CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Intravenous Immunoglobulins Improve Survival in Monoclonal Gammopathy-Associated Systemic Capillary-Leak Syndrome

Marc Pineton de Chambrun, MD,[a,b] Marie Gousseff, MD,[c] Wladimir Mauhin, MD,[a] Jean-Christophe Lega, MD, PhD,[d] Marc Lambert, MD, PhD,[e] Sophie Rivière, MD,[f] Antoine Dossier, MD,[g] Marc Ruivard, MD, PhD,[h] François Lhote, MD,[i] Gilles Blaison, MD,[j] Laurent Alric, MD, PhD,[k] Christian Agard, MD, PhD,[l] David Saadoun, MD, PhD,[m] Julie Graveleau, MD,[n] Martin Soubrier, MD, PhD,[o] Marie-Josée Lucchini-Lecomte, MD,[p] Christine Christides, MD,[q] Annick Bosseray, MD,[r] Hervé Levesque, MD, PhD,[s] Jean-François Viallard, MD, PhD,[t] Nathalie Tieulie, MD,[u] Pierre-Yves Lovey, MD,[v] Sylvie Le Moal, MD,[w] Béatrice Bibes, MD,[x] Giuseppe Malizia, MD,[y] Pierre Abgueguen, MD,[z] François Lifermann, MD,[aa] Jacques Ninet, MD, PhD,[bb] Pierre-Yves Hatron, MD,[e] Zahir Amoura, MD, MSc,[a] members of the EurêClark Study Group

[a]Service de médecine interne 2 and [b]Service de réanimation médicale, CHU La Pitié-Salpêtrière, APHP, Université Paris 6, France; [c]Service de médecine interne, CH Bretagne Atlantique, Vannes, France; [d]Service de médecine interne et vasculaire, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, CHU, Pierre-Bénite, France and UMR 5558, Laboratoire de Biométrie et Biologie Évolutive, CNRS, Université Claude-Bernard Lyon 1, France; [e]Service de médecine interne, Hôpital Claude Huriez, CHRU Lille, France; [f]Service de médecine interne, Hôpital Saint-Eloi, CHRU Montpellier, France; [g]Service de médecine interne, CHU Bichat, Paris, APHP, France; [h]Service de médecine interne, Hôpital d'Estaing, CHU de Clermont-Ferrand, France; [i]Service de médecine interne, Hôpital Delafontaine, Saint-Denis, France; [j]Service de médecine interne et rhumatologie, Hôpital Pasteur, Colmar, France; [k]Service de médecine interne, Pôle digestif, CHU Purpan, Toulouse, France; [l]Service de médecine interne, CHU Hôtel-Dieu, Nantes, France; [m]Service de médecine interne et immunologie clinique, CHU La Pitié-Salpêtrière, APHP, Paris, France; [n]Service de médecine polyvalente, CH Saint-Nazaire, France; [o]Service de rhumatologie, Hôpital Gabriel-Montpied, CHU Clermont-Ferrand, France; [p]Service de médecine Interne, CH Notre-Dame de la Miséricorde, Ajaccio, France; [q]Service de médecine interne, CH Avignon, France; [r]Service de médecine interne, CHU Grenoble, France; [s]Normandie univ, UNIROUEN, U1096, Service de médecine interne, Rouen, France; [t]Service de médecine interne, Hôpital Haut-Lévêque, CHU Bordeaux Sud, Pessac, France; [u]Service de rhumatologie, Hôpital Pasteur 2, CHU Nice, France; [v]Service d'hématologie, Hôpital du Valais-Institut Central, Sion, Switzerland; [w]Service de médecine interne, CH de Saint-Brieuc, France; [x]Service de médecine interne, CHP Saint-Grégoire, France; [y]Divisione di Gastroenterologia, Ospedale V. Cervello, Palermo, Italy; [z]Service des maladies infectieuses et tropicales, CHU d'Angers, France; [aa]Service de médecine interne, CH Dax, France; [bb]Service de médecine interne, CHU Edouard Herriot, Lyon, France.

ABSTRACT

BACKGROUND: Monoclonal gammopathy-associated systemic capillary-leak syndrome, also known as Clarkson disease, is a rare condition characterized by recurrent life-threatening episodes of capillary hyperpermeability in the context of a monoclonal gammopathy. This study was conducted to better describe the clinical characteristics, natural history, and long-term outcome of monoclonal gammopathy-associated systemic capillary-leak syndrome.

METHODS: We conducted a cohort analysis of all patients included in the European Clarkson disease (EurêClark) registry between January 1997 and March 2016. From diagnosis to last follow-up, studied outcomes (eg, the frequency and severity of attacks, death, and evolution toward multiple myeloma) and the type of preventive treatments administered were monitored every 6 months.

RESULTS: Sixty-nine patients (M/F sex ratio 1:1; mean ± SD age at disease onset 52 ± 12 years) were included in the study. All patients had monoclonal gammopathy of immunoglobulin G type, with kappa light chains in 47 (68%). Median (interquartile range) follow-up duration was 5.1 (2.5-9.7) years. Twenty-four patients (35%) died after 3.3 (0.9-8) years. Fifty-seven (86%) patients received at least one preventive treatment, including intravenous immunoglobulins (IVIg) n = 48 (73.8%), theophylline n = 22 (33.8%), terbutaline n = 22 (33.8%), and thalidomide n = 5 (7.7%). In the 65 patients with follow-up, 5- and 10-year survival rates were 78% (n = 35) and 69% (n = 17), respectively. Multivariate analysis found preventive treatment with IVIg (hazard ratio 0.27; 95% confidence interval, 0.10-0.70; $P = .007$) and terbutaline (hazard ratio 0.35; 95% confidence interval, 0.13-0.96; $P = .041$) to be independent predictors of mortality.

