Nephrol Dial Transplant (2000) 15 [Suppl 4]: 2–7

Nephrology
Dialysis
Transplantation

Patients and methods

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Introduction

The European Survey on Anaemia Management (ESAM) was designed as a prospective, 6-month follow-up observational survey. The most common dialysis parameters and all the data regarding anaemia management were included. The ESAM questionnaires were completed at baseline and each subsequent month, for a total of 6 months. They followed guidelines 1–18 of the European Best Practice Guidelines (EBPG) with specific questions related to the EBPG recommendations. Both haemodialysis and peritoneal dialysis patients were included in the survey and were enrolled over a 2-month period. In addition to demographic information, data on primary renal disease, concomitant pathology, initiation of epoetin and dialysis treatment, iron monitoring and supplementation, concomitant therapies, epoetin resistance and adverse effects were collected. A database was created, and the data were screened for possible errors and omissions. The statistical analyses used are described in each section of the ESAM.

Patients

Patients with end-stage renal failure treated with haemo- or peritoneal dialysis from 14 Western European countries were enrolled in this survey. When mandated by individual country requirements, bioethics review committees approved the study. During the enrolment period, participating centres were asked to select a randomized sample of 30% of their 'Monday dialysis' patients (with the exception of France and Germany, where the sampling target was reduced to 20% due to the proportionately larger population).

The total number of patients analysed was 14 527, which represents nearly 10% of the participating countries dialysis population [1]. The proportion of patients treated with haemodialysis and peritoneal dialysis was also similar to that in Europe as a whole. Of the total patient population, 13 121 (90.3%) were on haemodialysis and 1406 (9.7%) were on peritoneal dialysis. Table 1 summarizes the number of patients by country. France and Germany provided the largest proportion of the total sample (30.2 and 27.1%, respectively) which reflects the size of their national populations. France enrolled 27.1% of the haemodialysis patients and 26.5% of the peritoneal dialysis patients, while Germany provided 33.3% of haemodialysis patients. Italy also provided a large proportion of the peritoneal dialysis patients (25.7%) but enrolled few ($n=8$) haemodialysis patients due to a recently completed survey in this country. (Portugal chose not to participate in the ESAM because of the level of effort required for development of their nationwide renal registry. In the UK, data were contributed to the ESAM by the Renal Anaemia Audit (RAA) programme. Unfortunately, the match between RAA and the ESAM was not close enough to allow the UK's data to be included in the work being reported here.) It is important to recognize, however, that sample contributions by smaller countries contributed to the breadth of the sample and to the overall strength of the ESAM data. Although this survey may lack the scientific rigour and statistical validity of a randomized clinical trial, the large sample size provides significant statistical power for the investigation.

The mean age of the patients was 61 years and the median age, 64 years. Interestingly, there were more dialysis patients between 81 and 90 years of age than between 21 and 30 years. There was little variation in the mean age of the patients in different countries, from 56 years in Denmark to 64 years in Sweden. The median age was as low as 59 years in Denmark but was 67 years in Belgium, Luxembourg and Sweden (Table 2).

The most frequent cause of end-stage renal disease (ESRD) was chronic glomerulonephritis (25.5%) followed by diabetic nephropathy (17.7%), renovascular disease (13.9%) and tubulo-interstitial disease (13.3%) (Table 3). There were only a few diabetic patients treated with peritoneal dialysis.

Diabetes was much less prevalent in the patients included in ESAM than in other dialysis patient populations, such as the USRDS (33.2%) [2]. In the latter database, hypertension was the primary renal disease in 24%, and glomerulonephritis was present in 17.2%. In the ESAM population, the prevalence of diabetic nephropathy was somewhat variable among the different countries: from 8.7% in Italy and 9.3% in Norway, to 24.5% in Germany and 25.4% in Finland. Renovascular disease also showed wide variability: from

