

Systemic Diseases: From Amyloidosis to Cryoglobulinemia

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Hereditary fibrinogen A α -chain amyloidosis: Phenotypic characterization of a systemic disease and the role of liver transplantation. *Blood* 115: 2998–3007, 2010

Arie J. Stangou, Nicholas R. Banner, Bruce M. Hendry, Mohamed Rela, Bernard Portmann, Julia Wendon, Mark Monaghan, Philip MacCarthy, Muriel Buxton-Thomas, Christopher J. Mathias, Juris J. Liepnieks, John O'Grady, Nigel D. Heaton, and Merrill D. Benson

Fibrinogen amyloidosis due to mutations in the fibrinogen α -chain gene (AFib) localized on chromosome 4 and composed of six exons belongs to the group of nonneuropathic hereditary renal amyloidoses. It is the most common type of all hereditary renal amyloid diseases in the United States and Europe. Like other forms of amyloidosis, AFib amyloidosis is a protein misfolding disorder. Fibrinogen production is exclusively hepatic. Liver transplantation was therefore considered as a logical mode of treatment, whereas isolated renal transplantation was followed by kidney amyloid recurrence in most patients.

Stangou *et al.* have first revisited the current phenotypic description of AFib amyloidosis and second performed a systematic evaluation for liver and kidney transplantation (LKT) in a series of 22 patients (8 women, 14 men). Three of them had been misdiagnosed as primary systemic AL amyloidosis—a diagnostic error already reported (1).

The median age at presentation was 55 years (range 33 to 63 years). Proteinuria was the most common presenting feature (median 24-hour urine protein = 7.2 g; range 0 to 11.8 g). At the time of assessment, median GFR was 16 ml/min (range 0 to 52 ml/min). Renal biopsy was performed in 21 of 22 patients and revealed amyloidosis in all patients, with enlarged glomeruli replaced by amyloid with minimal or no extraglomerular involvement—a finding suggestive of this type of amyloidosis (1). Twenty of 22 patients progressed to ESRD. Two patients had liver amyloidosis, complicated in one by end-stage liver disease.

Coronary atherosclerotic disease was documented in 15 patients (68%), in half of the patients predating evolution of kidney impairment. Twelve patients had severe systemic vascular disease, involving aorta, splanchnic, or carotid arteries.

Two patients underwent carotid endarterectomy. Of interest, the excised material contained amyloid purely consistent of mutant fibrinogen A α -chain. Cardiac amyloidosis was not a rare localization. Echocardiography was abnormal in 11 of 21 patients (52%). Three of the four endomyocardial biopsies revealed substantial amyloid deposition. One patient developed dilated amyloid cardiomyopathy in association with coronary disease and myocardial amyloidosis, whereas cardiac amyloidosis usually leads to restrictive cardiomyopathy. In addition, cardiac parasympathetic dysfunction and risk of bradycardia were identified in 12 patients. Seven of them had pacemaker insertion. Autonomic involvement of the gastrointestinal tract was a feature in 15 patients.

Only 24% of patients had family history of renal disease. However, 81% had family history of systemic or coronary vascular disease. Family members who had such cardiovascular history were indeed carriers of AFib mutations.

Spontaneous splenic rupture occurred in four patients (one during hemodialysis and three during transplantation). The excised spleen contained widespread amyloid.

Nine of 14 patients accepted on the waiting list received combined liver and kidney allografts. At a median follow-up of 67 months, six of nine patients are alive and well with normal liver function. Five patients have good renal function. Cardiac amyloidosis has not progressed after LKT. ^{123}I -labeled serum amyloid P component (SAP) scintigraphy showed regression of systemic visceral amyloid deposits as early as at the first annual follow-up scan after LKT, whereas scintigraphy documented progressive amyloid deposition in two patients who had previously undergone isolated kidney transplant. Serial $^{99\text{m}}\text{Tc}$ -DMSA renal scintigraphy after preemptive LKT in two patients demonstrated stable native renal uptake.

Four patients with various liver diseases received, after full information, explanted livers from AFib patients. Only one “domino” recipient had SAP scans and echocardiography for up to 5 years with no evidence of *de novo* amyloid deposition.

The study by Stangou *et al.* extends the clinical scope of AFib amyloidosis. Stangou *et al.* encourage evaluation of isolated liver transplant early in the course of amyloid nephropathy to prevent systemic deposition and renal progression to ESRD. Amyloid fibrils in AFib contain exclusively variant fibrinogen. Circulating total fibrinogen consists of a mixture of wild-type/variant fibrinogen in a ratio of 1:1 to 3:2. Wild-type fibrinogen does not perpetuate amyloid disease. After liver transplant, the variant fibrinogen is eliminated and promptly replaced by

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wild-type fibrinogen. Liver transplantation may be truly curative, arresting amyloid progression.