CONCLUSIONS: We describe the largest cohort to date of patients with well-defined monoclonal gammopathy-associated systemic capillary-leak syndrome. Preventive treatment with IVIg was the strongest factor associated with survival, suggesting the use of IVIg as the first line in prevention therapy.

 • *The American Journal of Medicine (2017) 130, 1219.e19-1219.e27*

KEYWORDS: Clarkson disease; Intravenous immunoglobulins; Monoclonal gammopathy-associated systemic capillary-leak syndrome; Systemic capillary-leak syndrome

0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2017.05.023

Monoclonal gammopathy-associated systemic capillary-leak syndrome, also known as Clarkson disease, is a rare condition characterized by recurrent life-threatening episodes of capillary hyperpermeability in the context of a monoclonal gammopathy.[1] Since the initial description of the disease by Clarkson et al in 1960,[1] fewer than 250 cases have been reported worldwide.[2] During acute episodes, fluid and protein leakage from the intravascular compartment into the interstitium causes clinical signs of acute hypovolemia and interstitial edema. The laboratory work-up is pathognomonic, with marked hemoconcentration and paradoxical hypoproteinemia.[1,3,4] Diagnosis relies on recurring typical flares associated with monoclonal gammopathy (reported in >85% of patients),[1,4-7] after exclusion of differential diagnoses of secondary capillary-leak syndrome or hypoproteinemia.

CLINICAL SIGNIFICANCE

- Five- and 10-year survival rates in 65 patients with monoclonal gammopathy-associated systemic capillary-leak syndrome were 78% and 69%, respectively.
- Intravenous immunoglobulins improve survival of patients with monoclonal gammopathy-associated systemic capillary-leak syndrome.

Optimal management remains unclear, although in recent years, a growing body of evidence suggested that intravenous immunoglobulins (IVIg) might prevent attack recurrence.[5,8-15] Herein, we report the clinical characteristics, the natural history, and the outcome of 69 patients with monoclonal gammopathy-associated systemic capillary-leak syndrome.

METHODS

The European Clarkson Disease (EurêClark) Registry

As previously reported,[5,6] the EurêClark registry is an international study group, comprising 49 medical centers in 8 countries (France, Italy, Israel, Switzerland, Lebanon, Canada, Spain, and Turkey), which gathers monoclonal gammopathy-associated systemic capillary-leak syndrome observations and prospectively monitors episodes, preventive treatments, complications, and patient outcomes. In 1997, this registry was approved by local review boards (AP−HP no.14) and the "Commission Nationale de l'Informatique et des Libertés" (no. 1001704). All patients, or their next of kin, accepted the inclusion in the EurêClark database.

EurêClark Inclusion and Noninclusion Criteria

Patients were included from January 1, 1997 and prospectively monitored until March 31, 2016. Patients could be included even when the first episode preceded the starting date for inclusions.

Criteria for the diagnosis of Clarkson disease were as follows: 1) presence of a monoclonal gammopathy; 2) one or more episodes that met all of the following criteria[5]: clinical signs of acute hypovolemia (eg, sudden fatigue, thirst, dizziness, oliguria, and low blood pressure) and acute interstitial edema (eg, myalgias, paresthesia, nausea and vomiting, abdominal pain, and generalized or segmental edema); 3) hemoconcentration (elevated hematocrit or hemoglobin exceeding normal values for age and sex or >20% of the last reference value for a given patient) with paradoxical hypoproteinemia; 4) and exclusion of any other cause of secondary capillary-leak syndrome or hypoproteinemia.[2,7,16]

In case of suspicion of Clarkson disease, patients were referred to the EurêClark coordinating center, where medical history, clinical manifestations, and laboratory findings of every patient were evaluated and the diagnosis confirmed or invalidated. Patients without monoclonal gammopathy were not considered for inclusion in the registry, and no pediatric patients were included because none had monoclonal gammopathy. Some patients have been previously reported in earlier EurêClark studies.[5,6]

Data Collection and Definition

Standardized forms were used to collect baseline and follow-up data: epidemiologic, clinical data, and laboratory findings; number and frequency of attacks; and preventive treatments and outcomes. After patient inclusion, referring physicians were contacted by e-mail or telephone every 6 months to complete follow-up forms.

Severe attacks were defined as: systolic blood pressure <80 mm Hg, mean blood pressure <65 mm Hg, loss of consciousness, admission to the intensive care unit, or a combination of these. Chronic evolution was defined by a high number and frequency of episodes that made them nondifferentiable. Monoclonal gammopathy identification and quantification were performed using serum protein electrophoresis and immunofixation, always prior to any IVIg infusion. The diagnosis of myeloma was established according to the up-to-date international guidelines available at the time of each evaluation.

Preventive treatments were defined as drugs introduced to prevent recurrence or to lower the severity of episodes. Four preventive treatments were considered in this study: IVIg, theophylline, terbutaline, and thalidomide. According to drug tolerance, preventive treatment dosages were as follows: theophylline 400 to 1600 mg/day; terbutaline 15 to 25 mg/day, and thalidomide 50 mg/day to a maximum dosage of 100 mg/day. There was no prespecified protocol for the preventive treatment administration. Prior to the year 2000, the combination of theophylline and terbutaline was administered as the first therapy. Since the year 2000, IVIg are recommended as the first-line therapy. The first IVIg infusion was always initiated after the resolution of the previous attack, due to concern about the safety of IVIg

during severe episodes. The initial recommended IVIg treatment was the monthly intravenous administration of 2 g/kg of body weight. We recommended no specific type of IVIg, and the choice depended on the preference of each center. The monthly treatment with 2 g/kg was administered during a minimum of 1 year. In the absence of a 1-year recurrence and after the approval of the coordinating center, the IVIg treatment could be tapered to 1 g/kg monthly and then, after another year free of recurrence, to 0.5 g/kg monthly. After achieving the dosage of 0.5 g/kg monthly, we considered on a case-to-case basis whether to increase the interval between the IVIg infusions. In case of relapse, the IVIg treatment was returned to the previous step.

