Emerging treatments for amyloidosis

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Amyloidosis results from protein misfolding, and ongoing amyloid deposition can ultimately lead to organ failure and death. Historically, this is a group of diseases with limited treatment options and frequently poor prognosis. However, there are now 'targeted' therapeutics emerging in the form of stabilizers of the precursor protein, inhibitors of fibrillogenesis, fibril disruptors, and blockers of protein translation, transcription, and immunotherapy. We review many of these approaches that are currently being assessed in clinical trials.

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The term amyloidosis encompasses a group of diseases caused by the pathogenic misfolding of specific proteins that differ substantially with respect to organ involvement, management, and prognosis. Recent diagnostic developments have improved disease recognition, and the incidence of systemic amyloidosis is estimated to be at least *c.* 8 per million per year, although likely to be higher.[1] Immunoglobulin light-chain associated (AL) and secondary (amyloid A (AA)) amyloidoses are by far the most prevalent subtypes with renal involvement present in two-thirds and >90% of patients, respectively.[2,3] Renal presentation mainly reflects glomerular deposits with proteinuria, often overt nephrotic syndrome, and varying renal insufficiency.[4,5] However, where tubulointerstitial involvement predominates, particularly in some types of hereditary apolipoprotein A-1 amyloidosis, a gradual decline in renal excretory function, without significant proteinuria, occurs.[6] Untreated, median survival with AL amyloidosis is only 12 months; however, survival after treatment now exceeds 3 years,[7] and it remains critically important that we strive to further ameliorate both the morbidity and mortality burden associated with systemic amyloidosis. This review specifically focuses on the novel therapies that have lately entered the clinical testing arena or that loom on the horizon.

PATHOGENESIS

The amyloidoses are the consequence of protein misfolding and aggregation, subsequent insoluble fibril formation, and accumulation in the extracellular space, ultimately causing organ dysfunction and death.[8] More than 30 different amyloid fibril precursor proteins are known in humans, but all fibril types essentially share a similar ultrastructure.[9] The acquired highly characteristic β-pleated conformation of amyloid fibrils is associated with specific biophysical properties, including the ability to bind Congo red dye in a spatially ordered manner that produces diagnostic green birefringence when viewed under cross-polarized light[10,11] (Figure 1). Under electron microscopy, amyloid deposits appear as randomly arranged, rigid nonbranching fibrils of ~10 nm in diameter and of indeterminate length.[12]

The mechanisms by which amyloid deposits cause tissue damage have not yet been fully elucidated. The presence of large amounts of amyloid material can disrupt tissue architecture and mechanically interfere with the physiologic function of affected organs.[13] Prefibrillar oligomeric species

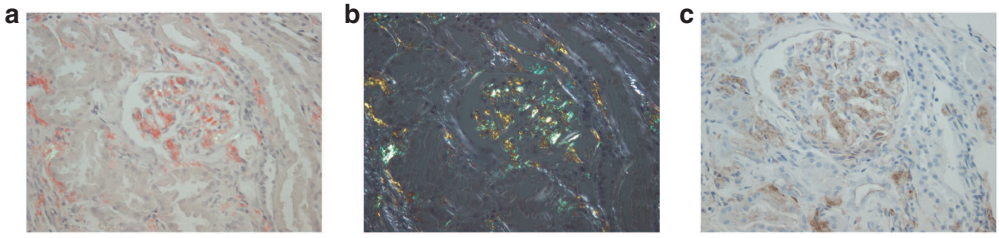

Figure 1 | Sections of a renal biopsy sample were stained with Congo red dye and viewed at ×200 magnification. (**a**) Amorphous deposits of eosinophilic material are visible within the glomerulus. (**b**) Pathognomonic green birefringence of amyloid deposits is visible when viewed under cross-polarized light. (**c**) Immunostaining of the amyloid deposits with anti-κ antibodies was strongly positive (brown stain).