Table 1. Patient sample sizes by country, type of dialysis

Country	*n*	ESAM sample				Estimated total dialysis patients (*n*)	ESAM as % of total
		Haemodialysis		Peritoneal dialysis			
		n	%	*n*	%		
Austria	686	614	4.7	72	5.1	2840	24.1
Belgium and Luxembourg	1095	1044	8.0	51	3.6	4735	23.1
Denmark	221	153	1.2	68	4.8	n.a.	
Finland	321	243	1.9	78	5.5	1000	32.1
France	3934	3561	27.1	373	26.5	27 000	14.6
Germany	4384	4366	33.3	18	1.3	52 000	8.4
Greece	1351	1298	9.9	53	3.8	7500	18.0
Italy	369	8	0.1	361	25.7	38 500	1.0
Netherlands	427	304	2.3	123	8.7	4700	9.1
Norway	162	140	1.1	22	1.6	540	30.0
Spain	692	657	5.0	35	2.5	18 400	3.8
Sweden	556	445	3.4	111	7.9	2700	20.6
Switzerland	329	288	2.2	41	2.9	2100	15.7
Total	14 527	13 121	100.2	1406	99.9	162 015	9.0

Table 2. Patient sample sizes: country by age of patient

Country	*n*	Mean	Median	SD
Austria	686	59	61	15.5
Belgium and Luxembourg	1095	63	67	14.9
Denmark	221	56	59	16.3
Finland	321	57	60	15.5
France	3934	62	66	16.1
Germany	4384	61	64	14.4
Greece	1351	59	62	14.3
Italy	369	60	63	16.1
Netherlands	427	58	60	16.1
Norway	162	62	66	16.4
Spain	692	60	64	15.3
Sweden	556	64	67	14.5
Switzerland	329	60	64	15.6
Total	14 527	61	64	15.3

6.3% in Finland and 8.4% in Germany, to 22.3% in Italy and 24.5% in Norway. However, these differences should be viewed with caution because of the variability of undefined disease as a cause of ESRD. Hypertension was present in two-thirds of the total ESAM population and coronary artery disease in one-quarter; these were the most frequently associated diseases (Table 4).

Eighty percent of the patients were treated with renal replacement therapy for 5 years or less (Table 5). Forty percent of the patients had been treated for <2 years, and 20% for <1 year. This is consistent with the 33% annual patient turnover rate documented in previous EDTA Registry reports.

Of the entire sample, 48.2% had been on epoetin therapy for 24 months or more (Table 6). On average, patients had been receiving epoetin therapy for 30.0 months (SD = 26.3) at the time of enrolment in the survey (Table 7).

As a general conclusion, it would appear that the sample included in the ESAM is representative of the European dialysis population regarding at least age, primary renal disease and co-morbidity.

Design

The ESAM used a descriptive, prospective design to examine anaemia management practices in both haemodialysis and peritoneal dialysis patients who were receiving epoetin therapy. Patients were enrolled during a 2-month period (September–October 1998), and were then followed for 5 months beyond their month of enrolment. Data for month 1 were collected retrospectively and data for months 2–6 prospectively. Patients were monitored for the entire 6-month period, whether or not epoetin therapy was continued for the duration of the study.

Table 8 summarizes the data collected at the time of enrolment into the survey. Key variables of interest include demographics, the primary cause of chronic renal failure, concomitant pathologies, first dialysis parameters and initiation of epoetin therapy, as well as the frequency of monitoring anaemia and iron status. Additional data were collected during the month of enrolment (month 1) and for the subsequent 5 months: selected clinical data and dialysis parameters, laboratory measurements, epoetin and iron therapy, vitamin supplementation and concomitant therapies (Tables 9 and 10). Clinical events or complications that occurred in the previous month were recorded in months 2–6. All data were collected by medical or other health care professionals.

Data collection

Data were collected using pre-printed case report forms. Each case report form was seven pages in length; each page produced a duplicate via pressure-sensitive paper. These forms were given to each parti-

Table 3. Patient sample sizes: prevalence of aetiology of chronic renal failure by country

