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Definition of Organ Involvement and Treatment Response in Immunoglobulin Light Chain Amyloidosis (AL): A Consensus Opinion From the 10th International Symposium on Amyloid and Amyloidosis

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We undertook this study to develop uniformly accepted criteria for the definition of organ involvement and response for patients on treatment protocols for immunoglobulin light-chain amyloidosis (AL). A consensus panel was convened comprising 13 specialists actively involved in the treatment of patients with amyloidosis. Institutional criteria were submitted from each, and a consensus was developed defining each organ involved and the criteria for response. Specific criteria have been developed with agreed on definitions of organ and hematologic response as a result of discussions at the 10th International Symposium on Amyloid and Amyloidosis held in Tours, France, April 2004. These criteria now form the working definition of involvement and response for the purposes of future data collection and reporting. We report criteria that centers can now use to define organ involvement and uniform response criteria for reporting outcomes in patients with light-chain AL. Am. J. Hematol. 79:319–328, 2005. © 2005 Wiley-Liss, Inc.

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INTRODUCTION

Thirty years ago, the treatment of immunoglobulin light chain amyloidosis (AL) was primarily supportive. Anecdotal reports on the use of dimethyl sulfoxide and colchicine were found to have little value in managing the disorder [1,2]. In that era, specific criteria for recognizing organ involvement and defining response were of little benefit and minimal utility. New therapies directed at the plasma cell [3], the source of the amyloidogenic light chain [4], and specific therapies [5] designed to destabilize the amyloid fibril have been developed [6,7]. Systemic

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chemotherapies, such as high dose requiring stem cell support (i.e., melphalan, 200 mg/m^2), intermediate dose (i.e., melphalan, 100 mg/m^2), and conventional dose (i.e., 20–25 mg/m^2 of melphalan or vincristine, doxorubicin, and dexamethasone therapy), are now being used regularly to effectively treat patients [8–10]. Each institution has its own specific criteria for evaluating organs involved with amyloid and defining a response. Often, the criteria differed from institution to institution, making it difficult to directly compare outcomes. Several centers have reported that outcomes are determined by the number of organs involved with amyloid. Therefore, counting the number of organs becomes more than an academic exercise [11].

The 10th International Symposium on Amyloid and Amyloidosis was held 18–22 April 2004, in Tours, France. In anticipation of this meeting, 13 leaders in the field were invited to submit their institutional criteria, from which the current guidelines were developed. With the adoption of these guidelines, it is hoped that uniform reporting criteria will be used in the diagnosis, assessment of organ involvement, and evaluation of response in AL.

WHAT IS REQUIRED FOR A DIAGNOSIS OF AMYLOIDOSIS?

AL must always be confirmed histologically [12]. A biopsy specimen should stain positively with Congo red and demonstrate apple-green birefringence under polarized light [13]. Although radionuclide imaging studies using technetium-labeled aprotinin [14] or iodinated serum amyloid P (SAP) component scans [15,16] can be used to image deposits, these are not a substitute for histologic characterization of amyloid deposits and are not widely available [17].

DIFFERENTIATING SYSTEMIC FROM LOCALIZED AMYLOIDOSIS

Most instances of localized amyloidosis do not require systemic therapy because the long-term prognosis is excellent with surgical or local therapies [18,19]. Localized AL amyloid results from in-situ production of light chains [20]. In virtually all instances in which the disease presents with urologic symptoms, deposits of amyloid found in the urinary bladder, urethra, and ureter are localized [21]. Amyloid in the conjunctiva [22,23] is a component of a localized process. Amyloid goiter may also be seen in secondary amyloidosis (AA) [24]. Amyloidosis of the tracheobronchial tree and larynx [25], although a potentially serious condition, is not a component of a systemic amyloidosis syndrome. The finding of amyloid deposits in the cardiac atria [26], pleura, and articular cartilage [27,28] may also represent localized amyloid, and additional evidence of visceral involvement is required before systemic amyloidosis is diagnosed. Amyloid deposits are commonly detected within a solitary plasmacytoma [29] or the carpal ligament [30]. These do not constitute evidence of systemic amyloidosis.

HOW IS THE AMYLOIDOSIS CHARACTERIZED AS AL TYPE?

