sample, SAP scans provide a whole body overview, and,
uniquely, can monitor changes in the amount of amyloid and response to treatment over months and years. Unfortunately hollow or moving organs such as the gut and heart cannot be assessed reliably by SAP scans, but it remains important to look for amyloid in other organs in patients with suspected or proven gut or heart amyloid. The development of SAP scans dramatically reduced the need for biopsies in our unit and helps us to tailor individual treatment.

**Is the amyloid scan dangerous, how is it performed, and does it have side-effects?**

There is no inherent reason why this test should produce adverse effects, and none have occurred in over 35,000 patient studies. The dose of radioactivity is very small and is comparable with a routine X-ray of the back. To put this into perspective, a patient living in London who has two SAP scans per year may receive less radiation than residents in some parts of south-west England, where background environmental levels of radiation are a little higher. The radiation dose is minimised by administering potassium iodide before the procedure, a natural mineral that reduces absorption of radiation. The SAP protein itself has been purified from healthy blood donors, and has been duly treated and tested to minimise any risk of contamination or infection, etc. Radiolabelled SAP is given by intravenous injection 6-24 hours before images are obtained by a whole body gamma camera scanner. The scanner is an open device on which patients lie fully clothed for about 40 minutes whilst the images are produced. A technician, and if desired a carer, stay in the room whilst the scan is performed. It is not necessary to avoid food, drinks or any medication beforehand.

**What other tests can help diagnose amyloidosis?**

**DPD scans**

For technical reasons SAP scanning does not provide information on amyloid deposits in the heart. Since 2010 we have been using a different radioactive marker, called 99mTc-DPD that does localise to heart amyloid, and DPD scans provide very useful information especially about ATTR amyloid deposits in the heart. The amount of DPD taken up by the heart correlates with the severity of ATTR deposits. ATTR deposits can be detected in the heart by DPD scans at an early stage, when other heart tests appear normal. We therefore perform a DPD scan in many patients with suspected or diagnosed ATTR amyloidosis. We perform these scans in the amyloid clinic, combining 3D image of the radioactivity, so-called Single Positron Emission Computerised Tomography (SPECT), with a routine CT (computerised tomography) scan, enabling us to see both the structure of the heart and the amount and position of the amyloid in it. The DPD tracer is injected into the vein and a scan is performed 5 minutes after the injection and then 3 hours later. For each scan, the patient lies down on the open scanner while a scan consisting of a “whole body sweep” is performed. This scan shows the entire body. The scanning camera is then rotated to provide the SPECT-CT of the heart while the patient remains in the same position on the scanner.

**Cardiac MRI scans**

Cardiac magnetic resonance (CMR) is a method using a magnetic field and radio waves to obtain detailed pictures of the heart, important developments of which have been pioneered at the NAC by Dr Marianna Fontana and her team. It is safe and painless, and does not involve any exposure to radiation. During the scan, contrast material may be injected into the patient’s vein. Patients lie still inside a closed “tunnel” type of scanner for up to one hour. The pictures and data produced by the computer can then be examined by doctors. The information provided by CMR is superior to that provided by echocardiography, with so-called multiparametric CMR able to provide highly diagnostic information as well as uniquely being able to quantify cardiac amyloid deposits. CMR can accurately measure the size of the amyloid deposits within the heart wall, with repeated measurements able to determine the build-up of amyloid deposits and their regression with treatment. CMR has been a massive advance in amyloidosis, and research at NAC has lately confirmed that cardiac amyloid can regress in many treated patients.
What treatments are available?

Even just 30 years ago amyloidosis was still widely considered to be untreatable but there are now treatments for most types of the disease, and these can be very effective. The actual treatment varies for each type of amyloidosis, but the principles and objectives are similar. At present no drug is available that has a direct effect on amyloid deposits, and current treatments are aimed at reducing the amount of the particular amyloid-forming protein in the bloodstream. When on-going amyloid deposition can be slowed or halted, the existing amyloid deposits often gradually regress. One way to think of it is to imagine filling a basin that has only a tiny outlet; filling the basin with water represents production of amyloid, and the outlet represents the body’s limited capacity to remove amyloid. If the tap is left to run, water builds up in the basin, despite some drainage. When the tap is turned down sufficiently, the water can slowly drain away.

No particular diet or lifestyle has been shown to affect amyloidosis, although, curiously, mice with amyloidosis that are given vitamin C supplements seem to remain in better health. If patients wish to pursue this, we recommend a modest supplement of 250 mg daily. Very large doses of vitamin C may be harmful. Dietary, salt or fluid restrictions may be necessary due to heart or kidney problems in some patients.

The other important aspect of treatment is protection and support of the organs affected by amyloid. Organs that contain amyloid, particularly the kidneys, are much more vulnerable to stress, for example, caused by high blood pressure, dehydration, serious infections, general anaesthetics and surgery. Careful attention to these matters is critically important in a patient with amyloidosis, even when things are going well.