Statistical Analysis

Results are expressed as frequencies (%), continuous variables as mean (standard deviation) or median [interquartile range 25-75], and compared using Student's *t* test or Wilcoxon-rank test when appropriate. Categorical variables were compared with Fisher's exact tests. Patients' demographic, clinical, and biological characteristics were tested in univariate analysis for association with end-of-follow-up mortality. Thereafter, Cox proportional hazard model using backward-stepwise variable elimination was run (with the variable exit threshold set at $P > .10$). Factors achieving $P \leq .20$ in univariate analysis and parameters previously reported to be strongly associated with death were entered into the multivariate model. Considering the time from diagnosis to death or the end of follow-up as the time to event, survival rates were estimated using Kaplan-Meier curves and compared using the log-rank test. Statistical significance was defined as $P < .05$. Analyses were computed with IBM SPSS Statistics 22.0 software (IBM Corp., Armonk, NY).

Table 1 General Characteristics of 69 Patients with Monoclonal Gammopathy-Associated Systemic Capillary-Leak Syndrome

Parameter	n*	Value
Patients		69
Women		35 (50.7)
Age at onset,† y		52 ± 12
Age at diagnostic, y		53.5 ± 12
Time from onset to diagnostic, mo		5.9 [0.1-20.5]
Monoclonal gammopathy		69 (100)
IgG heavy chain		69 (100)
Kappa light chain‡		47 (68.1)
Lambda light chain‡		24 (34.8)
Monoclonal protein level at diagnosis, g/L	55	4.4 [2-8]
Trigger		48 (69.5)
Infection§		45 (65.2)
Hormonal		4 (5.8)
Effort		2 (2.9)
Biological data		
Hemoglobin,‖ g/dL		20.3 [18.1-22]
Hematocrit,‖ %	62	59.6 [55-65.2]
Proteinemia,¶ g/L	60	45 [38-52.7]
Albuminemia,¶ g/L	59	23.6 [17-28]

Values are expressed as n (%), and continuous variables as mean ± standard deviation or median [interquartile range].
IgG = immunoglobulin G.
*Number of value available for the 69 patients.
†Onset was defined as the first attack reported.
‡Two patients had a biclonal gammopathy.
§Including flu-like illness, proven viral and bacterial infections.
‖Highest value available for each patient during any attack.
¶Lowest value available for each patient during any attack.

RESULTS

Patient Characteristics

Characteristics of the 69 patients included in the study, between January 1997 and March 2016, are reported in Table 1. The male/female ratio was 1:1, with mean age at disease onset and at diagnosis of 52 ± 12 years and 53.5 ± 12 years, respectively. All patients had an immunoglobulin (Ig)G monoclonal gammopathy, with kappa and lambda light chains in 47 (68.1%) and 24 (34.8%) patients, respectively (2 patients had biclonal gammopathy). The median level of monoclonal component at diagnosis was 4.4 [2-8] g/L. All patients met, at diagnosis, the criteria for monoclonal gammopathy of undetermined significance.

Outcomes

Median length of follow-up was 5.1 [2.5-9.7] years. The median number of attacks after diagnosis was 2 [0-6], including 1 [0-2] severe episode. This number was highly heterogeneous among patients, with a maximum numbers of attacks after diagnosis of 35.

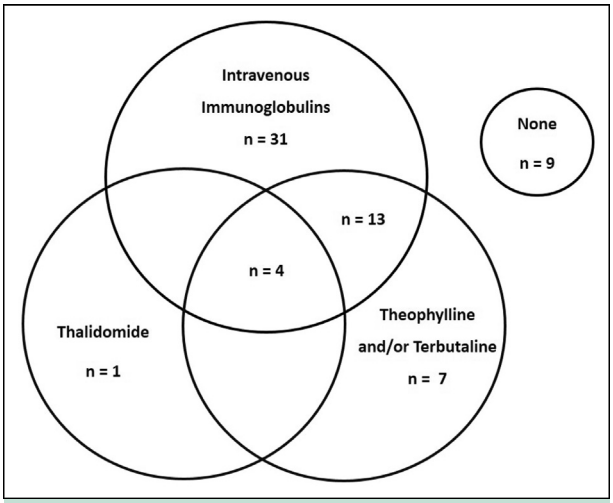

Figure 1 Treatment administration distribution in 65 patients with monoclonal gammopathy-associated systemic capillary-leak syndrome.

Fifty-seven (86.2%) patients received at least one preventive treatment during follow-up, including: IVIg (n = 48, 73.8%), theophylline (n = 22, 34%), terbutaline (n = 22, 34%), and thalidomide (n = 5, 7.7%). Twenty-three patients (35.4%) received more than one preventive treatment. The distribution of the treatments administered during follow-up is reported in Figure 1. Other outcomes and preventive treatment parameters are reported in Table 2.