The origin of the amyloid fibril in AL is an immunoglobulin light chain or rarely a fragment of an immunoglobulin heavy chain [31]. Virtually all patients will have a clonal plasma cell dyscrasia demonstrable [32], and the plasma cells themselves are the source of the amyloidogenic light chain. The presence of a monoclonal serum or urine light chain is helpful but not always sufficient to diagnose a systemic amyloidosis disorder as AL type [33]. All patients require immunofixation electrophoresis of serum (sensitivity 71%) and urine (sensitivity 84%) in an attempt to demonstrate the presence of a monoclonal light chain. Repeat immunofixation may be required with undiluted antisera in patients with initially negative results. All patients should have an immunonephelometric immunoglobulin serum-free light chain assay [34]. Quantitation of free light chains is a useful complement to immunofixation, because an abnormal κ:λ ratio is seen in 92% of patients. With all 3 assays, there is a 99% sensitivity.

Caution is required when patients have an intact monoclonal immunoglobulin molecule in the serum without evidence of circulating free light chains in the serum (Bence Jones proteinemia) or in the urine (Bence Jones proteinuria). The presence of a monoclonal gammopathy should not be used as the only evidence of AL, because a small fraction of patients with familial (AF), secondary (AA), and senile systemic amyloidosis (SSA) will have an incidental monoclonal gammopathy [35] and evidence of clonal plasma cell dyscrasia associated with amyloidosis of nonimmunoglobulin origin [36]. Accurate classification may include immunohistochemical staining of tissues with appropriate antisera [37]. AA amyloid is readily detected immunohistochemically and can be excluded with this technique.

Hereditary systemic amyloidosis with renal involvement may result from deposits of apolipoprotein A-I, apolipoprotein A-II, lysozyme [38], and fibrinogen, all of which produce clinical syndromes indistinguishable from AL [39]. Hepatic amyloidosis occurs in apolipoprotein A-I, lysozyme, immunoglobulin light chain, and AA types [40,41]. Cardiac amyloidosis and amyloid neuropathy are associated with scores of mutations of

transthyretin [42], and immunohistochemical staining with commercially available anti-transthyretin antisera [39] is specific [43]. When definitive immunohistochemical typing of amyloid cannot be achieved, specific genetic studies can be performed by polymerase chain reaction to recognize mutations in transthyretin [44,45], fibrinogen, lysozyme [46], and apolipoproteins A-I and A-II. Amyloid has been extracted successfully from fat deposits [47] for direct sequencing of the fibril protein [48]. Mass spectroscopic analysis of the extracted protein has been used successfully as a diagnostic tool [49,50]. The type of amyloid can be confirmed by sequence and mass spectroscopic analysis of protein extracted from formalin-fixed, paraffin-embedded tissues, and fat aspirates [51,52].

In summary, confirming the immunoglobulin light chain nature of amyloidosis requires the demonstration of a clonal plasma cell disorder, with free light chains in the serum or urine. One must consider the occasional possibility of a monoclonal gammopathy incidentally associated with AF or SSA. The application of chemotherapy to a patient with a nonimmunoglobulin form of amyloid is contraindicated [53], would provide no benefit, and could be harmful to the patient [54].

TABLE I. Organ Involvement: Biopsy of Affected Organ or Biopsy at an Alternate Site*

Kidney	24-hr urine protein > 0.5 g/day, predominantly albumin
Heart	Echo: mean wall thickness > 12 mm, no other cardiac cause
Liver	Total liver span > 15 cm in the absence of heart failure or alkaline phosphatase > 1.5 times institutional upper limit of normal
Nerve	Peripheral: clinical; symmetric lower extremity sensorimotor peripheral neuropathy
	Autonomic: gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration
Gastrointestinal tract	Direct biopsy verification with symptoms
Lung	Direct biopsy verification with symptoms
	Interstitial radiographic pattern
Soft tissue	Tongue enlargement, clinical
	Arthropathy
	Claudication, presumed vascular amyloid
	Skin
	Myopathy by biopsy or pseudohypertrophy
	Lymph node (may be localized)
	Carpal tunnel syndrome

*Alternate sites available to confirm the histologic diagnosis of amyloidosis: fine-needle abdominal fat aspirate and/or biopsy of the minor salivary glands, rectum, or gingiva.