An outline of the principles of treatment for different types of amyloid is provided separately below.

Is treatment effective?

For AL amyloidosis, hereditary ATTR amyloidosis and AA amyloidosis, the aim of treatment is to suppress the production of the respective amyloid forming protein in order to inhibit further amyloid deposition. So long as affected organs are not too badly damaged by amyloid, their function can stabilise and even improve. If new amyloid deposition is completely halted, up to 50% of the existing amyloid deposits can disperse each year, although the rate is much slower in some patients and in certain organs. Regression of amyloid is usually associated with improvement in general well-being as well as stabilisation or recovery of organ function. Unfortunately organs that are severely damaged before treatment may continue to deteriorate despite new amyloid deposition having been completely stopped.

Wild-type ATTR amyloidosis usually progresses slowly. Although there are at present no available treatments that suppress production of the amyloid-forming protein, supportive measures can be very effective in managing patients’ symptoms for many years.
Management and treatment of systemic AL amyloidosis

AL amyloidosis used to be called ‘primary’ systemic amyloidosis and is the most common form of amyloidosis. It is never hereditary. Patients with AL amyloidosis have an abnormal line of cells (called plasma or B cells) which are usually in the bone marrow, and which produce the amyloid forming protein. They are all derived from the division of a single original cell which became abnormal and escaped from the usual control mechanisms for cell division. All the daughter cells are identical to the parent cell and each other and thus comprise a so-called ‘clone’ of cells. The AL amyloid forming protein is part of a single identical protein produced by the whole clone and called a monoclonal immunoglobulin. Each monoclonal immunoglobulin is unique for the clone in each individual patient, and consists of two large components, the heavy chains, and two smaller components, the light chains. The light chains are the protein (L) which form amyloid (A) in AL amyloidosis. Abnormal free light chains can be measured in the blood in about 95% of patients with AL amyloidosis.

The underlying bone marrow disorder / monoclonal immunoglobulin producing disorder is known by many different names, including plasma cell disorder, plasma cell dyscrasia, paraprotein disorder and monoclonal gammopathy, and is very subtle in 80% of patients. This kind of subtle plasma cell abnormality is actually not uncommon in the general population, but it only leads to amyloidosis in about 2% of cases; in the absence of amyloidosis, it usually requires no treatment. The structure and properties of the abnormal monoclonal light chain proteins are unique in every single patient with AL amyloidosis, accounting for the very different symptoms that may occur. In about 20% of patients with AL amyloidosis, the growth of abnormal plasma cells is more florid, and can be overtly cancerous - a condition known as myeloma. Myeloma cells gradually replace healthy bone marrow cells, leading to bone pain and infections. Full blown myeloma is a bone marrow cancer that needs chemotherapy treatment in its own right, whether or not the plasma cells are producing an amyloid forming protein. A patient with myeloma may develop or first come to medical attention with AL amyloidosis but it is rare for an AL amyloidosis patient who does not have myeloma at presentation to develop myeloma.

Symptoms

AL amyloidosis develops in about 1 in 1500 people, and the frequency increases with age. Most patients with AL amyloidosis are aged over 45 years, but it occasionally occurs in young adults. The amyloid deposits tend to be laid down in many parts of the body, although usually one or two organs are predominantly affected. AL amyloid can occur almost anywhere in the body except the brain and it can therefore cause a wide variety of symptoms, many which may be quite vague. Significant involvement of the heart, kidneys, liver, digestive system or nerves is not unusual and may cause a variety of serious problems attributable to these organs. Non-specific symptoms such as weight loss, easy bruising and general fatigue are also common.

Investigations

Two days of tests at the National Amyloidosis Centre are typically required. These may include an SAP scan, a cardiac MRI, echocardiogram, ECG, and a series of tests on blood and urine samples. Sometimes a DPD scan of the heart can be helpful, and occasionally bone marrow examination or heart biopsy is required. We do not usually repeat biopsies if they have already been performed, but we like to review the biopsy samples in our own laboratory. In some cases we perform DNA analysis to exclude hereditary amyloidosis, and if necessary we organise additional investigations e.g. to look at nerve or lung function. In a few cases it can still be difficult to prove that amyloidosis is of AL type, and diagnosis then relies on thorough exclusion of ATTR, AA and hereditary types. It is also important to appreciate that the underlying plasma cell disorder can occasionally be so subtle that it cannot be measured, which can make it more difficult to know when a patient has received sufficient chemotherapy. Conversely, the mere demonstration of a plasma cell disorder and/or an abnormal light chain in a patient with amyloidosis does not prove that the amyloid is definitely of AL type.
**Treatment**

Treatment is directed at the underlying bone marrow disorder. In principle, chemotherapy in patients with AL amyloidosis who have low grade plasma cell dyscrasias is similar to those with myeloma. The aim of chemotherapy is to decrease the number of abnormal plasma cells which will proportionately reduce production of the amyloid forming light chain protein. Under these circumstances new amyloid formation will decrease, and existing amyloid deposits may gradually regress. Occasionally however, despite disappearance of the abnormal light chains after chemotherapy, which represent a so-called excellent clonal response, there may only be stabilisation of the amyloid deposits. Unfortunately regression of amyloid is slow and it often takes 6-12 months after the end of chemotherapy for patients to experience a significant improvement in health. Because of the serious nature of AL amyloidosis, it is desirable to suppress the bone marrow disorder as quickly and completely as possible. However, the treatment can be adjusted along the way according to response, adverse effects and personal preferences. The three month point is generally an important landmark to assess the light chain response to most intermediate dose chemotherapy regimens to decide whether to continue the same regimen, stop chemotherapy altogether or change to another regimen.