Finally, amyloidotic kidneys may be more vulnerable than normal kidneys. AFib patients who are listed for preemptive isolated liver transplant should be monitored monthly to ensure that GFR is maintained at levels >50 ml/min. Patients whose GFR falls below 50 should be altered to LKT.

The point of view of Stangou *et al.* has been challenged rapidly by Gillmore *et al.* in a letter to *Blood* (2). Gillmore *et al.* had reported follow-up of 71 patients with AFib amyloidosis (1). Surprisingly, their series included 20 of the 21 patients studied by Stangou *et al.* However, their interpretation and conclusions are quite different.

First, Gillmore *et al.* stress the difference between amyloid deposits and amyloidosis as a clinical disease. Echocardiographic features may be interpreted as the so-called “uremic cardiomyopathy.” Gillmore *et al.* have never encountered a patient with AFib who has developed clinically significant autonomic disease. Second, Gillmore *et al.* challenges the indication of LKT. The results of LKT in the series of Stangou *et al.* are not overly encouraging in recipients over the age of 50 years. The mortality rate was 33% and compares poorly with 1-year patient survival of 100% among 10 AFib patients who received 12 isolated kidney transplants (2). Gillmore *et al.* are still more critical on the encouragement for preemptive liver transplant. Mutations are poorly penetrant in this autosomal dominant disease. Most carriers never develop any disease. In addition, even if LKT is considered only in nephrotic patients, amyloidotic kidneys are extremely susceptible to irreversible kidney injury due to prolonged anesthesia or long-term antirejection therapy. LKT should be considered very cautiously in carefully selected patients. The debate is open.

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Long-term TNF- α blockade in patients with amyloid A amyloidosis complicating rheumatic diseases. *Am J Med* 123: 454–461, 2010

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Inflammatory diseases, such as rheumatic inflammatory diseases and Crohn disease, are now the most common causes of AA amyloidosis in Western countries. Anti-TNF drugs offer a suitable treatment for many of these highly active diseases refractory to other treatments. In short series, these drugs may also rapidly improve the clinical status of patients with AA amyloidosis secondary to inflammatory diseases. However, data on long-term survival and complications are lacking.

Fernandez-Nebro *et al.* have designed in Spain a multicenter prospective cohort study of 36 patients with AA amyloidosis (34 with renal involvement) treated with anti-TNF agents (drug exposure of approximately 103 patient-years). Infliximab was the drug of first choice, administered every 8 weeks in most patients. Etanercept and adalimumab were more rarely used. As an external control group, 35 propensity score-matched nonamyloid patients were chosen from a national registry. This is a prospective cohort study with a robust control group but with no placebo group.

At baseline, the mean age of the patients was 55 years. Sixty-four percent were female. Rheumatoid arthritis predominated. The cohort was generated from 2001 to 2006; the mean duration of follow-up was approximately 3 years. Kidney involvement was found in 94% of the patients: 26% had nephrotic syndrome and 72% had renal insufficiency.

At the end of follow-up, a kidney response was observed in 12 of 22 patients, kidney progression in 6, and stability in 16 of 36 patients. The anti-TNF treatment reduced the median levels of proteinuria whereas renal function remained stable in the whole cohort. The duration of amyloidosis and the level of proteinuria at the onset of anti-TNF therapy were independent predictors of treatment discontinuation. The level of acute phase reactants diminished quickly but did not reach a normal level.

The continuation rates of anti-TNF drugs among amyloidosis patients after 3 and 4 or more years were 61% and 52%, respectively; the 5-year cumulative survival of amyloidosis patients was 90.6% and the 10-year survival was 78.5%. During the follow-up period, eight patients (22%) died, five with progression of amyloidosis (hemodialysis was initiated in four of them). The level of proteinuria at onset was the only factor that predicted mortality. The proportion of patients with more organs clinically affected by amyloidosis was greater among the patients who died. The rates of adverse events were similar in both groups, but infections were 3 times as frequent among the amyloid patients and all fatal adverse events were infectious.

This study shows that anti-TNF drugs may be useful to treat patients with kidney amyloidosis complicating rheumatic inflammatory diseases. It may be expected that control (albeit incomplete) of inflammation has a beneficial effect on the progression of AA amyloidosis. However, the true positive effect of these drugs on survival remains to be demonstrated in larger series, and the risk of infection has to be better evaluated.