DEFINING ORGAN INVOLVEMENT

Kidney

(1) Renal biopsy evidence of amyloid deposits, with clinical or laboratory evidence of organ dysfunction (Table I).
(2) Biopsy proof of amyloid at an alternate site such as subcutaneous fat, bone marrow, rectum or labia minor, or salivary gland biopsy associated with a 24-hr urine protein excretion $\geq$ 0.5 g/day. Cardiac failure alone rarely produces this degree of proteinuria [55]. Other causes of proteinuria such as poorly controlled diabetes mellitus or uncontrolled hypertension should be excluded. The urine protein should be predominantly albumin to avoid confusion with those patients who have myeloma and are excreting large amounts of immunoglobulin light chain but do not have glomerular involvement with amyloid.

Heart

The heart is considered involved if either an endomyocardial biopsy demonstrates amyloidosis in the presence of clinical or laboratory evidence of involvement or echocardiographic evidence of amyloidosis is found in a patient with a positive result of noncardiac biopsy [56]. The presence of low voltage on 12-lead electrocardiography (all limb leads less than 5 mm in height) is a clue to cardiac involvement by amyloid [57]. Echocardiographic features of amyloidosis include a mean left ventricular wall thickness (septum and posterior wall) greater than 12 mm in the absence of hypertension or other potential causes of left ventricular hypertrophy [58]. Right ventricular free wall thickening in the presence of left ventricular thickening and in the absence of pulmonary or systemic hypertension strongly suggests myocardial infiltration. Patients who show right ventricular thickening, diastolic dysfunction, and a normal systolic blood pressure should be considered for endomyocardial biopsy. Reduction in the ejection fraction occurs as a late event.

Doppler echocardiography generally demonstrates evidence of diastolic dysfunction, but mild degrees of diastolic dysfunction are common among patients of age 50 years and older, and this should not be used in isolation to diagnose cardiac amyloidosis. Abnormalities in strain echocardiography [59], elevation of the N terminal Pro brain natriuretic peptide (NT-Pro BNP) [60], and elevation of cardiac troponins [61] are seen in a wide variety of cardiac disorders, and the sensitivity and specificity of these tests compared with echocardiography have not been evaluated sufficiently for these variables to be incorporated as criteria of cardiac involvement. Myocardial amyloid is excluded by normal values of NT-Pro BNP [62]. No patient with cardiac AL was found to have an NT-Pro BNP of < 55 pmol/L [60].

Liver

(1) Hepatic involvement with AL is defined as liver biopsy proof of interstitial deposits of amyloid and evidence of organ dysfunction. The bleeding risk after liver biopsy is 2% [63]. Vascular deposits limited to hepatic venules or portal triad vessels are insufficient to confirm hepatic involvement with amyloid.
(2) Hepatic involvement is implicated when amyloid is diagnosed at another site in a patient with hepatomegaly (total liver span greater than 15 cm by radionuclide scanning or computed tomographic imaging) or the serum alkaline phosphatase value is 1.5 times the upper limit of the institutional normal value. Hepatomegaly can also occur with congestive heart failure without amyloid infiltration of the liver (passive congestion).

Nervous System

Peripheral neuropathy. Amyloidosis predominantly affects small unmyelinated fibers and results in dysesthesias, paresthesias, and progressive sensory loss [64]. The preferential involvement of small fibers renders electromyography and nerve conduction velocities relatively insensitive. Patients can have symptomatic peripheral neuropathy with minimally abnormal or completely normal nerve conduction studies [65]. Therefore, the definition of nerve involvement is primarily a clinical one and can be established by a positive result of sural nerve biopsy or evidence of amyloid involvement at an alternate site with a typical symmetric ascending sensorimotor peripheral neuropathy. The presence of carpal tunnel syndrome alone does not constitute peripheral nerve involvement with AL amyloid.

Autonomic neuropathy. Autonomic dysfunction may range from mild asymptomatic postural hypotension to profound hypotension with bowel and bladder dysfunction. The finding of systemic hypotension (systolic blood pressure $\leq$90 mmHg) does not necessarily represent autonomic dysfunction, because it may occur in patients with low cardiac output [66].