Chemotherapy for AL amyloidosis can be broadly divided up as follows:

**Intermediate dose:** We recommend combination chemotherapy for first-line treatment of most patients. This involves several drugs given together over 1-4 days, usually for up to 6 courses, 3-4 weeks apart. Commonly used drug combinations include the ‘CVD’ (cyclophosphamide, velcade (bortezomib) and dexamethasone) protocol and the ‘CTD’ (cyclophosphamide, thalidomide and dexamethasone) protocol. Other protocols include ‘MD’ (melphalan (either orally or intravenously) and dexamethasone, ‘VD’ (velcade and dexamethasone) and ‘VMP’ (velcade, melphalan and prednisolone). Other drugs that are sometimes recommended include lenalidomide, pomalidomide and carfilzomib.

**Low dose:** We recommend low dose tablet chemotherapy for fewer than 10% of the patients. This is usually melphalan with prednisolone (steroids). This is normally taken for 5-7 days each month, in cycles that are repeated every 4-6 weeks. This type of chemotherapy may need to be continued for up to 18 months.

**High dose:** About one fifth of newly diagnosed patients with AL amyloidosis may be suitable for consideration of high dose intravenous chemotherapy as first-line treatment. It may also be suitable for some patients with relapsed or refractory disease. This is usually a high dose of intravenous melphalan, requiring ‘stem cell rescue’ - a single treatment lasting about one month. This might be the only treatment required, but it can, if necessary, be augmented by additional intravenous or low dose chemotherapy. This procedure is commonly referred to as autografting or autologous stem cell transplantation; the stem cells are collected from the patient prior to the high dose chemotherapy, and returned to the patient after chemotherapy in order to form a new bone marrow.

In myeloma, with or without amyloidosis, the plasma cells are cancerous, and it is common practice to recommend 3-4 courses of intermediate chemotherapy to reduce the abnormal cells in the bone marrow followed by an autologous stem cell transplant.

Each regimen has its own merits and disadvantages:

**Low dose** is relatively safe, but has a quite slow effect. It is often necessary to continue this type of treatment for 18 months, and it is very successful in only about 20-30% of cases. These tablets can make some patients feel quite unwell and fatigued, and tend to gradually deplete bone marrow reserves, which may exclude subsequent stem cell transplantation. Unfortunately, prolonged use of
this type of treatment can lead to irreversible bone marrow damage in up to 20% of patients in the long term.

**Intermediate dose** acts more rapidly but has more short-term toxicity. Each ‘cycle’ of treatment carries up to 1-2% risk of death due to toxicity (i.e. up to 5-10% for a complete course). If side-effects are severe, patients can step down to low dose treatments, or continue a more gentle form of intermediate dose chemotherapy. Most patients will receive between 4 and 6 monthly cycles of chemotherapy. The treatment may be oral or intravenous. Patients may lose hair and are likely to feel very fatigued during chemotherapy. Blood transfusions may be required and patients have an increased risk of infection during treatment. Patients over the age of 65-70 years more commonly experience serious complications. Depending on the type of drugs used, bone marrow reserve can be preserved so that further treatment, if necessary, is usually possible. Beneficial effects are seen in some patients within 6 months of starting treatment. This type of treatment is successful in around 65% of patients, many of whom require no further treatment for up to 5-10 years after the initial therapy.

**High dose** involves a single very high dose of chemotherapy after which ‘bone marrow stem cells’, previously purified from the patient’s own blood, are given back as a transfusion. The principle of this treatment is that the bone marrow is largely destroyed by the chemotherapy, and then the purified stem cells lodge in the bone marrow space and generate a new and hopefully healthy marrow from scratch. The marrow takes 2 or 3 weeks to regenerate and start producing all of the different types of blood cells. This procedure, often called stem cell transplantation, usually requires a 3-4 week hospital stay, mostly in semi-isolation to prevent infections. It is best suited to younger patients (usually those less than 60 years) and those who do not have serious amyloid disease in several different organs. Advantages are that the whole treatment is completed in just a few weeks and that it can result in improved health more quickly than other types of chemotherapy. About two-thirds of patients benefit substantially from this type of treatment, and some patients are much improved within 3-6 months. The attitudes to transplantation have changed over the years and we can do this far more safely than ever before. The chief drawback is the risk of serious adverse effects and even death in about 5% of those with amyloidosis, but the risk is as low as 2% in certain groups of patients.