Bortezomib with or without dexamethasone in primary systemic (light-chain) amyloidosis. *J Clin Oncol* 28: 1031–1037, 2010

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Therapy of AL amyloidosis (or Ig light-chain amyloidosis), with renal involvement in most patients, remains a major challenge. An editorial recently written by an expert in that field, Dr. M.A. Gertz, has a provocative title: “I don’t know how to treat amyloidosis” (1). There are good reasons for pessimism; there are also good reasons for hope. Heher *et al.* stress the latter point of view in their review article (2). In their conclusions, they state that: “Wider use

of kidney biopsy to identify monoclonal protein deposition in patients with mild degrees of kidney dysfunction may be indicated as therapeutic options improve.”

The regimen of melphalan and dexamethasone is now widely considered the standard for patients who do not receive stem-cell transplants. The study performed in Pavia, Italy, demonstrated a progression-free survival of 3.8 years and median overall survival of 5.1 years (3). The results of trials in AL amyloidosis are very heterogeneous because the mix of patients is very important in determining overall outcome (1). Indeed prognosis depends of age, proportion of patients with cardiac involvement, and the number of organs involved. The major predictor of survival in AL amyloidosis is the extent of cardiac involvement, and this can be estimated by measurement of cardiac troponin-T and NT-proBNP (N-terminal-probrain natriuretic peptide). In selected patients (younger age without significant organ dysfunction) high-dose melphalan with stem-cell transplantation may be associated with higher complete response and extended survival (4).

There is a need for effective treatment of patients with symptomatic heart involvement and of patients with refractory disease. This is the goal of the retrospective study performed by Kastritis *et al.* from three centers where 94 patients with AL amyloidosis were managed. Bortezomib (B), which is a reversible proteasome inhibitor, has been used. This drug has shown significant activity in patients with myeloma in relapsed or refractory settings and also as a first-line treatment. Plasma cells produce amyloidogenic light chains that lead to increases in endoplasmic stress and are largely dependent on proteasome function. Amyloidogenic light chains also have a direct toxic effect on cardiomyocytes.

In AL amyloidosis patients, B was prescribed at various doses in this multicenter retrospective study. However B was the first-line therapy in 19% of the patients at 1.3 mg/m² on days 1, 4, 8, and 11, with dexamethasone at 40 mg on days 1 through 4 every 21 days. Eleven percent of patients received B without dexamethasone.

Among the 94 patients analyzed, 76 (81%) had at least one prior therapy and 51% had refractory disease. The heart was involved in 73% and the kidneys were involved in 75% (11 [12%] were dialysis-dependent).

A hematologic response was achieved in an average of 72% of patients. A complete response was more frequent in previously untreated patients and in those who received B twice weekly.

A heart response was found in 29% of 69 patients, and a kidney response was found in 19% of 70 patients, strongly associated with hematologic response. All cardiac responders were alive after a median of 18 months. A drop in NT-proBNP accompanied cardiac response. The rates of renal responses were somewhat low, probably because of long-standing disease responsible for irreversible renal damage. The renal response may need longer follow-up because up to 25% of patients respond after >12 months. Of importance, renal impairment (even ESRD) was not associated with increased toxicity of B.

After a median follow-up of 12 months (range 0.6 to 48 months), 49% of patients had either hematologic or organ progression or died. Twenty-five patients (26%) died; 1-year sur-

vival was 76% and cardiac involvement was independently associated with survival.

In patients with renal impairment but not undergoing dialysis, only baseline NT-proBNP was significantly associated with survival. In the whole population of patients (excluding dialysis patients), only NT-proBNP and hematologic responses were independently associated with survival.

The most common nonhematologic toxicities were peripheral sensory neuropathy (40%) with or without neuropathic pain, exacerbation of orthostatic hypotension (36%), peripheral edema, and intestinal manifestations.

This paper shows that B is an effective and rapidly acting treatment: median of 28 days *versus* 2 to 4 months in dexamethasone-based regimens. As first-line therapy, B achieves a 47% complete remission rate. It also shows activity even in heavily pretreated or refractory patients. However, it should not be used in patients with severe symptomatic heart failure because of the high rate of adverse events (5).

New therapeutic possibilities emerged recently in AL amyloidosis after recent advances in myeloma treatment. The tolerance of lenalidomide in a small trial in patients with severe AL amyloidosis has been poor (6). Incorporation of B in the first-line treatment, particularly in high-risk patients, should be investigated in phase III trials.