Country	*n*	Chronic glomerulonephritis Valid %	Diabetic nephropathy Valid %	Reno-vascular disease Valid %	Tubulo-interstitial disease Valid %	Polycystic kidney disease Valid %	Hereditary renal disease Valid %	Failed renal transplant Valid %	Multiple myeloma Valid %	Undefined Valid %	Missing *n*
Austria	686	24.3	22.4	12.6	9.6	5.8	1.0	3.5	0.6	20.2	2
Belgium and Luxembourg	1095	21.2	16.7	19.4	18.6	7.5	1.7	1.4	1.0	12.4	17
Denmark	221	24.1	22.7	10.2	9.3	8.8	0.5	7.9	0.9	15.7	5
Finland	321	22.4	25.4	6.3	9.9	9.9	2.3	4.3	1.3	18.2	18
France	3934	26.3	12.0	19.1	15.8	7.1	3.6	1.9	1.2	12.9	173
Germany	4384	25.7	24.5	8.4	13.1	6.2	1.8	1.6	0.4	18.3	157
Greece	1351	27.6	14.0	8.9	10.6	6.7	1.5	3.1	0.2	27.3	26
Italy	369	30.4	8.7	22.3	10.4	5.4	2.8	0.8	0.0	19.2	14
Netherlands	427	24.2	13.0	18.8	9.5	8.1	3.4	3.7	1.0	18.3	18
Norway	162	38.4	9.3	24.5	2.6	7.3	2.0	0.0	1.3	14.6	11
Spain	692	22.5	15.1	13.2	16.0	6.1	1.9	2.7	0.6	22.0	16
Sweden	556	23.6	19.5	18.9	6.1	9.4	0.8	5.9	1.4	14.5	44
Switzerland	329	24.8	17.1	11.8	13.7	7.1	2.8	2.5	0.9	19.3	7
Total	14 527	25.5	17.7	13.9	13.3	6.9	2.3	2.3	0.8	17.3	508

Table 4. Prevalence of concomitant pathology

Pathology type	*n*	%
Hypertension	9652	66.4
Coronary artery disease	3693	25.4
Diabetes mellitus type II	2207	15.2
Cardiac failure	2196	15.1
Cardiac arrhythmias	1734	11.9
Hepatitis	910	6.3
Neoplasia	878	6.0
Diabetes mellitus type I	870	6.0
Chronic obstructive pulmonary disease	774	5.3
Chronic infection	540	3.7
Haemoglobinopathies	86	0.6
Total	14 527	

Note: multiple responses were permitted.

Table 5. Length of renal replacement therapy by country

Country	<1 year	1 year	2–5 years	6–10 years	11–20 years	>20 years
Austria	20.8	23.9	44.2	7.2	3.2	0.4
Belgium and Luxembourg	20.3	22.4	40.7	10.9	4.4	1.4
Denmark	20.5	26.9	41.1	8.2	2.3	0.9
Finland	36.1	20.7	36.3	6.6	0.3	0.0
France	17.6	20.3	38.2	12.6	8.9	2.5
Germany	19.1	20.6	41.5	12.8	5.3	0.7
Greece	15.9	19.6	42.9	15.6	5.6	0.3
Italy	26.7	25.3	38.9	6.6	2.5	0.0
Netherlands	22.5	23.4	41.3	8.2	2.9	1.7
Norway	39.1	30.4	28.6	1.2	0.6	0.0
Spain	18.6	24.0	37.0	12.0	7.6	0.9
Sweden	28.3	29.9	35.0	4.6	1.8	0.5
Switzerland	19.1	22.8	42.5	9.1	6.3	0.3
Total	19.8	21.7	40.0	11.5	5.8	1.2

Values are given as a percentage of the country sample.

Table 6. Length of time on epoetin prior to study

	n	Valid %
Less than 3 months	749	5.8
3–5 months	1008	7.8
6–11 months	1940	15.1
12–23 months	2951	23.0
24 months or more	6194	48.2
Total	12 856	99.9

Table 7. Mean/median length of time on epoetin prior to study

n	12 856
Mean (months)	30.0
Median (months)	22
SD (months)	26.3

cipating centre, together with a project handbook including instructions for completing the forms and obtaining the sample. Data collection was launched in September 1998, and the forms were sent monthly to the research office at the Centre for Health Services