Intermediate and high dose chemotherapy are inevitably associated with at least some nausea, poor appetite and tiredness. Temporary hair loss may occur. Vomiting during the chemotherapy can now largely be prevented.

This outline is meant to serve as a guide to the principles of treatment, but every patient with AL amyloidosis differs in many ways. The most suitable treatment regimen for a particular individual depends on many factors including age, quantity of amyloid and which organs are affected. Treatment must therefore be tailored to each specific case. Occasionally, chemotherapy is not recommended. This can be the case in patients with mild or non-progressive amyloidosis, or in a very small proportion of patients who are sadly too ill to benefit from chemotherapy. Ultimately however, the decision to proceed with chemotherapy, and the type given, will be guided by each patient’s wishes.

The ALchemy (AL amyloidosis chemotherapy) study is a large, on-going, “real world” study of chemotherapy in AL amyloidosis, funded by a grant from the charity Myeloma UK. The National Amyloidosis Centre started this study in 2009 in order to address several unanswered questions relating to patients with AL amyloidosis throughout the UK. Prior to ALchemy, patients with severe AL amyloidosis had not been studied and followed up systematically from the time of diagnosis (prospectively studied). Many patients were lost to follow up after their initial visits to the NAC. It was therefore hard to assess accurately exactly which chemotherapy treatments patients around the country were receiving, what side-effects they experienced and how the disease
and treatment impacted on their quality of life. ALchemy aimed to fill these gaps in our knowledge. All patients diagnosed with systemic AL amyloidosis in need of treatment are eligible for enrolment in the ALchemy study if they are able and willing to give informed consent and have had no (or minimal) prior therapy. Patients enrolled in the study are monitored closely by NAC clinical research nurses. The data already collected in this study has shown that intensive, early monitoring is both feasible and leads to better treatment outcomes. As a result, evaluation of response to treatment after just 3 treatment cycles (3 months), monthly blood samples and completion of treatment forms by patients’ local treating physicians and nurses have become part of our current standard practice.

New immunotherapy (antibody-based) drugs are currently in various stages of development, with promising results so far, offering further cause of optimism about the future of AL amyloidosis treatment.

**Does the treatment work?**

AL amyloidosis is usually a very serious condition, which, if left untreated, is progressive and typically fatal within 5 years. Chemotherapy for AL amyloidosis is beneficial in a considerable proportion of cases. Successful treatment inhibits progression of the disease and can result in regression of existing amyloid deposits. Whatever the type of chemotherapy, it is important to appreciate that improvement in amyloid related symptoms is often slow, and may not be apparent for 12-18 months. The success rate varies between treatments but in recent studies has been about 60% on average. In addition to chemotherapy, or in some cases, instead of chemotherapy, there are many other supportive measures that can help to reduce symptoms, maintain general wellbeing and assist the function of affected organs. Overall, approximately 20-30% of patients can expect to derive considerable benefit from low-dose chemotherapy after they have taken it for one year. Recent results from stem cell transplantation found that 88% of patients responded to treatment and 90% survived for 5 years, with many surviving much longer. Response rates to intermediate dose chemotherapy are around 65% overall. In recent studies of patients who had responded to treatment the majority required no further therapy 7 years later or more. The higher overall response figures for stem cell transplantation result from the stringent selection criteria in recent years. Stem cell transplantation is only offered to relatively younger patients in good overall health with early stage disease. These patients are most likely to benefit, while other patients are more likely to be endangered by the procedure. Long term monitoring for recurrence is required in all patients, though further treatment can be successful.
Management and treatment of hereditary amyloidosis: general information

Hereditary amyloidosis is less common than AL amyloidosis. It is due to the inheritance of an abnormal gene (a ‘mutation’) which leads to life-long production of a potentially amyloid forming protein. Most familial forms of amyloid do not cause any symptoms until middle age or later. They are all inherited in an autosomal dominant fashion. This means that if any particular individual has the condition, each one of their children has a one in two chance of inheriting the mutation, and that each of their brothers or sisters also has a 50% of having the abnormal gene. In contrast, individuals who do not have the abnormal gene themselves cannot pass the condition on to their children. Not all individuals who inherit one of these mutations will actually develop clinical problems. Some individuals develop only a small and insignificant amount of amyloid in their body, and others seem to accumulate none at all. This genetic phenomenon is called incomplete penetrance, and explains why some patients with hereditary amyloidosis do not have any family history of similar disease. Penetrance varies markedly among different families, and information about a particular family is very important for estimating the likelihood that a young healthy individual with a mutation will eventually develop the disease.