Multiple myeloma occurred in 5 (7.2%) patients. Twenty-four patients (34.8%) died after a median duration of 3.3 [0.9-8] years: 20 (83.3%) during a severe attack and 4 (16.7%) from multiple myeloma. Four patients died during their first episode, and were not included in the follow-up analysis. One-, 2-, 5- and 10-year survival rates were 97%, 95%, 78%, and 69%, respectively. The Kaplan-Meier curve of probability of survival is shown in Figure 2.

Table 2 Outcome, Preventive Treatment, and Survival of 69 Patients with Monoclonal Gammopathy-Associated Systemic Capillary-Leak Syndrome

Parameter	Value
Patients	69
Duration of follow-up, y	5.1 [2.5-9.7]
Number of attacks prior to diagnosis	2 [1-3]
Severe attacks	1 [1-2]
Chronic evolution prior to diagnosis*	4 (5.8)
Number of attacks after diagnosis	2 [0-6]
Severe attacks	1 [0-2]
Chronic evolution after diagnosis*	9 (13)
Complications	
Compartment syndrome	23 (33.3)
Myeloma	5 (7.2)
Death	24 (34.8)
Severe attack	20 (83.3)
Myeloma	4 (16.7)
Patients†	65
Preventive treatment	56 (86.2)
More than one preventive treatment	23 (35.4)
Intravenous immunoglobulins	48 (73.8)
Duration, y	4.3 [2.3-7.5]
Theophylline	22 (33.8)
Duration, y	2.5 [1.4-3.6]
Terbutaline	22 (33.8)
Duration, y	2.3 [0.7-3.9]
Thalidomide	5 (7.7)
Duration, y	1.4 [0.8-7]
Probability of survival	
1-year n = 60*	97%
2-year n = 58*	95%
5-year n = 35*	78%
10-year n = 17*	69%
15-year n = 6*	49%

Values are expressed as n (%), and continuous variables as mean ± standard deviation or median [interquartile range].

*Number of patients still at risk of dying, excluding patients whose follow-up is ended or lost.

†Four patients died during their first attack and were not included in the follow-up analysis.

Factor Association with End-of-Follow-up Mortality

The comparison between survivors (n = 45) and patients who died (n = 20) during follow-up is reported in Table 3. Nonsurvivors had significantly more recurrence of severe episodes after diagnosis (19 [95%] vs 19 [42.2%], $P < .0001$) and myeloma (5 [25%] vs 0 [0%], $P = .002$) than did survivors. Survivors received significantly more frequent preventive treatment with IVIg (40 [88.9%] vs 8 [40%], $P < .0001$) than did nonsurvivors. According to multivariate analysis using a Cox proportional model to identify mortality-associated factors (Table 4), only preventive treatment with IVIg (HR 0.27; 96% confidence interval [CI], 0.10-0.70; $P = .007$) and terbutaline (HR 0.35; 95% CI, 0.13-0.96; $P = .04$) were independent predictors of mortality. Five- and 10-year survival rates in patients treated with IVIg were 91% and 77%, respectively, compared with 47% and 37% in patients not treated with IVIg (log rank test $P < .0001$, Figure 3).

Subgroup Comparison

Patients treated with IVIg (n = 48) had significantly less recurrence of attacks and fewer severe attacks (31 [64.6%] vs 16 [94.1%], $P = .03$ and 22 [45.8%] vs 16 [94.1%], $P < .0001$, respectively) compared with patients not treated with IVIg (n = 17, Table 5).

Conversely, patients treated with terbutaline (n = 22) had significantly more recurrence of episodes and more severe episodes (20 [90.9%] vs 27 [62.8%], $P = .02$ and 17 [77.3%] vs 21 [48.8], $P = .035$) than patients not treated with terbutaline (n = 43, Table 6).

Finally, patients without severe recurrence (n = 27) received IVIg more frequently (26 [96.3%] vs 22 [57.9%], $P < .0001$) and less often terbutaline (5 [18.5%] vs 17 [44.7%], $P = .035$) than did patients with severe recurrence (n = 38, Table 7). It is worth noting that patients with

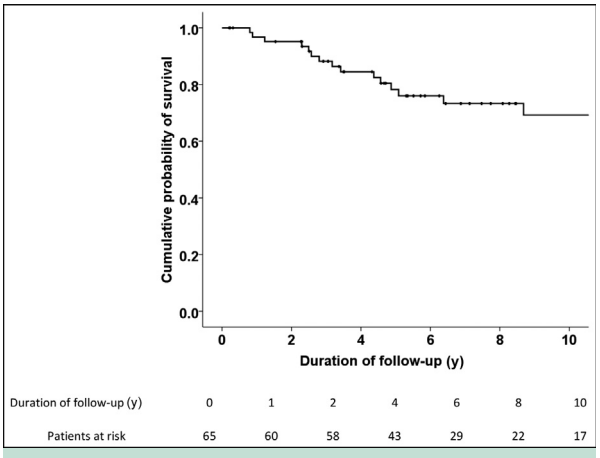

Figure 2 Kaplan-Meier curve of cumulative probability of survival in 65 patients with monoclonal gammopathy-associated systemic capillary-leak syndrome.

