

Risk factors for death and the 3-year survival of patients with systemic sclerosis: the French ItinérAIR-Sclérodermie study

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Objectives. This longitudinal study investigated survival, risk factors and causes of death in the multicentre ItinérAIR-Sclérodermie cohort of patients with SSc without severe pulmonary fibrosis or severe left heart disease at baseline.

Methods. At 3-year follow-up, vital status was obtained from investigators or French national death records. Causes of death were classified as SSc-related or otherwise. Data were censored at 37 months, time of death or loss to follow-up, whichever was earlier. Survival was estimated using the Kaplan–Meier method. Multivariate survival analyses were conducted using the Cox model.

Results. In total, 546 patients were followed for a median duration of 37 months, representing 1547 patient-years. At baseline, the majority of patients were female, with lcSSc, mean age 54.9 ± 13.0 years and mean duration of SSc of 8.8 ± 8.1 years. In total, 47 patients died, giving a 3-year survival of 91.1% and cumulative mortality of 3.04 deaths per 100 patient-years; 17 deaths (32.2%) resulted from pulmonary arterial hypertension (PAH) and eight (17.1%) from cancer. Of the 47 patients with PAH at baseline, 20 died during follow-up, giving a 3-year survival of 56.3%. In a multivariate analysis, PAH [hazard ratio (HR) 7.246], age at first symptom (HR 1.052), duration of SSc (HR 1.047 per year) and Rodnan skin score (per one point) (HR 1.045) were associated with increased mortality.

Conclusion. This 3-year study observed survival and mortality estimates that were comparable with previous reports. PAH increased the HR for mortality in patients with SSc, justifying yearly echocardiographic screening.

KEY WORDS: Systemic sclerosis, Survival, Pulmonary arterial hypertension, Pulmonary hypertension.

Introduction

During recent decades, the survival of patients with SSc has improved considerably, largely as a result of improvements in the treatment of SSc renal crisis. Changes have also been observed within this time period in the pattern of deaths attributed to organ-specific manifestations of SSc. Steen and Medsger [1] recently documented these changes in causes of mortality in SSc patients from a single centre during the past 25 years. The 10-year survival rate was observed to improve steadily from 54% to 66% between the 1980s and the current era [1]. In addition, the frequency of deaths due to renal crisis has decreased dramatically, with pulmonary fibrosis and pulmonary arterial hypertension (PAH) having emerged as the current leading causes of mortality [1].

We recently conducted a prospective, multicentre study to estimate the prevalence of PAH in SSc patients without severe pulmonary fibrosis or severe left heart disease [2]. Our screening programme estimated the frequency of PAH to be 7.85% in a population of 599 patients. We also demonstrated that a screening algorithm based on dyspnoea, Doppler echocardiographic evaluation of the velocity of tricuspid regurgitation (VTR) and right-

heart catheterization enabled early detection of PAH at a mild stage [2]. A 3-year longitudinal follow-up of this cohort was planned and conducted in order to estimate survival, to describe causes of death and to individualize factors associated with survival in patients with SSc. The results of this study are reported here.

Methods

Patients

A total of 21 French university hospitals experienced in the management of SSc participated in the ItinérAIR-Sclérodermie study [2]. One centre did not participate in the collection of the 3-year follow-up data; therefore, the present study involved 20 centres. Patients with SSc who fulfilled the ACR criteria who visited participating hospitals between September 2002 and July 2003 for regular follow-up visits were invited to enter the study [2, 3]. Patients were classified as having lcSSc or dcSSc according to Le Roy *et al.* [4]. Since the ItinérAIR-Sclérodermie study was primarily implemented for the investigation of PAH, for the sake of homogeneity, patients who were considered to be more prone to developing other types of pulmonary hypertension (PH) were not enrolled. These included patients with severe left-heart disease at baseline (defined as left ventricular ejection fraction <45%, mitral or aortic regurgitation >grade 2, mitral area <1.5 cm² or aortic area <1 cm²) who were considered to be at risk of developing post-capillary PH. Patients with severe restrictive lung disease at baseline [defined as forced vital capacity (FVC) or total lung capacity (TLC) <60% of the predicted] who were considered to be at risk of developing PH associated with severe pulmonary fibrosis were also excluded.