Genetic testing

We can analyse the genes that are associated with all known forms of hereditary amyloidosis. These DNA studies are usually performed on a simple blood sample that will be coded and tested anonymously. It usually takes about 4 weeks to obtain the full results. Individuals who are presently healthy, but are at-risk of having inherited a potentially amyloid causing mutation, may choose to undergo such DNA tests, but only after counselling with a physician from the National Amyloidosis Centre. Direct access to this service is available in our centre, and telephone enquiries are welcomed.

Different amyloid-causing mutations can cause completely different clinical features. The commoner types of hereditary amyloidosis are described below.
Management and treatment of ATTR amyloidosis (hereditary and wild-type (non-hereditary))

ATTR amyloidosis is a form of systemic amyloidosis caused by amyloid deposits made up of a protein called transthyretin (TTR). ATTR amyloidosis can be either hereditary or acquired (non-hereditary). TTR is always present in the blood, where it transports thyroid hormone and vitamin A (retinol), hence the name: ‘trans-thy-retin’. All the TTR in the blood is produced by the liver. TTR in the brain and the eye is made separately by a structure called the choroid plexus, which is located within the brain and produces the cerebrospinal fluid that bathes the brain and spinal cord.

Types of ATTR amyloidosis

Hereditary ATTR amyloidosis is caused by a mutation in the gene for TTR, inherited from one parent. The disease therefore runs in families, though the timing, development and severity of the disease can vary greatly.

In acquired (non-hereditary) ATTR amyloidosis, the amyloid is formed by the normal, so-called wild-type protein. This disease is not hereditary. It is known as wild-type ATTR (ATTRwt) amyloidosis (formerly called senile systemic amyloidosis (SSA)).

The clinical presentation and effects of ATTR amyloidosis vary widely depending on which organs are mostly affected.

Hereditary ATTR amyloidosis

People with mutations in the TTR gene produce abnormal, amyloidogenic, ‘variant’ TTR throughout their lives. Amyloid deposits start to form and then build up until they cause clinical disease, mainly affecting the nerves and/or heart, and sometimes the kidneys and eyes. Symptoms may appear at any time from early adult life onwards. This condition runs in families.

About 150 different amyloidogenic (amyloid forming) mutations have been recognised in people from all around the world. TTR mutations are relatively common in some parts of the world and extremely rare in others, and different mutations may cause different disease manifestations.

Hereditary ATTR amyloidosis has traditionally been described according to whether disease manifestations mainly affect the nerves (familial amyloid polyneuropathy (FAP)) or the heart (familial amyloid cardiomyopathy (FAC)). However it is now understood that in clinical practice there is significant overlap in disease manifestations not only between patients with different mutations but also among those with the same mutations. Most TTR mutations can cause amyloid deposits in both the nerves and the heart. The International Society of Amyloidosis has therefore recommended the use of the term hereditary ATTR amyloidosis for all patients with TTR gene mutations and ATTR amyloid deposits.

Hereditary ATTR amyloidosis is a very rare disease. The commonest type, associated with the Val30Met mutation, is thought to affect about 10,000 people in the whole world. It has hitherto clearly been by far the most commonly recognised form of hereditary systemic amyloidosis.

The Val122Ile mutation, in which ATTR amyloid deposits mainly affect the heart and often also cause carpal tunnel syndrome, is most common in men of African ancestry over age 60. This condition was only recognised 20 years ago, is apparently not rare in this population and is widely underdiagnosed.
Non-hereditary (wild-type) ATTR amyloidosis

Wild-type ATTR amyloidosis (wtATTR, formerly known as senile systemic amyloidosis) affects elderly people, mostly men. There is no mutation in the TTR gene so the condition is not hereditary (it does not run in families). The normal, wild-type TTR protein forms the amyloid deposits, with the only obvious major clinical effect in the heart although there may also be carpal tunnel syndrome in some people.

It has long been known that wild-type TTR commonly forms microscopic amyloid deposits in elderly people but clinical disease caused by this amyloid was very rarely diagnosed. However, discovery of new imaging techniques, now used extensively at the NAC, has shown that wild-type ATTR amyloidosis is much more common than previously recognised. Until 2014 this disease was called senile systemic amyloidosis, or cardiac TTR amyloidosis. It was decided at the XIV International Symposium on Amyloidosis in 2014 that this condition should be referred to as wild-type transthyretin amyloidosis or wild-type ATTR amyloidosis.

Treatment

Treatment of all types of amyloidosis is currently based on the following principles:

- Reducing the supply of amyloid forming precursor proteins.
- Supporting the function of organs containing amyloid.

When amyloid precursor protein supply is controlled:

- existing amyloid deposits often regress (become smaller).
- new amyloid deposits stop appearing.
- organ function is often preserved and may also recover.

Reducing variant TTR supply

Genetic-based therapies

- Small interfering RNA.
- Antisense oligonucleotides.

These two approaches aim to ‘switch off’ the gene for TTR in the liver cells, so that TTR (both mutant and wild-type) is simply not produced. Recent clinical trials of these drugs in patients with hereditary ATTR amyloidosis and symptomatic neuropathy had very encouraging results, serving as a landmark in the field of amyloidosis treatment.

