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Treatment of Immunoglobulin Light Chain Amyloidosis: Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Statement

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Abstract

Immunoglobulin light chain amyloidosis (AL amyloidosis) has an incidence of approximately 1 case per 100,000 person-years in Western countries. The rarity of the condition not only poses a challenge for making a prompt diagnosis but also makes evidenced decision making about treatment even more challenging. Physicians caring for patients with AL amyloidosis have been borrowing and customizing the therapies used for patients with multiple myeloma with varying degrees of success. One of the biggest failings in the science of the treatment of AL amyloidosis is the paucity of prospective trials, especially phase 3 trials. Herein, we present an extensive review of the literature with an aim of making recommendations in the context of the best evidence and expert opinion.

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Immunoglobulin light chain amyloidosis (AL amyloidosis) and immunoglobulin heavy chain amyloidosis (AH amyloidosis) are typically low-tumor-burden plasma cell disorders characterized by deposition of insoluble fibrils composed of immunoglobulin chains. Most of the literature to date refers to AL amyloidosis because typing of amyloid fibrils on a case-by-case basis was uncommon until the 21st century. To date, there is no evidence for a clear difference in prognosis or presentation between AL and AH amyloidosis, so herein, both types will be referred to as AL amyloidosis.

Without treatment, AL amyloidosis has an inexorable progressive course due to uncontrolled organ damage. Although AL amyloidosis is the most common form of systemic amyloidosis, with an incidence of approximately 1 case per 100,000 person-years in Western countries,[1] there are other forms of systemic amyloidosis (Table 1).[2,3] Typing the amyloid is imperative because treatment strategies depend on the source of precursor protein.[4-6] In the case of systemic AL amyloidosis, the precursor protein is bone marrow plasma cell–derived immunoglobulin light (or rarely heavy) chains, and targeting plasma cells is the mainstay of therapy. In contrast, the next most commonly recognized forms of systemic amyloidosis are due to the precursor protein transthyretin, which is made in the liver. A disease phenotype similar to that of AL amyloidosis can be caused by either wild-type amyloid transthyretin (age related or wt-ATTR) or by mutated ATTR (hereditary or mut-ATTR).

Little is known about why amyloid targets specific tissues in one patient vs another.

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TABLE 1. Classification of the Most Common Amyloidoses

Type of amyloidosis	Precursor protein component	Clinical presentation
AL (previously referred to as primary amyloidosis)[a]	κ or λ immunoglobulin light chain	Systemic or localized, see text
AH	γ, μ, α immunoglobulin heavy chain	Systemic or localized, see text
AA (previously referred to as secondary amyloidosis)	Serum amyloid A protein	Renal presentation most common; associated with chronic inflammatory conditions; typically acquired, but hereditary in cases of familial periodic fever syndromes
ALECT2	Leukocyte chemotactic factor 2	Renal presentation; acquired
ATTR		
Mutated transthyretin[b] (commonly referred to as familial amyloid polyneuropathy)	Mutant TTR	Hereditary; peripheral neuropathy, autonomic neuropathy, vitreous opacities, and cardiomyopathy
Wild-type TTR[b] (age-related or senile amyloidosis)	Normal TTR	Restrictive cardiomyopathy; carpal tunnel syndrome
Aβ2M	β_2-microglobulin	Carpal tunnel syndrome, arthropathy on large joints
Other hereditary amyloidoses		
AFib (also called familial renal amyloidosis)	Fibrinogen α-chain	Renal presentation
ALys	Lysozyme	Renal presentation most common
AApoA-I	A-I Apolipoprotein	Renal presentation most common
AGel	Gelsolin	Cranial neuropathy

[a]AL amyloidosis is the only form of amyloidosis that is secondary to a clonal plasma cell disorder; AL amyloidosis can be associated with multiple myeloma in approximately 10% to 50% of patients.
[b]TTR refers to transthyretin, which is commonly referred to as prealbumin.

Amyloid fibrils found in human tissues are not merely composed of pure amyloid precursor protein. Other proteins are found in the amyloid deposits, most commonly serum amyloid protein, apolipoprotein E, apolipoprotein A1, and apolipoprotein A4.[7]

The most important aspects of treating patients with AL amyloidosis are making a correct diagnosis as early as possible and finding the best chemotherapy and supportive trials for that individual patient. Clearly, clinical trials are the goal. In an environment with an absence of clinical trials, a paucity of randomized clinical trials, and an abundance of difficult and sometimes conflicting data, we present an extensive review of the literature with the aim of making recommendations in the context of the best evidence and expert opinion as we have done in the past for patients with multiple myeloma (MM)[8] and Waldenstrom macroglobulinemia.[9]

DIAGNOSIS OF AL AMYLOIDOSIS

The diagnostic biopsy sample may be from the tissue causing symptoms—eg, heart or kidney—or from a more accessible tissue, such as subcutaneous fat or bone marrow. The sensitivity of a biopsy sample from a symptomatic organ is higher than that from the more accessible tissues, ie, more than 95% for a symptomatic organ, 75% to 80% for fat, and 50% to 65% for bone marrow.[10] Special stains, such as Congo red, thioflavin T, and sulfated alcian blue, are required to recognize amyloidosis. The gold standard for amyloid diagnosis is Congo red avidity with apple-green birefringence under polarized light. Electron microscopy is also helpful