Because many patients with amyloidosis have nephrotic syndrome [67], the resultant hypoalbuminemia may result in plasma volume contraction. As a consequence, orthostatic hypotension should be considered a manifestation of autonomic neuropathy very cautiously because there are many potential causes of orthostatic hypotension in patients with amyloidosis [68]. A decrease in the diastolic blood pressure [69] may or may not be directly related to autonomic failure. Weight loss may not be considered evidence of autonomic (or intestinal) involvement, because this is common in patients [70].

Gastrointestinal Tract

Dysfunction that results from amyloid infiltration of the gastrointestinal tract is often difficult to differentiate from autonomic dysmotility. Biopsy evidence of interstitial involvement via endoscopy or colonoscopy helps differentiate between them [71]. Nearly 80% of patients will demonstrate vascular only amyloid deposits on an endoscopic biopsy. These deposits are asymptomatic and should not be considered evidence of intestinal organ involvement for the purpose of counting the number of organs involved. Patients with symptomatic gastrointestinal tract involvement will have diarrhea, motility disturbances, and weight loss that strongly resemble autonomic failure [72]. Documentation of involvement via direct biopsy is feasible if it is desired to confirm intestinal involvement.

Lungs

Caution is required when diagnosing pulmonary AL because nodular pulmonary amyloidosis and tracheobronchial amyloidosis are both localized manifestations of AL [73]. The only form of pulmonary involvement that usually represents systemic AL is diffuse interstitial pulmonary amyloidosis. Virtually all patients will have biopsy demonstration of interstitial pulmonary deposits via transbronchial lung biopsy or video-assisted thoracoscopic biopsy. Thus, the diagnosis of pulmonary systemic amyloid requires biopsy or evidence of amyloid in another visceral organ with typical radiographic changes of diffuse interstitial lung disease. Computed tomographic scanning is more sensitive than plain radiography in detecting these deposits. Pleural effusions are usually not prominent, and the echocardiogram is frequently normal [74]. Because patients with severe heart failure will develop interstitial pulmonary edema, changes on the chest radiograph may be confused with pulmonary involvement [75]. Pleural effusions may be caused by direct pleural infiltration with amyloid.

Soft Tissue

Soft-tissue involvement encompasses a host of amyloid presentations. It can include enlargement of the tongue [76] with submandibular swelling, recurrent periorbital purpura, amyloid lymphadenopathy, vascular amyloid manifested by claudication of the limbs or jaw, involvement of the muscles manifested by skeletal muscle pseudohypertrophy, painful periarticular amyloid deposition [77], and the shoulder pad sign [77]. Claudication is generally recognized in patients who have direct biopsy evidence of amyloid in other organs and clear jaw or vascular claudication [78]. Tongue, muscle [79], and joint involvement are

recognized by physical examination. Biopsy of the tongue is rarely performed because it produces a significant degree of pain and a small risk of bleeding.

In conclusion, when assessing organ involvement, the seven categories are heart, kidney, liver, nerve, intestine, lung, and soft tissue. Soft-tissue involvement includes skin [80], muscle, and temporal artery (Table I). Direct organ biopsy is not required for diagnosis if there is biopsy proof at an alternate site confirmed with evidence of organ dysfunction, as defined above.

TABLE III. Organ Disease Progression

Heart	Interventricular septal thickness increased by 2 mm compared with baseline An increase in New York Heart Association class by 1 grade with a decreasing ejection fraction of $\geq$10%
Kidney	50% increase (at least 1 g/day) of urine protein to greater than 1 g/day or 25% worsening of serum creatinine or creatinine clearance
Liver	50% increase of alkaline phosphatase above the lowest value
Nerve	Progressive neuropathy by electromyography or nerve conduction velocity

CRITERIA FOR EVALUATION

Functional Organ Response and Progression

In multiple myeloma, the defined end points are predominantly hematologic and include reductions in the monoclonal protein [81] with a confirmatory reduction in tumor mass in the bone marrow [82]. Because the primary manifestation of AL is end organ dysfunction, the goal of therapy is to stabilize or reverse the organ dysfunction. Current therapies attempt to do this by inhibiting the production of the amyloidogenic light chain whose source is the clonal plasma cell in the bone marrow [83]. Therefore, in AL, responses can be hematologic or organ based.