Data collected at baseline

Patient demographics, SSc characteristics (including history since first symptoms and occurrence of RP), Rodnan skin score [5] and signs and symptoms evocative of PAH were collected at baseline.

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Pulmonary function testing to measure TLC, FVC, forced expiratory volume in 1 (FEV₁)/FVC, diffusing capacity for carbon monoxide (DL_{CO}), and blood gases were also repeated at baseline, unless performed within the previous 6 months. The presence of ANAs, including anti-topo-isomerase and anti-centromere antibodies was investigated.

Data collected at follow-up visits

Data pertaining to cardiovascular risk factors (tobacco consumption, diabetes mellitus, hypertension, hypercholesterolaemia), Rodnan skin score and presence or absence of digital ulcers were collected. Each patient underwent a 12-lead electrocardiogram. Pulmonary function tests were recommended to be repeated every year. If a patient died since the last performed visit, the date and cause of death were collected.

Patients lost to follow-up

Each participating physician was asked to make an effort to document the vital status of the patient both annually and at the end of the 3-year follow-up period. If no contact with patients could be established, a query was sent to the registry of births and deaths at their regional city hall.

Diagnosis of PAH

Patients with a confirmed diagnosis of PAH were identified at baseline. The remaining patients were screened for PAH at baseline and on a regular basis during the follow-up period using an algorithm that included evaluation of dyspnoea based on the modified New York Heart Association functional class and Doppler echocardiographic evaluation of VTR [2]. Diagnosis of PAH was confirmed using right heart catheterization (RHC). PAH was defined as a mean pulmonary arterial pressure ≥ 25 mmHg at rest or ≥ 30 mmHg during exercise, with mean pulmonary arterial wedge pressure < 15 mmHg on RHC.

Statistical methods

Statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC, USA). Data are expressed as mean (s.d.) for continuous variables and as number (percentages) for categorical variables. The follow-up duration was determined to be the time elapsed from entry into the study until the date of last news (last visit or death). Data were censored at 37 months, the time of death or loss to follow-up, whichever was earlier. The duration between study entry and last news was plotted using the Kaplan–Meier method. The cumulative incidence of deaths

was calculated as the ratio of the number of deceased patients over the duration of follow-up expressed in patient-years. The CI of the cumulative incidence was calculated by dividing the Gaussian confidence interval of the number of events by the duration of follow-up expressed in patient-years.

Causes of death were classified as ‘SSc-related’ (SSc renal crisis, PAH, pulmonary fibrosis, gastrointestinal, cardiac and multi-organ failure) or ‘non SSc-related’ (cancer, atherosclerotic, cardiovascular and cerebrovascular disease, infection, sudden death, other) or unknown, by the same method as Steen and Medsger [1]. The association between centre or baseline characteristics and the risk of mortality were explored using univariate and multivariate analyses. For each test, hazard ratios (HRs) and their 95% CIs were identified. Variables associated with outcome at $P < 0.20$ were included in a multivariable Cox model with the forward stepwise option. The significance level for removing a variable from the model was set at $P > 0.05$. For interval-independent variables, the assumption that the logarithm of HR changed linearly with each unit change was assessed graphically. The assumption that HR was constant over time was assessed by proportionality test using time-dependent derived variables for each variable retained in the model. Furthermore, for binary variables, log-minus-log survival was plotted showing a constant difference between strata. Goodness of fit was assessed by likelihood ratio. Deviance residuals were plotted against each variable retained in the model. Martingale residuals and deviance residuals were plotted against the linear predictor scores.