Table 3 Comparison Between Survivors and Nonsurvivors in 65† Patients with Monoclonal Gammopathy-Associated Systemic Capillary-Leak Syndrome

	n*	Alive n = 45	Dead n = 20	*P*-Value
General characteristics				
Women		24 (53.3)	9 (45)	.6
Age at onset,‡ y		52.9 ± 13	51.3 ± 11.1	.9
Age at diagnostic, y		53.8 ± 12.7	52.7 ± 11.3	.9
Duration of follow-up, y		5.8 [3.4-10.8]	4.5 [2.5-10.3]	.3
Start of follow-up after year 2000		39 (86.7)	8 (40)	<.0001
Time from onset to diagnostic, mo		4.6 [0.1-19.5]	11.1 [1.2-23.9]	.2
Trigger		28 (62.2)	17 (85)	.08
Monoclonal gammopathy				
Kappa light chain		34 (75.5)	11 (55)	.1
Monoclonal component level at diagnosis, g/L	54	4 [1.5-8.8]	4.1 [1.6-8.8]	.2
Biological data				
Hemoglobin,§ g/dL		20 [18.1-22.4]	20,1 [17.9-21]	.4
Hematocrit,§ %	62	59.6 [55-65]	59.3 [57-68]	.8
Proteinemia,‖ g/L	60	45 [33.5-52]	41 [39-53]	.9
Albuminemia,‖ *g/L*	59	24 [16.5-28.7]	20.5 [17.9-27.2]	.8
Capillary-leak episodes				
Number of attacks prior to diagnosis		2 [1-3]	2 [1.2-4]	.1
Severe attacks		1 [1-1.5]	1 [1-2]	.3
Chronic evolution		2 (4.4)	2 (10)	.5
Recurrence of attacks after diagnosis		28 (62.2)	19 (95)	.007
Severe attacks		19 (42.2)	19 (95)	<.0001
Number of attacks after diagnosis		1 [0-8]	3 [1.25-7.25]	.09
Severe attacks		0 [0-2]	1 [1-6]	.001
Chronic evolution		4 (8.9)	5 (25)	.1
Complications				
Compartment syndrome		16 (35.5)	4 (20)	.2
Myeloma		0 (0)	5 (25)	.002
Treatments				
Preventive treatment		43 (95.5)	13 (65)	.003
More than one preventive treatment		16 (35.5)	7 (35)	1
Intravenous immunoglobulins		40 (88.9)	8 (40)	<.0001
Duration, y		4.1 [2.4-7.5]	4.5 [2.2-9.9]	.8
Theophylline		14 (31.1)	8 (40)	.5
Duration, y		2.5 [0.9-5.1]	2.3 [0.8-3.2]	.5
Terbutaline		16 (35.5)	6 (30)	.8
Duration, y		2.5 [0.6-4.7]	1.7 [0.06-2.8]	.1
Thalidomide		2 (4.4)	3 (15)	.1

Values are expressed as n (%), continuous variables as mean ± standard deviation or median [interquartile range].
*Number of value available for the 65 patients.
†Four patients died on their first attack and were not included in the follow-up analysis.
‡Onset was defined as the first attack reported.
§Highest value available for each patient during any attack.
‖Lowest value available for each patient during any attack.

severe relapse had a more frequent median level of monoclonal protein at diagnosis ≥5 g/L (17 [44.7%] vs 7 [25.9%], $P = .006$).

DISCUSSION

Monoclonal gammopathy-associated systemic capillary-leak syndrome is a puzzling condition responsible for recurrent shocks of unknown origin. Despite increasing evidence over the recent years, data about long-term evolution and efficacy of preventive treatments remain scarce.[1]

Herein, we further characterize the disease's clinical characteristics, long-term evolution, and mortality-associated factors in the largest cohort reported to date.

The demographic characteristics of our cohort differ from those previously reported. Indeed, the mean age at diagnosis was over 50 years, 10 years older than other cohorts.[2,4,5,7,9] This age difference probably reflects the exclusion of pediatric cases. Moreover, a mean age of approximately 50

Table 4 Cox Proportional Hazard Model Univariate and Multivariate Analysis of All-Cause Mortality Associated factors in 65* Patients with Monoclonal Gammopathy-Associated Systemic Capillary-Leak Syndrome

	Univariate			Multivariate		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Women	0.90	0.37-2.18	.8			
Age at onset,† y	1.01	0.97-1.05	.4	1.01	0.96-1.06	.6
Start of follow-up after year 2000†	0.53	0.19-1.45	.2	1.31	0.38-4.47	.6
Kappa light chain	0.40	0.16-0.97	.04			
Monoclonal protein level at diagnosis ≥5 g/L	1.31	0.42-4.11	.6			
Myeloma†	2.48	0.87-7.08	.09	1.33	0.46-3.84	.6
Compartment syndrome	0.81	0.26-2.54	.7			
Recurrence of attacks after diagnosis	3.38	0.44-25.7	.2			
Severe attacks†	7.46	0.98-56.8	.052	5.47	0.67-44.2	.1
Number of attacks after diagnosis	0.97	0.91-1.03	.3			
Severe attacks	1.02	0.93-1.12	.6			
Preventive treatments	0.18	0.07-0.49	.001			
Intravenous immunoglobulins†	0.22	0.09-0.54	.001	0.27	0.10-0.70	.007
Theophylline	0.80	0.32-2.01	.6			
Terbutaline†	0.48	0.18-1.29	.1	0.35	0.13-0.96	.04

CI = confidence interval; HR = hazard ratio.
*Four patients died on their first attack and were not included in the follow-up analysis.
†Factors included in the multivariate analysis.

years agrees with the natural epidemiology of monoclonal gammopathy, whose index of first flare occurs during the fifth decade.[17,18] As part of the inclusion criteria, monoclonal gammopathy was present in every patient, whereas rates in previous studies ranged from 76% to 82%.[4,7,16,19] Heavy chain was always an IgG, as well, in all but 5 previously reported patients: 3 had an IgA (2 with typical attacks[20-22] and one with a chronic form at onset[23]), and 2 had an IgM (with chronic forms[24,25]). Predominance of kappa light chain is concordant with previous reports.[2,4,16,26] Five patients developed myeloma during their follow-up. Considering the number of patients in the cohort (n = 69), the median duration of follow-up (5 years), and a theoretical risk of progression of monoclonal gammopathy toward myeloma (1% each year),[17,18] the prevalence of myeloma in our cohort seems to be consistent with the natural evolution of monoclonal gammopathy. There was no association between the initial level of the monoclonal component and the end-of-follow-up mortality. However, there was an association with the frequency of severe relapse after diagnosis. Patients with a high level of monoclonal component at diagnosis were more susceptible to severe relapse. This finding emphasizes the role of the monoclonal gammopathy or the plasma cell clone in the pathophysiology of Clarkson disease.