Heart Response and Progression

The primary method of assessment of the heart is the echocardiogram (Tables II and III) [84]. However, interobserver variability is an important issue when rating response or progression from the echocardiogram alone. Patients with cardiac amyloid who have a complete hematologic response and improvement in other organs (for example, decrease in proteinuria or decrease in liver size) frequently have little change in wall thickness. Nevertheless, diuretic requirements often decrease markedly, and exercise tolerance improves. A symptomatic improvement of 2 New York Heart Association classes without increase in diuretic need is suggestive of cardiac improvement, if wall thickness has not increased. Progression of cardiac disease can be defined as an increase of 2 mm or more in wall thickness compared with baseline. The ejection fraction in amyloidosis is usually preserved until late in the disease, and changes in this variable are insensitive for assessing disease progression. However, worsening of congestive heart failure strongly suggests progression of cardiac disease even if wall thickness remains unchanged. Because of the interobserver variability, it is advisable for one interpreting echocardiographer to compare echocardiograms directly rather than relying on written reports. Insufficient data exist on the serial use of cardiac biomarkers (Tropinin, BNP, NT-Pro BNP) to assess response and progression of cardiac AL.

TABLE II. Organ Response

Heart	Mean interventricular septal thickness decreased by 2 mm, 20% improvement in ejection fraction, improvement by 2 New York Heart Association classes without an increase in diuretic use, and no increase in wall thickness
Kidney	50% decrease (at least 0.5 g/day) of 24-hr urine protein (urine protein must be > 0.5 g/day pretreatment) Creatinine and creatinine clearance must not worsen by 25% over baseline
Liver	50% decrease in abnormal alkaline phosphatase value Decrease in liver size radiographically at least 2 cm
Nerve	Improvement in electromyogram nerve conduction velocity (rare)

Kidney Response and Progression

A 50% decrease in 24-hr urine protein excretion (predominantly albumin) in the absence of a 25% increase of the serum creatinine concentration (minimum of 0.5 mg/dL) or a 25% decrease in creatinine or iothalamate clearance constitutes a response (Tables II and III). The reduction in urinary protein loss must also be greater than 0.5 g for the response criteria to be fulfilled. This is to avoid coding a response due to variations in the urinary protein collections. Because 24-hr urine protein measurements can vary substantially within the same patient, some caution is required to avoid coding a random fluctuation as a response. Progression of amyloidosis in the kidney is defined by a 50% increase in the urinary protein excretion. The absolute increase, however, should be greater than 1 g/day to avoid coding progressive disease when an increase represents a random fluctuation (ie, the urinary protein increase from 500 to 800 mg would not constitute progression because the absolute change, 300 mg, is less than 1 g). A 25% worsening of serum creatinine (minimum of 0.5 mg/dL) or creatinine

clearance constitutes evidence of progression independent of urinary protein loss. Patients who do not fulfill the criteria for progressive disease or responsive disease are considered stable.

Liver Response and Progression

A reduction in the size of the liver documented by radiographic or radionuclide imaging is important. The craniocaudal liver scan (computed tomographic or ultrasonographic) is useful (Tables II and III). The span can decrease by greater than 30% 1 year following stem-cell transplantation in responders. A decrease in the alkaline phosphatase value represents the primary measure of hepatic response. In patients who have hepatic involvement, the alkaline phosphatase abnormality should decrease by 50%. In other words, if the institutional normal value is 100 U/L, and the patient's alkaline phosphatase value is 200 U/L, it must decrease below 150 U/L to be considered a hepatic response. Progression is defined as an increase of greater than 50% above the lowest recorded value. If the institutional normal value for alkaline phosphatase is 100 U/L, and the patient's alkaline phosphatase value is 160 U/L, then a value of 240 U/L is required to reflect progressive disease. Right-sided heart failure can produce modest changes in alkaline phosphatase concentration. Recognition of this phenomenon is necessary when interpreting outcomes.

Nervous System Response and Progression

Assessment of response and progression in the nervous system is difficult because of the lack of objective means of measuring response (Tables II and III). The electromyogram is relatively insensitive in detecting improvement in nerve conduction, although frequently it can document progressive disease with involvement of other nerves as well as further slowing of nerve conduction velocity [85]. With current therapy, reversal of amyloid peripheral neuropathy is uncommon and is often difficult to separate from supportive measures used to treat the neuropathy (i.e., gabapentin or amitriptyline). Response in these patients is best evaluated by using the hematologic criteria described below. Techniques used to assess diabetic neuropathy are not in widespread use but have been shown to reproducibly gauge neuropathic changes [86,87].