A drug called patisiran belongs to the small interfering RNA drug class and has been shown to reverse neuropathy in a majority of patients who participated in a phase 3 study called the APOLLO trial. This trial enrolled 225 patients with hereditary ATTR amyloidosis and randomised them to receive either patisiran or placebo (dummy pills) by intravenous injection every three weeks for 18 months. Patients who received patisiran fared significantly better than those who received placebo, in terms of neuropathy symptoms, quality of life, daily activities and disability. According to standardised scores, neuropathy symptoms improved with patisiran. Patisiran was safe and well tolerated.

Another drug called inotersen belongs to the antisense oligonucleotide drug class. The NEUROTTR trial was a phase 3 study which enrolled 172 patients with hereditary ATTR amyloidosis and randomised them to receive either inotersen or placebo for 15 months. Patients who received inotersen did significantly better than those who received placebo, in terms of neuropathy symptoms, quality of life, daily activities and disability. A few patients receiving inotersen experienced drops in platelet counts and abnormal kidney function. Once this was observed, all patients receiving inotersen were monitored with regular blood tests.
Since 2019 patisiran and inotersen have been approved by the regulatory authorities including NICE and NHS England for treating neuropathy caused by hereditary ATTR amyloidosis. So far trials have only assessed the impact of these drugs on nerve damage caused by ATTR amyloidosis. Effects on cardiac ATTR amyloidosis have not been formally assessed and patients with wild-type ATTR amyloidosis were not included in the drug trials.

Tafamidis
Tafamidis was developed as a specific drug for ATTR amyloidosis. It is bound by TTR in the blood. This binding is thought to stabilise the TTR and makes it less amyloidogenic. The pivotal trial of tafamidis included 441 patients, some of whom had wild-type ATTR amyloidosis while others had hereditary ATTR amyloidosis. Patients who received the active drug had better outcomes than those who received placebo, including fewer hospitalisations for heart disease, a 30% reduction in death over a period of 2.5 years, reduced decline in functional capacity and improved quality of life. Tafamidis is approved in Europe for treatment of hereditary ATTR amyloidosis patients with stage 1 symptomatic polyneuropathy to delay neurological impairment and before liver transplantation, but it is not currently available within the NHS. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved tafamidis for cardiomyopathy caused by ATTR amyloidosis although it is not approved in the US for ATTR polyneuropathy. It is currently under evaluation by NICE to establish whether it will be funded by the NHS.

Diflunisal
This belongs to a class of drugs called ‘non-steroidal anti-inflammatory drugs’ (NSAIDs). These drugs are in common use as pain killers, for conditions such as arthritis. Diflunisal is bound by TTR in the blood. This binding is presumed to make the TTR less amyloidogenic. Trials are currently underway to assess the effect of diflunisal on the progression of neuropathy and cardiomyopathy in patients with hereditary ATTR amyloidosis. Results from the first study report were encouraging, but the numbers of patients involved was small and the extent of benefit was modest. The trial involved 130 patients with hereditary ATTR amyloidosis affecting the nerves, 64 of whom received diflunisal for two years while 66 received placebo. The rate of progression of neuropathy was slower in the patients who received diflunisal than in those who did not. Results of trials of diflunisal in cardiac ATTR amyloidosis are not yet available. It is important to note that NSAIDs such as diflunisal may have serious side-effects, which may be especially dangerous in patients who are already unwell with amyloidosis. These side-effects include:

- bleeding from the stomach and gut.
- worsening of kidney function.
- worsening of heart failure.

Diflunisal use for ATTR amyloidosis is an ‘off-label’ indication, and only amyloidosis specialists should prescribe it.

The NAC can now offer patients with ATTR amyloidosis, subject to various eligibility criteria demanded by the pharmaceutical companies, various opportunities for treatment with the new drugs or for participation in clinical trials. For details of ongoing trials at the NAC see www.ucl.ac.uk/amyloidosis/national-amyloidosis-centre/clinical-research-national-amyloidosis-centre.

Liver transplantation
All the TTR in the blood, which forms the amyloid deposits everywhere except in the eye and the blood vessels around the brain, is made in the liver. In the past, liver transplantation was a treatment option for some patients with hereditary ATTR amyloidosis, mainly for younger patients.
with the Val30Met mutation. Since the advent of the new drugs, liver transplantation is generally no longer recommended.

**Heart transplantation**
For hereditary ATTR amyloidosis, combined heart and liver transplant has been performed in a few dozen cases around the world. This operation is only an option for a very small minority of patients, and it carries significant risks.

**Supporting amyloidotic organ function**
In all types of amyloidosis it is important that treatment should support the function of organs containing amyloid. In ATTR amyloidosis this may include:

**Heart disease treatment**
ATTR amyloid deposits in the heart cause the heart to stiffen which can lead to symptoms of heart failure. Patients can benefit from supportive treatment measures for heart failure. However many standard medications used for heart failure are not helpful for patients with cardiac amyloidosis. Careful attention to fluid balance is important. This may include restriction of fluid and salt intake, diuretic drugs and daily recording of the patient’s weight.