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Rituximab plus Peg-interferon- α /ribavirin compared with Peg-interferon- α /ribavirin in hepatitis C-related mixed cryoglobulinemia. *Blood* 116: 326–334, 2010

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Mixed cryoglobulinemia (MC) is a systemic vasculitis that affects small- and medium-sized vessels. Renal involvement is

considered a major cause of morbidity and mortality (1). Hepatitis C virus (HCV) infection is detected in more than 90% of patients with MC. The treatment therefore has two targets: to induce a sustained virologic response (SVR) and to control the downstream B cell clonal expansion producing a pathogenic IgM with rheumatoid factor activity. Targeting only one of these goals leads to short-lived or incomplete responses.

Thus, Saadoun *et al.* have designed a prospective cohort study to compare the effects of antiviral therapy alone (control group) with those of antiviral combined with rituximab (RTX), a chimeric anti-CD20 monoclonal antibody (called subsequently RTX group). The therapeutic schedule was four weekly intravenous infusions of RTX during the first month, each at 375 mg/m² in most patients, followed in month 2 by antiviral combination with Peg-IFN- α /ribavirin for 48 weeks, whatever the HCV genotype. The mode of distribution between both groups is not clearly indicated by the authors. Inclusion criteria were chronic active HCV infection, signs of MC vasculitis, and a minimum of 6 months of follow-up after discontinuing any treatment. Patients with hepatitis B surface antigen or anti-HIV antibodies were excluded.

Ninety-three HCV-MC patients with a median age of 60 years were included. Main clinical features of MC included polyneuropathy (72%), purpura (66.6%), and kidney involvement (33.3%). Thirteen patients had B cell non-Hodgkin lymphoma. Forty-two patients were naïve to antiviral therapy, whereas the remaining 51 were resistant to a previous antiviral treatment. Characteristics of the patients were rather similar in both groups; the most striking difference was the presence of kidney involvement: 18.2% in the control group and 55% in the RTX group.

The virologic response did not differ between the two groups: SVR was achieved in approximately 60% of the patients. Severe liver fibrosis was independently associated with viral persistence. Petrarca *et al.* have reported safety and efficacy of RTX in 19 patients with HCV-MC and severe liver disease (15 had liver cirrhosis, with ascitic decompensation in 6 patients) (2).

A clinical response was obtained in approximately 73% of patients in both groups. However, the time to clinical remission was shorter in the RTX group: 5.4 months *versus* 8.4 months ($P < 0.004$). Unsurprisingly the immunologic response rate was higher in the RTX group. B cell depletion in the peripheral blood was achieved in all patients except one in the RTX group. Seventeen patients (18%) experienced a clinical relapse, equally distributed in the two groups and associated with immunologic and virologic relapses. After retreatment, most patients in both groups developed complete clinical responses.

The overall median follow-up was 48 months. Five patients died (5.4%). No difference in survival was noted between the two groups. Treatment interruptions occurred in 11% of patients and were equally distributed between the two groups. Serum sickness was the most common benign

adverse effect in the RTX group. However, Sene *et al.* have reported a severe flare-up of MC and serum sickness-like syndrome under RTX, especially in patients with high levels of serum cryoglobulin (3).

The most striking difference between both therapeutic groups deals with the renal response. The rate of complete remission was much higher in the RTX group: 81% *versus* 40%. In the 21 patients with renal disease in the RTX group, proteinuria decreased from 3.5 to 0.35 g/d, and serum creatinine diminished from 217.5 to 137 μ mol/L (whereas it increased from 150 to 169 μ mol/L in the other group). No renal histopathological data are available.

The combination of RTX and Peg-IFN- α /ribavirin may be the first choice treatment of HCV-MC patients with kidney involvement (*i.e.*, membranoproliferative GN). The value of RTX in HCV-MC patients is confirmed by the prospective randomized study of Dammacco *et al.* published in the same issue of *Blood* (4). It included only 22 patients. The therapeutic protocol was slightly different: four intravenous RTX infusions were performed initially, concomitantly with initiation of Peg-IFN- α /ribavirin, and two additional RTX infusions were added on months 6 and 11. In the control group, only antiviral treatment was prescribed. The percentage of patients with kidney involvement was lower (22.7%) than in the study by Saadoun *et al.* Thus, only five and four patients had renal disease in the two groups, respectively. The renal response was similar, but no conclusion can be drawn from such a small sample of patients. Complete response of HCV-MC was achieved in 54.5% of patients in the RTX group *versus* 33.3% in the other. The beneficial effect of therapy may last for more than 3 years (4).

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