Ethical approval

The study was approved by an independent review board (Comité de Protection des Personnes of Lille, France). Informed consent was obtained from every patient at study entry and at each follow-up visit. Analysis of data was conducted independently under the supervision of a multidisciplinary scientific committee.

Results

Patient demographics and baseline characteristics

From a total of 599 patients enrolled in the original ItinAIR–Sclérodermie cohort, 550 patients agreed to participate in the 3-year follow-up. One centre and four patients from the remaining 20 centres declined to participate; a further four patients were lost to follow-up. Therefore, the analysis of survival was conducted on 546 patients.

Baseline characteristics of these patients are summarized in Table 1. Despite the exclusion from the study of patients with

TABLE 1. Characteristics of patients at baseline

Parameter	All patients (n = 546)	Patients who died during follow-up (n = 47)	Patients alive at end of follow-up (n = 499)
Mean age \pm s.d., years	54.9 \pm 13.0	62.8 \pm 14.0	54.1 \pm 12.6
Male, n (%)	87 (15.9)	15 (31.9)	72 (14.4)
Mean age at first non-RP symptom \pm s.d., years	46.0 \pm 13.7	52.9 \pm 15.0	45.4 \pm 13.4
Mean age at SSc diagnosis \pm s.d., years	47.8 \pm 13.7	54.6 \pm 15.0	47.2 \pm 13.4
Mean time since first onset of RP \pm s.d., years	14.6 \pm 12.4	14.9 \pm 11.7	14.6 \pm 12.5
Mean time since first non-RP symptom \pm s.d., years	8.8 \pm 8.1	9.9 \pm 8.4	8.7 \pm 8.1
dcSSc, n (%)	150 (27.5)	21 (44.7)	129 (25.9)
Mean Rodnan skin score \pm s.d.	13.2 \pm 10.6	19.6 \pm 14.0	12.6 \pm 10.0
Moderate dyspnoea (NYHA FC II), n (%)	141 (25.8)	18 (38.3)	123 (24.6)
Severe dyspnoea (NYHA FC III–IV), n (%)	59 (10.8)	17 (36.2)	42 (8.4)
VTR ≥ 2.8 m/s, n (%)	69 (12.6)	15 (31.9)	54 (10.8)
PAH at baseline, n (%)	47 (8.6)	20 (42.6)	27 (5.4)
Basal pulmonary fibrosis, n (%)	86 (15.8)	14 (29.8)	72 (14.4)
Prior digital ulcer(s), n (%)	280 (51.3)	26 (55.3)	254 (50.9)
TLC $< 80\%$ of the predicted value, n (%)	79 (16.6) ^a	14 (43.8) ^b	65 (14.6) ^c
FVC $< 80\%$ of the predicted value, n (%)	71 (14.1)	14 (29.8)	57 (11.4)
DL _{CO} $< 60\%$ of the predicted value, n (%)	122 (25.0) ^d	16 (55.2) ^e	106 (23.0) ^f
Anti-topoisomerase antibodies, n (%)	136 (28.0) ^g	14 (40.0) ^h	122 (27.1) ⁱ
Anti-centromere antibodies, n (%)	234 (51.9) ^j	21 (61.8) ^k	213 (47.1) ^l

^an = 477; ^bn = 32; ^cn = 445; ^dn = 489; ^en = 29; ^fn = 460; ^gn = 486; ^hn = 34; ⁱn = 452; ^jn = 486; ^kn = 35; ^ln = 451. NYHA FC: New York Heart Association functional class.

severe pulmonary function impairment, 15.8% of the patients exhibited basal pulmonary fibrosis at baseline; TLC and FVC were observed to be between 60% and 80% of the predicted values in 16.6% and 14.1% of the patients, respectively. DL_{CO} at baseline was <60% of the predicted values in 25% of the patients.