Table 1 | The major amyloid subtypes

Amyloid subtype	Fibril precursor	Treatment	Clinical involvement
AL	Monoclonal-free immunoglobulin light chains	Chemotherapy directed at the underlying plasma cell dyscrasia Potentially novel agents	Renal (50–80%), cardiac, liver, spleen, bones, GI, autonomic and peripheral neuropathy, soft tissue
AA	Serum amyloid A protein	Treatment aimed at the specific underlying inflammatory condition Potentially eprodisate	Renal (>95%), liver, spleen, adrenals, autonomic neuropathy
ATTR: wild-type	Wild-type transthyretin	Mainly supportive with optimization of fluid status	Cardiac, soft tissue
ATTR: hereditary	Variant transthyretin	Cardiac transplantation Potentially novel agents Liver ± cardiac ± renal transplantation Tafamadis Potentially novel agents	Dominant neurological ± cardiac involvement (dependent upon specific TTR variant)
β_2M	β_2-Microglobulin (associated with chronic dialysis)	Mainly supportive, for example, splints, braces, collars. High-flux dialyzer membranes, frequent hemodialysis, β_2M adsorption columns to reduce formation Renal transplantation	Osteoarticular, bone cysts, soft tissue. Late visceral deposition including cardiac, GI, and spleen
AFib (hereditary)	Variant fibrinogen Aα	Renal ± liver transplantation Potentially novel agents	Renal
Apolipoprotein AI (hereditary)	Variant apolipoprotein AI	Renal +/− liver transplantation Potentially novel agents	Renal (mainly medullary), liver, heart, skin, larynx
Apolipoprotein AII (hereditary)	Variant apolipoprotein AII	Renal transplantation Potentially novel agents	Renal
Lysozyme (hereditary)	Variant lysozyme	Renal transplantation Potentially novel agents	Renal, liver, GI, spleen, lymph nodes, lung, thyroid, salivary glands

Abbreviations: AA, amyloid A; AFib, fibrinogen Aα-chain; AL, immunoglobulin light chain amyloidosis; ATTR, amyoidogenic transthyretin; β_2M, β_2-microglobulin; GI, gastrointestinal; TTR, transthyretin.

may also be toxic and contribute to organ dysfunction; cytotoxicity, in these cases, seems to be related to structural flexibility and exposure of hydrophobic residues.[14]

The major types of systemic amyloidosis are described in Table 1. Ideally, immunofluorescence on fresh tissue or, failing that, immunohistochemistry on fixed sections should be used to distinguish between the different types.[12] Sometimes a characteristic distribution of deposits on light microscopy alone can provide diagnostic pointers—for example, isolated heavy glomerular involvement in fibrinogen Aα amyloidosis.[15] Genetic testing is invaluable in diagnosing and excluding the known hereditary forms of amyloidosis, and fibril typing by mass spectrometry is increasingly used when immunostaining fails to provide definitive results.[16]

TRANSTHYRETIN AMYLOIDOSIS (ATTR)

Transthyretin (TTR) is a 55-kDa homotetrameric plasma protein that transports thyroxine and Vitamin A and is associated in its wild-type (wt) form with acquired amyloidosis, termed wild-type TTR (wtTTR) amyloidosis and formerly known as senile systemic amyloidosis.[17,18] More than 100 genetic variants of TTR are associated with autosomal dominant hereditary amyloidosis, and these usually involve the peripheral and autonomic nervous system and/or the heart.[19,20] Notable variants include TTR Val30Met, which is the most common cause of familial amyloid polyneuropathy (FAP), and Val122Ile, which occurs in ∼4% of African Americans and is associated with late-onset familial amyloid cardiomyopathy, although with quite low penetrance.[21–25] Untreated FAP is a progressive disease resulting in death within 7–15 years;[26] although renal amyloid deposits occur, only 34.6% develop chronic kidney disease and 10% progress to end-stage renal failure.[27]

The conversion of circulating TTR protein into amyloid requires dissociation of the normal tetrameric protein into monomers, conformational change, and assembly to form the fibrils.[19,21] The propensity to form amyloid is influenced by specific amino-acid substitutions and environmental factors such as pH and oxidative stress.[28]