Table 8. Variable definitions/units for data collected at enrolment

Variable	Definition/unit of measure
Identification/demographics	
Patient initials	2 or 3 letters to identify the patient
Sex	Male or female
Age	Years
Date of enrolment in the ESAM survey	Day/month/year
Country	
Aetiology of chronic renal failure	If multiple aetiologies, respondents were asked to state only the one that most probably initiated chronic renal failure
Chronic glomerulonephritis	
Diabetic nephropathy	
Renal vascular disease	
Tubular interstitial nephropathy	
Polycystic kidney disease	
Hereditary renal disease	
Post-transplant (after rejection of allotransplant)	
Multiple myeloma	
Undefined	
Concomitant pathology	As concomitant pathology can be multiple, multiple answers were allowed
Hypertension	(Blood pressure $>145/95$ mmHg)
Coronary disease	Yes or no
Cardiac failure	Yes or no
Cardiac arrythmia	Yes or no
Diabetes type I (insulin-dependent)	Yes or no
Diabetes type II (non-insulin-dependent)	Yes or no
Hepatitis	Yes or no
Chronic obstructive pulmonary disease	Yes or no
Neoplasia	Yes or no
Haemoglobinopathy	Yes or no
Chronic infection (inflammatory diseases needing antibiotics)	Yes or no
Transfusion <4 months before inclusion	Yes or no
Dialysis/epoetin	
Date of first dialysis	Month/year
Date of first epoetin use (can be earlier than date of first dialysis)	Month/year
Hb level at start of epoetin therapy	g/dl to one decimal point
Target Hb (haemoglobin level desired for the patient)	g/dl to one decimal point
Monitoring of anaemia and iron status	
Start of therapy (in correction phase)	Frequency of monitoring expressed in weeks
Maintenance therapy definition (after correction phase, when haematocrit is stable)	Frequency of monitoring expressed in weeks

and Nursing Research, Catholic University of Leuven, Belgium, where data were logged in. Data collection was completed in April 1999.

Data management

The data were reviewed manually for errors and omissions by the research team in Leuven. They were then

Table 9. Variable definitions/units for haemodialysis data collected in month 1 and months 2–6

Variable	Definition/unit of measure
Haemodialysis data collected in month 1	
Clinical data	
Dry body weight	At the end of the dialysis session (kg)
Blood pressure	At start of dialysis session (mmHg)
Dialysis parameters	
Hours of dialysis/week	Total number of hours, minutes on dialysis per week ml/min
Blood flow rate (last dialysis)	
Dialysis membranes (last dialysis) (cellulose, cellulose acetate, cellulose triacetate, cellulo-synthetic, polyacrylonitrile, polyamide, polyether carbonate, polysulfone, others)	Type of membrane used (yes or no for each)
Vascular access (last dialysis) (AVF: native or synthetic; catheter access)	Type of vascular access used (yes or no for each)
Biological parameters (to be determined before dialysis)	
Haemoglobin	g/dl to one decimal point (conversion: mmol/l $\times$ 1.611 = g/dl)
Iron parameters (previous month)	
Serum ferritin	µg/l
Transferrin	g/l = (serum iron/TIBC) $\times$ 100
% transferrin saturation	%
% hypochromic red blood cells	%
Serum albumin	g/l
C-reactive protein (CRP)	mg/l
iPTH (last available)	pg/ml
Aluminium level (last available)	µmol/l
Kt/V	[(Urea clearance rate) $\times$ (time on dialysis)]/urea distribution volume
EPO protocol	
Epoetin	Yes, for first month; yes or no in subsequent months
Correction dose (during first 3 months[a])	Yes
Maintenance dose (after 3 months[a])	Yes
Dose/week	IU/kg/week
No. of injections per week	
Injection route	Intravenous (i.v.) or subcutaneous (s.c.)
Iron protocol	
Total daily dose of oral iron supplementation	mg
Total monthly dose of i.v. iron administration	mg
Frequency of dosing	Number of times per month
Type iron i.v. (dextran; gluconate; saccharate; others)	Yes or no for each
Vitamin supplementation	
E, C, D, B_{12}	Yes or no for each
(Note: commercially available polyvitamins given with food were not included)	Weekly dose for each (for vitamin D, oral or i.v. application)
Concomitant therapy (more than one option can be chosen)	
ACE inhibitors (specify)	Yes or no, mg
Ca-channel blockers	Yes where indicated

Table 9. (*Cont.*)

Variable	Definition/unit of measure
Vasodilators	Yes where indicated
Androgen therapy	Yes where indicated
Beta blockers	Yes where indicated
Diuretics	Yes where indicated
Alpha 1 antagonist	Yes where indicated
Angiotensin II receptor antagonist	Yes where indicated
Immunosuppresive drugs	Yes where indicated
L-Carnitine	Yes, mg/week
Haemodialysis: additional data collected in months 2–6	
Clinical events	
Infectious disease (those requiring antibiotics)	Yes where indicated
Bleeding (significant blood loss)	Yes where indicated
Cardiovascular event (new event occurring during last month)	Yes where indicated
Surgery	Yes where indicated
AVF thrombosis	Yes where indicated
Neoplasia onset	Yes where indicated
Renal transplantation	Yes where indicated
Transfer to peritoneal dialysis	Yes where indicated
Transfusions (red cell)	Yes, ml
Transfer to other centre	Yes where indicated
Death (cause of death: cardiovascular, infection, neoplasia, other)	Yes, state precise cause