Survival and causes of death

The median duration of follow-up was 37 months, representing a total of 1547 patient-years. A total of 47 patients died during the follow-up period, giving a cumulative mortality rate of 3.04 deaths per 100 patient-years (95% CI 2.17, 3.90). The 3-year Kaplan–Meier estimate of survival was 91.1% in the whole population. When stratified according to the absence or presence of PAH, observed survival estimates were 94.4% in patients without PAH at baseline and 56.3% in patients with PAH at baseline (Fig. 1).

Causes of death were SSc-related in 24 patients (51.1% of all causes of death; Table 2). Eight patients died of cancer with all except one patient having a form of intrathoracic cancer: four patients died from lung cancer, one from pleural cancer, one from a mediastinal tumour, one from pulmonary metastases of an unknown primary cancer and one died from breast cancer. Six of these patients were never smokers and one had ceased smoking some years previously. The two leading causes of death were PAH and cancer, which accounted for 32.2% and 17.1% of deaths, respectively (42.5% and 20.5%, respectively for known causes of death). Renal crisis accounted for 6.4% of the deaths (7.7% for known causes of death).

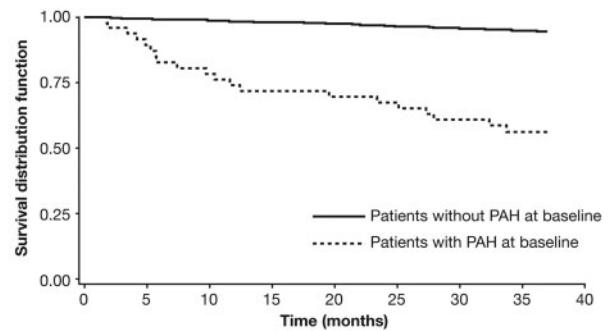
Associations between baseline characteristics and mortality

Results of univariate analyses are given in Table 3. Baseline measurements of DL_{CO} and VTR were strongly associated with survival. The 3-year Kaplan–Meier survival estimate was 96.3% among patients with baseline DL_{CO} >60% of the predicted values *vs* 87.4% among patients with baseline DL_{CO} <60% of the predicted values ($P < 0.0001$). Similarly, the 3-year Kaplan–Meier survival estimate was 95.5% among patients with VTR <2.8 m/s *vs* 77.5% among patients with VTR ≥2.8 m/s ($P < 0.0001$). Centre was not associated with outcome (data not shown).

Following a multivariate analysis, the presence of PAH [HR 7.246 (95% CI 4.000, 13.158)], age at first non-RP symptom [HR 1.052/year (95% CI 1.025, 1.080)], duration of SSc [HR 1.047/year (95% CI 1.008, 1.087)] and Rodnan skin score (per one point) [HR 1.045 (95% CI 1.023, 1.066)] were observed to be significant predictive factors for mortality (Table 4). Neither SSc subtype nor the extent of dyspnoea was identified by this technique to be associated with mortality. DL_{CO} was not available for all patients at entry and was therefore not investigated in the multivariate analysis. A VTR ≥2.8 m/s was introduced in a further model in lieu of PAH. In this model, VTR ≥2.8 m/s and Rodnan skin score were both associated with a higher risk of mortality [HR 5.368 (95% CI 2.62, 11.01) and 1.04 (95% CI 1.01, 1.09), respectively].

Discussion

This study was a 3-year follow-up of a large, multicentre cohort of patients with SSc in France and was designed to investigate the survival rates, causes of death and factors associated with survival in SSc. A total of 546 patients with SSc and without severe pulmonary fibrosis or left heart disease at baseline were followed for a median duration of 37 months, representing 1537 patient-years. We have estimated the 3-year Kaplan–Meier survival to be 91.1% and the cumulative mortality of these patients to be 3.04 deaths per 100 patient-years. The roles of PAH and cancer among the leading causes of death were also confirmed. A VTR ≥2.8 m/s and DL_{CO} <60% of predicted values at baseline were observed to be strongly associated with poor prognosis. A multivariate analysis illustrated that PAH was a major risk factor for death, with an HR of 7.246.