**Neuropathy**

**Treatment of peripheral neuropathy symptoms**
Medications that may help to alleviate neuropathic pain include gabapentin, pregabalin and duloxetine. Medical staff can give advice regarding appropriate foot care and footwear. This is important in order to prevent painless ulcers at pressure points and to protect areas of the foot that lack sensation.

**Treatment of autonomic neuropathy symptoms**
If there is orthostatic hypotension (drops in blood pressure and faintness on standing up from sitting or lying positions), elastic stockings may be recommended. Patients may benefit from instruction in how to change position carefully from lying to sitting, sitting to standing and standing to walking. Drug treatment with midodrine may also be helpful to maintain blood pressure and allow higher diuretic doses. Care should be taken to avoid dehydration if there is vomiting and diarrhoea. Intravenous fluids and anti-nausea drugs may be necessary, but it is important to avoid fluid overload if there is heart disease. There are drugs that can help to control diarrhoea and constipation, and others that can help to combat erectile dysfunction.
Management and treatment of non-ATTR hereditary amyloidosis

The other types of hereditary systemic amyloidosis are rare, and by and large do not cause nerve damage. In general, they present with high blood pressure and kidney disease in middle-age. The liver or heart can sometimes be affected.

Hereditary fibrinogen A alpha chain amyloidosis

A number of mutations in the fibrinogen A alpha chain gene are known to cause amyloid. The most common fibrinogen A alpha chain variant, Val526, generally presents with kidney disease after the age of 50, leading to complete kidney failure within a few years. Many individuals with this particular mutation never get clinical disease. When kidney failure develops, kidney transplantation often has good long-term outcome, with many patients surviving for over 15 years. This type of amyloid can recur in kidney transplants within 7-10 years. The amyloid forming protein is produced only in the liver and it is possible to completely halt the disease by liver transplantation. In a small number of patients, combined liver and kidney transplantation may be recommended.

Hereditary apolipoprotein AI amyloidosis

Several mutations in the gene for apolipoprotein AI cause amyloidosis. Patients with this form of hereditary amyloidosis usually present with high blood pressure and kidney disease in middle age. The amyloid often builds up in organs other than the kidneys including the liver and occasionally the nerves. Despite this, kidney failure is usually the most serious consequence of this type of amyloidosis. A number of patients have undergone kidney transplantation with excellent long-term outcome. Liver transplantation may be required in patients with severe amyloid damage to the liver, or sometimes as a means to reduce or halt progress of the disease in other organs (as in FAP and hereditary fibrinogen A alpha chain amyloidosis above). Some patients with this condition have amyloid deposits in the heart and a few have undergone heart transplantation with good outcomes.

Hereditary gelsolin amyloidosis

This type of hereditary systemic amyloidosis is rare, occurs mainly in Finland and is known as Familial Amyloidosis Finnish type (FAF). Until very recently just two mutations in the gelsolin gene were known to cause FAF. We have recently identified a third mutation. This condition causes eye, skin and cranial nerve symptoms. Although there are always amyloid deposits in the kidneys, the kidney function is usually not affected.

Hereditary lyzosyme amyloidosis

This is one of the rarest types of hereditary systemic amyloidosis, and has only been found so far in a few families. Like hereditary apolipoprotein AI amyloidosis, it usually presents with kidney problems but there can be extensive amyloid in other organs, especially the stomach lining. This form of amyloid tends to build up very slowly indeed and patients can remain stable for many years.

Treatment

The principles of treatment for non-ATTR hereditary amyloidosis are the same as for other types of amyloidosis. Whilst there is, as yet, no treatment that blocks amyloid deposition or speeds up its removal, treatment is aimed at supporting the function of failing organs and, in some instances, reducing production of the genetically abnormal amyloid forming protein by liver transplantation. Kidney failure often dominates the clinical picture and a kidney transplant may effectively restore normal health for a long time.
Outlook for patients with hereditary amyloidosis

The outlook for patients with hereditary amyloidosis depends on the protein type, the specific genetic defect and on the particular characteristics of the disease in a given patient, all of which are extremely variable. In general, the prognosis of hereditary amyloidosis is much better than for systemic AL amyloidosis, though there are implications for family members, for whom we can provide genetic counselling and DNA testing.
Management and treatment of systemic AA amyloidosis

AA amyloidosis used to be known as ‘secondary’ or ‘reactive’ systemic amyloidosis. This is because it occurs in patients who have some kind of long-standing inflammatory disorder. Examples include rheumatoid arthritis (adults and children), inflammatory bowel disease, tuberculosis, other chronic infections and familial Mediterranean fever (FMF). The list of inflammatory diseases that have occasionally given rise to AA amyloidosis is enormous and includes some very rare conditions, some of which do not necessarily cause symptoms in their own right. Although AA amyloidosis can never be hereditary as such, the underlying inflammatory diseases that predispose to it do sometimes run in families; a notable example of this is FMF – see separate information sheet below. The nature of the long-standing inflammatory disease is difficult to determine in a small proportion of patients who develop AA amyloidosis, some of whom are not even aware that they have had any such inflammatory disease at all.