Soft-Tissue Response and Progression

It is unusual to see a reduction in the size of the tongue with any form of systemic therapy (Tables II and III). Likewise, resolution of claudication symptoms or normalization of skeletal pseudohypertrophy or periarticular soft tissue amyloid is rare. Computed tomography and magnetic resonance imaging have been used to assess soft tissue changes [88,89]. Hematologic response criteria should be used in these situations and physical descriptors used for soft-tissue manifestations of disease.

Pulmonary Response and Progression

Radiographic evidence of improvement in pulmonary interstitial amyloid is rare (Tables II and III). Radiographs are useful, as are computed tomographic studies of the lungs, to demonstrate change. Corticosteroids can have an important impact on gas exchange, and the use of the diffusing capacity of carbon monoxide is not a reliable serial measure of improved lung function because it requires a high level of patient compliance [90] and can be affected by steroids and the patient's cardiac status. Hematologic criteria are preferable in assessing improvement in this amyloid syndrome.

Hematologic (Immunochemical) Response Criteria

The hematologic response criteria for amyloidosis have been modeled after those used for multiple myeloma [91] (Table IV). However, the interpretation is more complex than in multiple myeloma. The incidence of pure light-chain proteinemia is much higher than it is in multiple myeloma. Therefore, accurate quantification of a serum monoclonal light chain has been difficult until recently [92]. Because of excellent

TABLE IV. Hematologic (Immunochemical) Response Criteria

Complete response	Serum and urine negative for a monoclonal protein by immunofixation Free light chain ratio normal Marrow < 5% plasma cells
Partial response	If serum M component > 0.5 g/dL, a 50% reduction If light chain in the urine with a visible peak and >100 mg/day and 50% reduction If free light chain >10 mg/dL (100 mg/L) and 50% reduction
Progression	From CR, any detectable monoclonal protein or abnormal free light chain ratio (light chain must double) From PR or stable response, 50% increase in serum M protein to > 0.5 g/dL or 50% increase in urine M protein to > 200 mg/day; a visible peak must be present Free light chain increase of 50% to >10 mg/dL (100 mg/L)
Stable	No CR, no PR, no progression[a]

[a]CR, complete response; PR, partial response.

reproducibility and ease of use, nephelometric and turbidimetric immunoassays of M components currently are the most common methods for quantifying immunoglobulins. However, when assaying M components, these methods are often inaccurate because the antibodies and calibrators used with the assay are developed using the vast variety of diverse normal immunoglobulins, whereas M components exhibiting limited or incomplete antigenic determinants may react incompletely with the antiserum and behave peculiarly compared with the calibrator. Thus, the concentration of M components is often underestimated or overestimated.

Because of these peculiar immunologic properties, the best way to assess the concentration of an M component is by densitometry. If the M component is migrating in the region of the electrophoretic gel and is increased, whereas the other immunoglobulins are decreased, the concentration of M component can be measured most accurately by densitometry. Second, the high incidence of albuminuria makes accurate quantitation of urinary light chain excretion more complicated than it is in multiple myeloma [93]. Often, the monoclonal protein loss is small and comprises only a small percentage of the total urinary protein loss so that accurate serial quantitation of the urinary monoclonal protein is fraught with technical problems. Third, the percentage of plasma cells in the bone marrow of AL patients averages approximately 5%, and because these are frequently visual estimates, an accurate confirmation of a reduction that is not attributable to sampling or variability between hematopathologists is difficult. The use of the serum free light chain assay has been important for quantification of hematologic responses [94] and has been proposed as a useful tool to define hematologic response [95]. At this time, insufficient data exist to replace urine M protein measures in the response criteria.

Complete Hematologic (Immunochemical) Response: All Required

Disappearance of the monoclonal protein from the serum and concentrated urine specimen detected by immunofixation is part of a hematologic response. The number of plasma cells in the bone marrow must be less than 5%, and the serum free light chain ratio becomes normal, supported by a negative immunofixation result. In patients who do not have renal insufficiency, the absolute value of the involved serum-free light chain must also be normal [96].