		M0–M6	M6–M12	M12–M18	M18–M24	M24–M30	M30–M36	M36–M37
Patients without PAH at baseline	Patients at risk (N)	499	493	481	478	466	453	390
	Censored	2	7	1	6	8	59	27
	Events	4	5	2	6	5	4	1
Patients with PAH at baseline	Patients at risk (N)	47	38	34	33	31	28	21
	Censored	1	0	0	0	0	5	1
	Events	8	4	1	2	3	2	0

FIG. 1. Kaplan–Meier estimate of survival vs time stratified according to PAH at baseline.

TABLE 2. Causes of death observed in the total population

Causes of death, n (%)	All patients (n = 546)
Total number of deaths	47 (8.6)
Scleroderma-related causes of death	24 (4.4)
PAH	17
Pulmonary fibrosis	2
Gastrointestinal	2
Renal crisis	3
Non-scleroderma-related causes of death	23 (4.2)
Cancer	8
Infection	4
Cardiovascular or cerebrovascular atherosclerosis	2
Other cause	2
Unknown cause	7

TABLE 3. Risk of death associated with baseline characteristics (univariate analysis)

Parameter	Univariate analysis HR (95% CI)	<i>p</i>
Male sex	2.60 (1.41, 4.81)	0.002
Age (per year)	1.06 (1.03, 1.09)	<0.0001
Age at first non-RP symptom (per year)	1.04 (1.02, 1.07)	0.0003
Time since first SSc sign (per year)	1.01 (0.98, 1.05)	0.39
dcSSc	2.21 (1.24, 3.92)	0.007
Rodnan skin score (per 1 point)	1.04 (0.94, 0.98)	<0.0001
Moderate dyspnoea (NYHA FC II)	2.45 (1.29, 4.67)	0.007
Severe dyspnoea (NYHA FC III–IV)	4.15 (1.93, 8.93)	0.0003
VTR ≥2.8 m/s	5.74 (2.81, 11.75)	<0.0001
PAH at baseline	10.41 (5.81, 18.52)	<0.0001
DL _{CO} <60% of predicted (per 1%)	1.05 (1.03, 1.08)	<0.0001
TLC (percentage of predicted)	95 (93, 98)	<0.0001
FVC (percentage of predicted)	96 (94, 98)	<0.0001
Anti-topoisomerase antibodies	0.58 (0.30, 1.14)	0.12
Anti-centromere antibodies	0.56 (0.28, 1.11)	0.10

NYHA: New York Heart Association functional class.

TABLE 4. Risk of mortality associated with baseline characteristics (multivariate analysis)

Parameter	S.E.	χ^2	<i>P</i>	HR (95% CI)	
Age at first non-RP symptom, years	0.051	0.013	14.440	0.0001	1.052 (1.025, 1.080)
Duration of SSc	0.046	0.019	5.722	0.016	1.047 (1.008, 1.087)
PAH at baseline	1.979	0.302	42.909	<0.0001	7.246 (4.000, 13.158)
Rodnan skin score (per 1 point)	0.0436	0.0104	17.392	<0.0001	1.045 (1.023, 1.066)

The 5-year survival of patients with SSc has been reported to lie between 34% and 73%, with mortality estimated to be four times greater than that of the general population [6]. More recent reports, however, have suggested that survival may be greater than that previously estimated (~65–70% at 10 years) [1, 7, 8]. Such an improvement in prognosis may result from earlier diagnosis, a multidisciplinary approach to treatment of the disease, a greater awareness of expert opinion in the treatment of patients, and the use of angiotensin-converting enzyme inhibitors in the treatment of SSc renal crisis in the current era. The patients in the present study were enrolled by 20 scleroderma expert centres in France and reflect a SSc population without severe lung fibrosis or severe left heart disease at entry. The cumulative mortality observed in this study of 3.04 deaths per 100 patient-years is in accordance with recent reports and is very close to the rate of 2.49 deaths per 100 patient-years observed in a Spanish study [7].