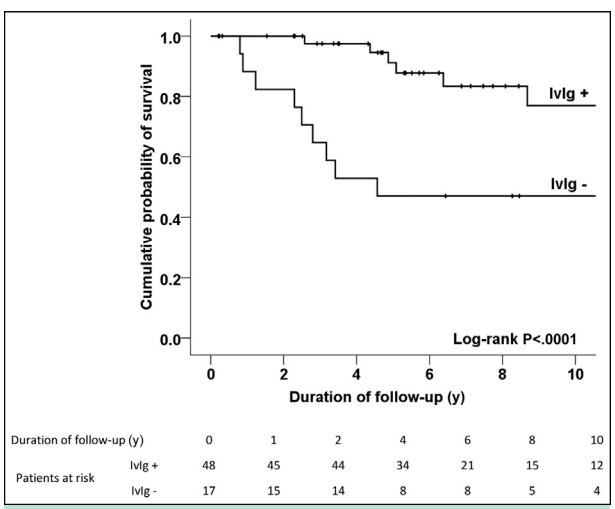

Figure 3 Kaplan-Meier curve of cumulative probability of survival in 65 patients with monoclonal gammopathy-associated systemic capillary-leak syndrome with or without preventive treatment with intravenous immunoglobulin. Probabilities of survival were compared using the log rank test. IVIg + = patients treated with intravenous immunoglobulin; IVIg − = patients not treated with intravenous immunoglobulin.

Preventive treatments in our cohort were strongly correlated with time. Indeed, prior to the use of IVIg, the combination of terbutaline and theophylline was administered as the only preventive therapy. After the year 2000, IVIg was administered as a second-line therapy, in cases of theophylline and terbutaline failure. During the last decade, patients were treated with IVIg as a first-line therapy and theophylline, terbutaline, or thalidomide were considered only in cases of IVIg failure. IVIg was the primary preventive treatment administered in our cohort (74%). Only one-third of our patients received beta-agonists, compared with 42% to 92% of the patients previously reported.[4,5]

Table 5 Comparison Between Patients Treated or Not with Intravenous Immunoglobulins in 65* Patients with Monoclonal Gammopathy-Associated Systemic Capillary-Leak Syndrome

	IVIg n = 48	No IVIg n = 17	*P*-Value
Women	23 (47.9)	10 (58.8)	.5
Start of follow-up after year 2000	7 (14.6)	11 (64.7)	<.0001
Alive at the end of follow-up	40 (83.3)	5 (29.4)	<.0001
Age at onset,† y	51.3 ± 13	55.7 ± 9.6	.2
Age at diagnosis, y	52.2 ± 12.9	57 ± 9	.2
Duration of follow-up, y	5.4 [3.4-10.2]	4.5 [2.4-11.7]	.6
Time from onset to diagnostic, mo	6 [0.1-21.8]	9.2 [0.6-21.7]	.5
Myeloma	1 (2.1)	4 (23.5)	.015
Number of attacks prior to diagnosis	2 [1-3.75]	2 [1-3.5]	.9
Severe attacks	1 [1-2]	1 [1-2]	.8
Recurrence of attacks after diagnosis	31 (64.6)	16 (94.1)	.03
Severe attacks	22 (45.8)	16 (94.1)	<.0001
Number of attacks after diagnosis	1.5 [0-10.5]	2 [1.5-5]	.4
Severe attacks	0 [0-2]	1 [1-3.5]	.01

Values are expressed as n (%), continuous variables as mean ± standard deviation or median [interquartile range].
IVIg = intravenous immunoglobulins.
*Four patients died on their first attack and were not included in the follow-up analysis.
†Onset was defined as the first attack reported.

Table 6 Comparison Between Patients Treated or Not with Terbutaline in 65* Patients with Monoclonal Gammopathy-Associated Systemic Capillary-Leak Syndrome

	Terbutaline n = 22	No Terbutaline n = 43	*P*-Value
Women	14 (63.6)	19 (44.2)	.2
Start of follow-up after year 2000	12 (54.5)	35 (81.4)	.04
Alive at the end of follow-up	16 (72.7)	29 (67.4)	.8
Age at onset,† y	52.7 ± 11.4	52.3 ± 12.9	.9
Age at diagnosis, y	53.8 ± 10.6	53.3 ± 13.1	.8
Duration of follow-up, y	7.3 [4.7-12.8]	4.5 [2.5-8.1]	.014
Time from onset to diagnostic, mo	6.9 [0.5-21]	8.1 [0.1-22.3]	.5
Myeloma	1 (4.5)	4 (9.3)	.6
Number of attacks prior to diagnosis	2 [1-3]	2 [1-4]	.5
Severe attacks	1 [1-2]	1 [1-2]	.2
Recurrence of attacks after diagnosis	20 (90.9)	27 (62.8)	.02
Severe attacks	17 (77.3)	21 (48.8)	.035
Number of attacks after diagnosis	5 [2-14]	1 [0-5]	.003
Severe attacks	2 [0.75-5]	0 [0-1]	.006

Values are expressed as n (%), continuous variables as mean ± standard deviation or median [interquartile range].
*Four patients died on their first attack and were not included in the follow-up analysis.
†Onset was defined as the first attack reported.