[a]Correction and maintenance doses originally were defined differently in the handbook. This definition was later altered and analysis has been done on the basis of the new definition The original definition was: correction dose, at start of epoetin therapy; maintenance dose, when Hb was stable for at least 2 months.

scanned electronically and a database was created. The data were edited using a series of domain and consistency edits as prescribed by a panel of clinical experts. Care was taken to ensure that domain edits were defined so as to identify data in error, rather than data not conforming with routine clinical practice.

Two data sets were constructed for analysis purposes; each was structured to maximize statistical power and validity for answering central questions of the study. First, a database was constructed from data made up by cases that had complete haemoglobin and epoetin dose information for all 6 months. This database was used to examine questions related to epoetin dose and haemoglobin, especially when examining time series effects. Secondly, a database was constructed for other analyses from cases that were complete for haemoglobin and epoetin dose information for the first month and for at least one additional month.

Statistical analyses

The analysis of data involved extensive use of descriptive statistics and simple cross-tabulations, together with relevant statistical tests. Both parametric and non-parametric testing was undertaken as warranted by assessments of data distributions. Univariate and multivariate patterns of association were tested, based on results from initial descriptive findings.

Table 10. Variable definitions/units for peritoneal dialysis data collected in month 1 and months 2–6

Variable	Definition/unit of measure
Peritoneal dialysis data collected in month 1	
Clinical data	
Body weight	At most recent consultation (kg)
Blood pressure	At most recent consultation (mmHg)
Type of peritoneal dialysis	
Continuous ambulatory peritoneal dialysis (CAPD)	Yes
Continuous cyclic peritoneal dialysis (CCDP)	Yes
Optimized cyclic peritoneal dialysis (OCPD)	Yes
Intermittent peritoneal dialysis (IPD)	Yes
Nightly intermittent peritoneal dialysis (NIPD)	Yes
Tidal peritoneal dialysis (Tidal PD)	Yes
Total volume per day	ml/day
Biological parameters (to be determined before dialysis)	
Haemoglobin	g/dl (conversion: mmol/l × 1.611 = g/dl)
Iron parameters (determined during previous month)	
Serum ferritin	µg/l
Transferrin	g/l = (serum iron/TIBC) × 100
% transferrin saturation	%
% hypochromic red blood cells	%
Serum albumin	g/l
C-reactive protein (CRP)	mg/l
iPTH (last available)	pg/ml
Aluminium level (last available)	µmol/l
Total weekly Kt/V	Residual Kt/V + peritoneal Kt/V where Kt/V = [(urea clearance rate) × (time on dialysis)]/ urea distribution volume
Creatinine clearance l/week/m^2	l/week/body surface area
EPO protocol	Same as haemodialysis (Table 9)
Iron protocol	Same as haemodialysis (Table 9)
Vitamin supplementation	Same as haemodialysis (Table 9)
Concomitant therapy	Same as haemodialysis (Table 9)
Peritoneal dialysis data collected in months 2–6	
All variables	Same as haemodialysis (Table 9)

Demographics and epidemiology

Patients ranged in age from 7 to 99 years, with a mean age for the sample of 61 years (SD = 15.3) and a median age of 64 years (Table 2). Figure 1 provides a summary of the sample by age and type of dialysis. Haemodialysis patients comprised 90.3% of patients in the survey. The median age of haemodialysis patients was 64 years (mean = 61.2 years; SD = 15.1). The median age of peritoneal dialysis patients was 62 years (mean = 59.5 years; SD = 16.7).