The proportion of deaths attributed to SSc observed in this study (51.1%) is highly comparable with the 50% observed by Steen and Medsger [1], despite the present study having excluded patients with severe lung fibrosis at entry. The main cause of death in our study was PAH, with a cumulative mortality of 19.6 deaths per 100 patient-years in the 47 patients with PAH known or screened at entry. This observation supports the increasing impact of this complication on the survival of patients with SSc. The poor prognosis of SSc patients with PAH emphasizes the need for physicians to follow international and European guidelines, which recommend the systematic, annual screening of SSc patients for PAH using Doppler echocardiography [9, 10]. Although SSc renal crisis is no longer a leading cause of death, three out of 546 patients died as a result of this manifestation.

Among the non-SSc-related causes of death, cancers—particularly lung cancer—appear to play a major role, an observation that has been reported previously [1, 8]. Tobacco use has been reported to increase the risk of lung cancer in SSc patients by 7-fold [11]. It should be noted, however, that none of the four patients in this study who died from lung cancer were current or former smokers. Among the four patients who died from lung cancer in the present study, basal lung fibrosis was present in only one. Previous studies have suggested that patients with SSc are at an increased risk of cancer *vs* the general population [12, 13], and the role of pulmonary fibrosis in lung cancer is still subject to debate. Our results support the monitoring of SSc patients for lung cancer. The cessation of tobacco use and limitation of exposure to X-rays may also be beneficial.

Among factors associated with survival, SSc subtype, DL_{CO} and overall VTR should be highlighted. Whereas dcSSc and Rodnan skin scores were associated with poorer survival in univariate analysis, only Rodnan skin score was retained in the multivariate Cox model. This may have resulted from our decision to exclude patients with severe lung disease. Our data also demonstrate that a DL_{CO} <60% of predicted values at baseline is associated with increased mortality. In our population, a severely altered DL_{CO} may indicate significant pulmonary vascular disease, since patients with severe interstitial lung disease were excluded at baseline.

Our findings also suggest that VTR can be used to identify patients at greater risk of mortality. In a screening programme for PAH performed in patients with sickle cell disease, Gladwin *et al.* [14] observed that mortality was higher in patients with a VTR >2.5 m/s. We found no difference in survival between patients with a VTR <2.5 m/s *vs* those with VTR within the 2.5–2.8 m/s range. Conversely, patients with a VTR ≥2.8 m/s were observed to exhibit poorer prognosis with an HR of 5.74 in univariate analysis. When introduced in the multivariate model in lieu of PAH, VTR ≥2.8 m/s was a strong predictor of death with an HR of 5.37. Our observations support the hypothesis that a VTR threshold of ≥2.8 m/s is more accurate than one of ≥2.5 m/s in predicting survival in SSc patients. However, this VTR threshold

is not specific to PAH, as post-capillary PH can also be diagnosed by RHC even in the absence of left ventricular abnormalities on echocardiography [2, 15].

While this study provides important observations, there are a number of theoretical limitations that must be acknowledged. The exclusion at entry of patients with severe lung fibrosis or with severe left heart disease may have led to an underestimation of SSc-related cause of death. Another potential limitation is that one of the centres from our original ItinérAIR-Sclérodermie study did not participate in the 3-year follow-up, and that an unknown pool of SSc patients followed by non-specialist centres may also exist. In addition, there may be differences in the referral pattern between the participating centres.

In conclusion, we observed a 3-year Kaplan–Meier estimate for survival of 91.1% in our population of SSc patients, and of 56.3% in patients with PAH at baseline. The cumulative mortality rate of patients with SSc observed in our multicentre cohort was 3.04 deaths per 100 patient-years, despite the exclusion of SSc patients with severe pulmonary fibrosis or severe left heart disease at baseline. Our observations have underlined the leading roles of PAH and cancer in mortality among patients with SSc. The development of PAH was observed to increase the HR for mortality in patients with SSc by more than 7-fold during a 3-year period. We consider that the poor prognosis of SSc patients with PAH justifies a yearly echocardiographic screening.