Overall 5- and 10-year survival rates of the 65 patients with follow-up were 78% and 69%, respectively, consistent with the survival rate of 24 patients from the Mayo Clinic cohort,[4] but slightly higher than the survival rate reported in 2 reviews (5- and 10-year survival of 70% and 66%, respectively).[16,26]

Importantly, preventive treatment with IVIg and terbutaline were the only factors significantly associated with survival in multivariate analysis. Neither the use of thalidomide nor theophylline was associated with improved survival. IVIg's efficacy in preventing recurrence of episodes has been reported in several case reports and short series during the last decade.[8-15] We previously reported the efficacy of a preventive treatment in reducing mortality in 28 patients,[5] but lacked statistical power to determine which treatment between IVIg and beta-agonists was responsible for this effect. Herein, we widen the evidence supporting IVIg's efficacy on severe attacks and mortality prevention. Patients treated with IVIg were more likely to be free of recurrence or severe recurrence, and to be alive at the end of follow-up. Furthermore, all but one patient who did not experience a severe relapse were treated with IVIg.

Multivariate analysis also considered terbutaline as an independent predictor of survival, although it was not associated with survival in univariate analysis. Patients with severe recurrence were more likely to be treated with terbutaline than patients without severe recurrence. Moreover, recurrence and severe recurrence were more frequent in patients treated with terbutaline than in patients not treated with terbutaline. These contradictory results could suggest the existence of a confounding factor in the interpretation of terbutaline efficacy. Yet, this could also suggest that terbutaline did not lower recurrence but only the severity of episodes, responsible for an overall effect on mortality.

Altogether, these results suggest the use of IVIg as first-line prevention therapy in patients with monoclonal gammopathy-associated systemic capillary-leak syndrome. Results regarding the efficacy of terbutaline should be considered carefully, and terbutaline could be considered in cases of IVIg failure.

Our study has several limitations. First, because patients were recruited over 2 decades, treatment regimens were inevitably heterogeneous. Second, we included and compared new and old patients whose cases had already been published. However, this allowed us to report the largest cohort to date and to increase the power of our statistical analysis. Last, we did not analyze the effects of other preventive treatments (eg, calcium channel blockers, corticosteroids, Ginkgo biloba extract, and pentoxifylline) in the survival analysis, which might induce a potential bias. Yet, these treatments were administered in only a limited number

Table 7 Comparison According the Occurrence of a Severe Attack after Diagnosis in 65* Patients with Monoclonal Gammopathy-Associated Systemic Capillary-Leak Syndrome

	Severe Recurrence n = 38	No Severe Recurrence n = 27	*P*-Value
Women	19 (50)	14 (51.9)	1
Start of follow-up after year 2000	21 (55.3)	26 (96.3)	<.0001
Alive at the end of follow-up	19 (50)	26 (96.3)	<.0001
Age at onset,† y	50.7 ± 11.3	54.8 ± 13.1	.2
Age at diagnosis, y	52.1 ± 11.3	55.5 ± 13.4	.3
Duration of follow-up, y	6.65 [3.4-12.7]	4.5 [2.3-7.1]	.01
Time from onset to diagnostic, mo	8.9 [0.5-22.8]	0.6 [0.1-16.5]	.1
Monoclonal component level at diagnosis ≥5g/L	17 (44.7)	7 (25.9)	.006
Myeloma	4 (10.5)	1 (3.7)	.4
Number of attacks prior to diagnosis	2 [1-4]	2 [1-3]	.1
Severe attacks	1 [1-2]	1 [1-2]	.4
Attacks after diagnosis	38 (100)	9 (33.3)	<.0001
Severe attacks	38 (100)	0 (0)	na
Number of attacks after diagnosis	5 [2-14]	0 [0-1]	na
Severe attacks	2 [1-5]	0 [0-0]	na
Preventive treatments	30 (78.9)	26 (96.3)	.02
Intravenous immunoglobulins	22 (57.9)	26 (96.3)	<.0001
Theophylline	19 (50)	3 (11.1)	.001
Terbutaline	17 (44.7)	5 (18.5)	.035
Thalidomide	5 (13.2)	0 (0)	.07

Values are expressed as n (%), continuous variables as mean ± standard deviation or median [interquartile range].
*Four patients died on their first attack and were not included in the follow-up analysis.
†Onset was defined as the first attack reported.

of patients, over short periods of time, and their efficacy is highly controversial.

CONCLUSION

This study reports on a large cohort of patients with well-defined monoclonal gammopathy-associated systemic capillary-leak syndrome. Five- and 10-year survival rates were 78% and 69%, respectively. Multivariate analysis determined preventive treatment with IVIg as the primary factor associated with survival. These results suggest the use of IVIg as the first-line preventive agent in monoclonal gammopathy-associated systemic capillary-leak syndrome.

ACKNOWLEDGMENTS

The authors thank all the physicians caring for the patients and who referred them to the registry. We also thank the patients for agreeing to participate in our registry.