Partial hematologic (immunochemical) response. Monoclonal proteins are difficult to quantify accurately below 0.5 g/dL (5 g/L) by serum protein electrophoresis. Because the partial response criteria are predicated on a 50% reduction in the monoclonal protein, patients who do not have a monoclonal protein greater than 0.5 g in the serum cannot be evaluated quantitatively for response unless there is an abnormal free light chain. Fortunately, patients with AL rarely have an M component in a polyclonal background. Among 474 patients with amyloid, the serum electrophoretic pattern showed a localized band or spike in 48% of patients. The median value was 1.4 g/dL, and 72% had a monoclonal component greater than 1 g by cellulose acetate electrophoresis. Agarose gel electrophoresis and capillary zone electrophoresis are more sensitive in detecting smaller amounts of monoclonal protein [97] and are best suited for those with small M proteins.

A partial response is defined by a greater than 50% reduction in the value of the serum monoclonal protein when measurable and a 50% reduction in 24-hr urine monoclonal light chain excretion when measurable. To be measurable, the urine light chain excretion must exceed 100 mg/day and a definable band must be seen on urine protein electrophoresis. A discrete band is uncommon in renal amyloidosis patients, and urine M-protein reductions are easiest to quantify in cardiac or neuropathic amyloidosis. If the serum and urine monoclonal protein do not fulfill the criteria for measurable disease, they are considered evaluable only and can be coded only as present or absent.

Patients without a quantifiable M component are the ones in whom the serum-free light chain measurement is the most valuable [98]. A 50% reduction in the serum free light chain concentration has been demonstrated to have important survival value and is associated with clinically improved organ function [10]. A 50% reduction in the involved serum free light chain is considered evidence of a partial hematologic (immunochemical) response. However, the initial pretreatment serum-free light chain value should be greater than 10 mg/dL (100 mg/L) for it to be considered measurable. Although the normal value for the free light chain is 3–4 mg/dL [99], values that are only slightly above this can decrease into the normal range because of laboratory variation [100]. It is recommended that light chain values below 10 mg/dL (100 mg/L), although abnormal, not be considered a criterion for evaluation of hematologic response. Variations in reagent lots and methods may affect results for patients who are monitored serially and can compromise the test's clinical utility. Caution should be used in interpreting data between laboratories and if antisera lots vary over time or between manufacturers [100].

Minor response criteria. The category of minor response has not been defined for amyloidosis as it has for multiple myeloma.

Progressive Disease

There are two criteria for progressive disease. The first is progression for those patients who achieved a complete hematologic response to therapy. In these individuals, a relapse would be defined by reappearance (immunofixation) of the original monoclonal protein in the serum or urine or an increase in the serum free light chain from the normal range into the abnormal range. For the serum-free light chain, the increase must be at least a doubling from the normal range to be considered progression. An increase from 3 to 4 mg/dL would not be considered progression (owing to laboratory variation) [100]; rather, a doubling to at least 6 mg/dL would be required for progressive disease. Immunofixation is an important adjunct to confirm that the change in the free light chain concentration is related directly to reappearance of the monoclonal protein.

The second criterion is progression after a partial hematologic response to therapy or from stable disease. Hematologic progression is evidenced by a 50% increase in the amount of the monoclonal protein from its lowest measured value. To avoid coding progression owing to laboratory variation, the increase in the serum monoclonal light chain must be greater than 0.5 g/dL (5 g/L) by electrophoresis, and the 50% increase in urinary light chain must be greater than 200 mg/day. In addition, there should be a concomitant increase in the serum free light chain concentration of 50%, and this must increase to a value greater than 10 mg/dL (100 mg/L) for coding progression. The percentage of bone marrow plasma cells is not included in the partial response or progression criteria. The low number of plasma cells in most patients and the difficulty in accurately concluding when a 50% increase or decrease in the percentage of plasma cells has actually occurred make this an inadequate measure of response.

Stable Disease

This is defined for all patients who do not achieve a complete or partial response and do not fulfill the criteria for progressive disease.

CONCLUSION

Defining organ involvement and response criteria for amyloidosis has always been challenging. The mission of the 13 members of the consensus panel was to define criteria that could be used worldwide by physicians who treat patients with this disease and to permit uniform reporting criteria of treatment-related outcomes. It is certain that these criteria will undergo revision at the 11th International Symposium on Amyloidosis. Further incorporation of free light chain measurements and cardiac biomarkers into response criteria is warranted.

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