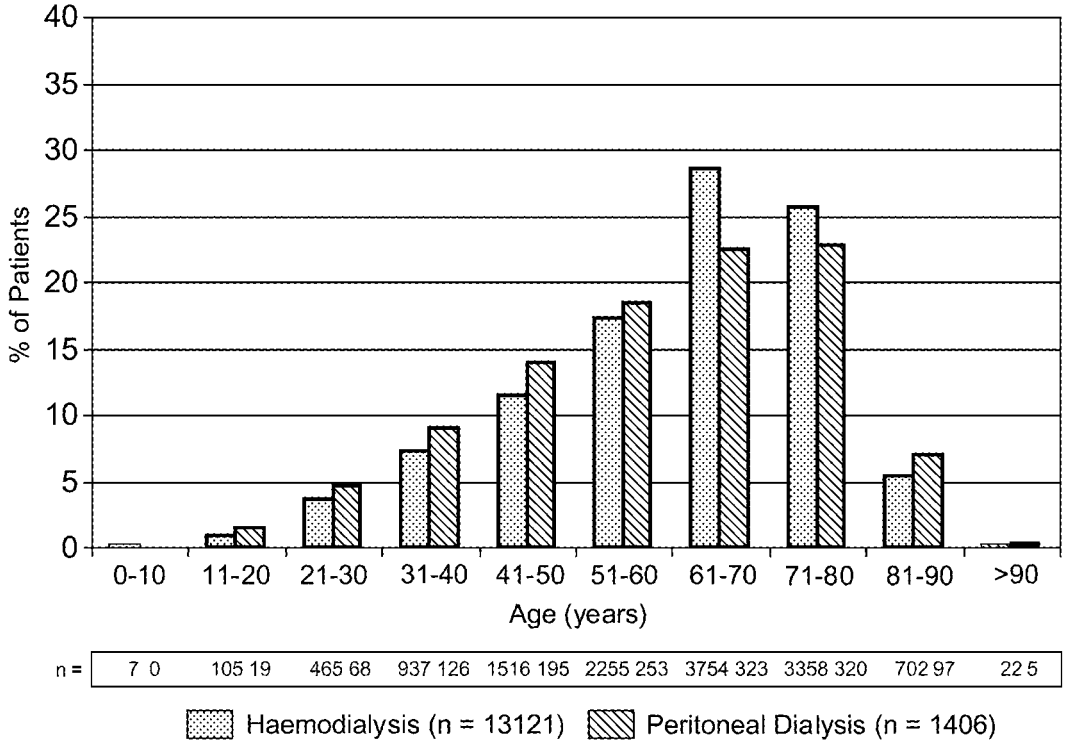

Fig. 1. Age by type of dialysis.

The most common causes of end-stage renal failure were chronic glomerulonephritis (25.5%), diabetic nephropathy (17.7%), renovascular disease (13.9%) and tubulo-interstitial disease (13.3%) (Table 3). Less common causes included polycystic kidney disease (6.9%), hereditary renal disease (2.3%), failed renal transplant (2.3%) and multiple myeloma (0.8%). For 17.3% of patients, the cause of renal failure was undefined. When examining the cause of renal failure by country, a similar distribution was found although there were some differences between countries. Chronic glomerulonephritis was the most frequently reported in all participating countries, ranging from 21.2% in Belgium/Luxembourg to 38.4% in Norway.

Hypertension was the most commonly observed concomitant pathology (66.4%), followed by coronary artery disease (25.4%), diabetes mellitus types I and II (20.2%), cardiac failure (15.1%) and cardiac arrhythmias (11.9%). Less common pathologies were hepatitis (6.3%), neoplasia (6.0%), chronic obstructive pulmonary disease (COPD) (5.3%), chronic infection (3.7%) and haemoglobinopathies (0.6%).

Approximately 7% of all patients in the survey had been on renal replacement therapy for 11 years or more (Table 5), and 20% had been on dialysis for <1 year. The majority of patients (81.5%) had been on renal replacement therapy for 5 years or less. By-country analysis revealed some countries with relatively fewer patients on dialysis for 11 years or more, and a larger proportion of patients on dialysis for 5 years or less (Norway, Italy, Finland, Sweden and Austria). France had a relatively large proportion of patients on dialysis for 11 years or more (11.4%).

Of the entire sample, 5.8% had been on epoetin therapy for <3 months (Table 6). On average, patients had been receiving epoetin therapy for 30.0 months (SD = 26.3) at the time of enrolment in the survey (Table 7). Approximately 0.5% of the total sample had been receiving epoetin since before 1988, while 90.7% received their first dose of epoetin between 1993 and 1998, and 23.6% started epoetin therapy in 1998. Again, some differences in average length of time on epoetin were noted between countries, but the same overall patterns seemed to exist. At the time of the survey, 5.1% of patients were receiving correction doses of epoetin (defined as the dose received during the 3 months following initiation of treatment), while 83.2% were receiving maintenance doses. For 11.6% of patients, the phase of treatment was not reported or could not be determined.

References

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