References

1. Clarkson B, Thompson D, Horwith M, Luckey EH. Cyclical edema and shock due to increased capillary permeability. *Am J Med*. 1960;29(2):193-216.
2. Duron L, Delestre F, Amoura Z, Arnaud L. Syndrome de fuite capillaire idiopathique et formes secondaires : une revue systématique de la littérature. *Rev Méd Interne*. 2015;36(6):386-394 [in French].
3. Atkinson JP, Waldmann TA, Stein SF, et al. Systemic capillary leak syndrome and monoclonal IgG gammopathy; studies in a sixth patient and a review of the literature. *Medicine (Baltimore)*. 1977;56(3):225-239.
4. Kapoor P, Greipp PT, Schaefer EW, et al. Idiopathic systemic capillary leak syndrome (Clarkson's disease): the Mayo clinic experience. *Mayo Clin Proc*. 2010;85(10):905-912.
5. Gousseff M, Arnaud L, Lambert M, et al. The systemic capillary leak syndrome: a case series of 28 patients from a European registry. *Ann Intern Med*. 2011;154(7):464-471.
6. Amoura Z, Papo T, Ninet J, et al. Systemic capillary leak syndrome: report on 13 patients with special focus on course and treatment. *Am J Med*. 1997;103(6):514-519.
7. Druey KM, Greipp PR. Narrative review: the systemic capillary leak syndrome. *Ann Intern Med*. 2010;153(2):90-98.
8. Lambert M, Launay D, Hachulla E, et al. High-dose intravenous immunoglobulins dramatically reverse systemic capillary leak syndrome. *Crit Care Med*. 2008;36(7):2184-2187.
9. Xie Z, Chan EC, Long LM, Nelson C, Druey KM. High-dose intravenous immunoglobulin therapy for systemic capillary leak syndrome (Clarkson disease). *Am J Med*. 2015;128(1):91-95.
10. Abgueguen P, Chennebault JM, Pichard E. Immunoglobulins for treatment of systemic capillary leak syndrome. *Am J Med*. 2010;123(6):e3-e4.
11. Almagro P, Martí JM, Garcia Pascual L, Rodriguez-Carballeira M. Successful treatment of systemic capillary leak syndrome with intravenous immunoglobulins. *Rev Clin Esp*. 2012;212(4):218-219.
12. del Olmo Revuelto MA, Abajo del Álamo C, Santos Pérez MI. [Use of intravenous immunoglobulins in a patient with systemic capillary leak syndrome]. *Med Clin (Barc)*. 2014;142(8):377-378 [in Spanish].
13. Scanvion Q, Lefèvre G, Hachulla E, Hatron P-Y, Lambert M. Subcutaneous immunoglobulin therapy prevents systemic capillary leak syndrome attack. *Am J Med*. 2016;129(7):e77-e78.
14. Zipponi M, Eugster R, Birrenbach T. High-dose intravenous immunoglobulins: a promising therapeutic approach for idiopathic systemic capillary leak syndrome. *BMJ Case Rep*. 2011;2011. http://dx.doi.org/10.1136/bcr.12.2010.3599.

15. Shin JI, Lee JS. Beneficial effect of intravenous immunoglobulins on systemic capillary leak syndrome in patients with monoclonal gammopathy. *Crit Care Med*. 2009;37(2):795, author reply 795.
16. Gousseff M, Amoura Z. [Idiopathic capillary leak syndrome]. *Rev Med Interne*. 2009;30(9):754-768 [in French].
17. Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2002;346(8):564-569.
18. Therneau TM, Kyle RA, Melton LJ, et al. Incidence of monoclonal gammopathy of undetermined significance and estimation of duration before first clinical recognition. *Mayo Clin Proc*. 2012;87(11):1071-1079.
19. Kawabe S, Saeki T, Yamazaki H, Nagai M, Aoyagi R, Miyamura S. Systemic capillary leak syndrome. *Intern Med*. 2002;41(3):211-215.
20. Droder RM, Kyle RA, Greipp PR. Control of systemic capillary leak syndrome with aminophylline and terbutaline. *Am J Med*. 1992;92(5):523-526.
21. Tahirkheli NK, Greipp PR. Treatment of the systemic capillary leak syndrome with terbutaline and theophylline. A case series. *Ann Intern Med*. 1999;130(11):905-909.
22. Xie Z, Ghosh CC, Patel R, et al. Vascular endothelial hyperpermeability induces the clinical symptoms of Clarkson disease (the systemic capillary leak syndrome). *Blood*. 2012;119(18):4321-4332.
23. Lesterhuis WJ, Rennings AJ, Leenders WP, et al. Vascular endothelial growth factor in systemic capillary leak syndrome. *Am J Med*. 2009;122(6):e5-e7.
24. Xie Z, Chan E, Yin Y, et al. Inflammatory markers of the systemic capillary leak syndrome (Clarkson Disease). *J Clin Cell Immunol*. 2014;5:1000213.
25. Fardet L, Kerob D, Rybojad M, et al. Idiopathic systemic capillary leak syndrome: cutaneous involvement can be misleading. *Dermatology (Basel)*. 2004;209(4):291-295.
26. Dhir V, Arya V, Malav IC, Suryanarayanan BS, Gupta R, Dey AB. Idiopathic systemic capillary leak syndrome (SCLS): case report and systematic review of cases reported in the last 16 years. *Intern Med*. 2007;46(12):899-904.

Funding: None.

Conflict of Interest: None.

Authorship: MPdC, MG, WM, and ZA designed the study, and collected and analyzed data. MPdC and ZA wrote the article. All other members of the EurêClark study group took care of patients, referred them to the EurêClark coordinating center, and participated in data collection.

Requests for reprints should be addressed to Zahir Amoura, MD, MSc, Service de Médecine Interne 2, Institut E3M, Hôpital La Pitié−Salpêtrière, 47−83, bd de l'Hôpital, Paris 75651 Cedex 13, France.

E-mail address: zahir.amoura@aphp.fr

SUPPLEMENTARY DATA

Supplementry text accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2017.05.023.