Rheumatology key messages

- The 3-year Kaplan–Meier survival estimate of 91.1% in the ItinérAIR-Sclérodermie population is reduced to 56.3% among patients with baseline PAH.
- A Doppler echocardiographic VTR ≥2.8 m/s is a strong predictor of death.

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Disclosure statement: V.G. is a full-time employee (as Medical Director) of Actelion Pharmaceuticals France, a pharmaceutical company manufacturing bosentan, a treatment of PAH. However, as this study is of epidemiological nature, they feel there was no conflict of any sort in conducting, interpreting and reporting of the results of this study. P.C. has received honoraria (<€10 000) as a member of the Scientific Committee of Actelion Pharmaceuticals France on Scleroderma. L.G. is a consultant for and has received fees and grants from Actelion Pharmaceuticals France. All other authors have declared no conflicts of interest.

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Appendix

List of ItinAIR-Sclérodemie investigators in alphabetical order by city

Bordeaux 1: Jean-François Viillard, Marie-Sylvie Doutre, Thierry Schaeverbeke, Marc-Alain Billès, Patricia Réant and Claire Dromer; Bordeaux 2: Joël Constans, Philippe Gosse and

Philippe Lemetayer; Clamart, Antoine-Béclère: Marc Humbert, Olivier Sitbon, Xavier Jaïs, Abdul Monem Hamid, Vincent Ioos and Gérard Simonneau; Créteil, Henri-Mondor: Anne Cosnes and Cécile Roiron; Grenoble: Patrick Carpentier, Jean-Luc Cracowski, Carole Saurier, Muriel Salvant, Carole Schwebel and Christophe Pison; Lille: Eric Hachulla, Pierre-Yves Hatron, David Launay, Viviane Queyrel, Marc Lambert, Sandrine Morell-Dubois, Hilaire Charlanne, Pascal de Groote and Nicolas Lamblin; Lyon: Jacques Ninet, Fadi Jamal, Geneviève Dérumeaux and Jean-Yves Bayle; Marseille: Jean-Robert Harle, Frédérique Returnaz, Gilbert Habib, Sébastien Renard and Martine Reynaud-Gaubert; Nancy: Daniela Cirstea, Jean-Dominique de Korwin, Christine Suty-Selton and François Chabot; Nantes: Christian Agard, Mohamed Hamidou, Jean-Pierre Gueffet, Patrice Guérin, Erwan Bressolette and Alain Haloun; Paris, Bichat: Thomas Papo, Olivier Lidove, Catherine Picard-Dahan and David Messika-Zeitoun; Paris, Cochin 1: André Kahan, Yannick Allanore, Laure Cabanes and Christian Spaulding; Paris, Cochin 2: Loïc Guillevin, Luc Mouthon and Alice Berezné; Paris, La Pitié-Salpêtrière: Camille Francès, Salim Trad, Emmanuel Molinari, Anne-Claude Koeger and Dominique de Zuttere; Paris, Saint-Antoine: Jean Cabane, Kiet Phong Tiev, Stéphanie Ederhy, Nadjib Hammoudi and Mohamed Ziani; Paris, Saint-Joseph: Isabelle Lazareth, Ulrique Michon-Pasturel, Yara Antakly-Hanon and Jacques Serfati; Paris, Saint-Louis: Dominique Farge and Suzanne Ménasché; Rennes: Patrick Jégo, Jacqueline Chevrant-Breton and Marcel Laurent; Strasbourg: Jean Sibilia, Hélène Petit and Ari Chaouat; Toulouse: Daniel Adoue, Nathalie Blot-Souletie and Bruno Degano; and Tours: Elisabeth Diot, Laurent Machet, Frédéric Patat, Christian Marchal and Cédric Giraudeau.