Inflammatory diseases are accompanied by changes in the chemistry of the blood. The concentration of one particular blood protein called serum amyloid A protein (SAA) can increase from healthy levels of less than 3 mg per litre to more than 1000 mg per litre in the presence of inflammation, and it can remain elevated for as long as the inflammatory disease remains active. For unknown reasons, in a small proportion of such patients, SAA can at some point begin to be converted into AA amyloid fibrils, and become lodged in various tissues throughout the body. The average duration of inflammatory disease before AA amyloidosis occurs is around 20 years, but it can occur after just a few years in some cases. AA amyloid deposits tend to be greatest in the spleen, which does not usually cause any symptoms, and the kidneys where it most often does cause clinical problems. Damaged kidneys may lead to loss of healthy blood proteins in the urine and severe fluid retention (proteinuria and nephrotic syndrome), and can ultimately lead to complete kidney failure, requiring dialysis. AA amyloid can build up in the liver and gut at a later stage, though rarely in the heart.

Treatment

Once the process of AA amyloid deposition has begun, as long as the underlying inflammatory disease remains active, excessive amounts of SAA continue to be produced and deposited as amyloid in the organs. The aim of treatment in AA amyloidosis is to control the underlying inflammatory disease and thereby reduce the amount of SAA in the blood. The lower the SAA concentration, the slower the rate of new amyloid deposition. If the level is maintained close to normal (i.e. less than 10 mg/l), there is at least a 50% chance that existing amyloid deposits will gradually regress, which maximises the chance of improvement in amyloidotic organ function. Even if the amyloid deposits merely stabilise, kidney function can improve. Persistent elevation of the SAA concentration is associated with a poor outcome in the long term.

Treatment depends on the nature of the underlying inflammatory disorder, as well as individual factors such as treatments already received. We measure levels of SAA in the blood monthly and can therefore determine whether the inflammation is adequately controlled. The SAA level is therefore a vital guide to treatment. Patients with AA amyloidosis who visit the National Amyloidosis Centre are provided with a kit for sending monthly blood samples to us by post. We typically perform the SAP amyloid scan annually to quantify the amyloid deposits. Serial scans will show how effectively a particular patient can clear away their amyloid deposits, and give an indication of the level of inflammation that is ‘safe’ in any particular case. We are pleased to send SAA results directly to patients to encourage their understanding and involvement in their own management.

The commonest inflammatory disease underlying AA amyloidosis is rheumatoid arthritis, for which there are now several new treatments that can be very effective in lowering SAA production. These include ‘biological’ treatments, which are protein drugs given by injection that can suppress the
cycle of inflammation. Examples include anti-TNF drugs such as infliximab, etanercept and adalimumab. The vital aspect of clinical management, whatever treatment is pursued, is to demonstrate that it is effective in suppressing the inflammatory disease in terms of SAA concentration in the blood. Various different treatments may need to be tried before this can be achieved, and occasionally chemotherapy drugs in modest doses can be very effective in suppressing inflammation when more conventional drugs fail.

Some underlying inflammatory diseases have very specific and highly effective treatments, for example the drug colchicine in patients with familial Mediterranean fever, and the biologic drugs canakinumab in patients with Cryopyrin-Associated Periodic Syndrome syndrome (CAPS) and anakinra in patients with some other rare periodic fever syndromes. A few underlying inflammatory diseases can even be treated by surgery, for example Castleman’s disease ‘tumours’.

**Outlook for patients with AA amyloidosis**

Most patients with AA amyloidosis can now be treated with drugs that can slow down, stop or reverse the disease, and the outlook is often good. There are a large number of drugs which can be used to treat the underlying inflammatory diseases, and several new powerful anti-inflammatory treatments have recently been developed. Many of our patients have survived for decades since their AA amyloid was diagnosed. Kidney failure remains a serious problem for some patients, but even in these cases, kidney transplantation can restore excellent health. It is rare for AA amyloid to significantly affect a transplanted kidney, at least in part because the drugs always used to prevent graft rejection are powerfully anti-inflammatory.
ALECT2 amyloidosis

This rare type of systemic amyloidosis was first described in 2008. The amyloid precursor protein is a blood protein called leucocyte chemotactic factor 2 (LECT2). This condition has been diagnosed in people of a variety of ethnic origins – Punjabi, South American, Mexican and North African. This condition is not yet fully understood. Mutations in the LECT2 gene that may lead to ALECT2 amyloidosis have not been identified and LECT2 levels in the blood are normal. Patients with this condition always have kidney problems, but they may also have amyloid deposits in the adrenal glands, the spleen and the liver. The disease usually progresses slowly.