

# The French haemophilia cohort: rationale and organization of a long-term national pharmacosurveillance system

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**Summary.** Medicinal products of biological origin still carry a specific iatrogenic risk, mainly because of their starting material, mode of preparation and variability. Careful postmarketing surveillance systems are therefore necessary. To assess the long-term safety of haemophilia treatment with plasma-derived and recombinant clotting factor products, a cohort study was set up in France in 1994. Participants were patients with haemophilia A and B, with or without previous clotting factor therapy. Clinical events, treatments, biological data and adverse events were recorded on standard forms. Blood samples were separated into serum, plasma and peripheral blood mononuclear cells, frozen, and banked in a central laboratory. The same data and samples were collected at yearly follow-up visits. As of December 1999, 1234 haemophiliacs were enrolled in 39 haemophilia centres. At enrolment, 50.2% of patients were under

15 years of age, and the cumulative number of days of exposure to the product was below 50 in 35.1% of cases. The median duration of follow-up was 26.9 months, with a total of 2729 patient-years (135 947 days of exposure and 211 million units of factor VIII or IX). To date, only 17 patients were lost to follow-up. The initial results show good compliance with this health-watch policy among patients and clinicians specializing in haemophilia. The regular follow-up data and centralized sample bank will serve to investigate rapidly any suspected outbreaks as soon as reliable biological tests become available in the future.

**Keywords:** clotting factor preparations, cohort study, France, haemophilia, health-watch policy, pharmacoepidemiology.

## Introduction

In the 1980s, clotting factor concentrates for the treatment of haemophiliacs carried a major risk of viral infection because they were prepared from the pooled plasma of several thousand donors. Since 1985, improved donor selection measures, serological screening of plasma, and viral inactivation/removal steps during the fractionation process of clotting factor preparations have virtually eliminated

the risk of infection by enveloped viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV). However, nude viruses such as parvovirus B19 and hepatitis A virus (HAV), which are less sensitive to current viral inactivation methods, can still be transmitted by plasma-derived factors VIII and IX if specific additional steps, such as nanofiltration, are not used. The discovery in recent years of new infectious agents, such as GB virus C, the TT virus, and the agent responsible for new variant Creutzfeldt–Jakob disease (nvCJD), has led to a fear of epidemics, particularly among haemophiliacs repeatedly treated with massive doses of clotting factors. Recombinant factor VIII products [1,2] were first marketed in

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France in 1993, and have not been associated so far with documented viral transmission.

The emergence of inhibitors is currently the most frequent severe adverse event in haemophilia patients treated with clotting factors. These antibodies target epitopes of the relevant clotting factor, leading to their partial or complete inhibition and subsequently, resistance to the usual replacement therapy. The treatment of bleeding episodes, and the reduction in the inhibitor titre, raise complex therapeutic problems [3]. This adverse event classically occurs in young patients with severe haemophilia, within the first 50 cumulative days of exposure (CDE) to factor VIII or IX. In patients with severe haemophilia A, the reported cumulative incidences are highly variable, between 2 and 52% [4–6], mainly because of differences among study populations, cut-off points used to define the emergence of an inhibitor, and study designs (especially the frequency of inhibitor screening). Thus, comparisons of the incidence of inhibitors in the use of plasma-derived and recombinant products are difficult, and no significant difference has so far been demonstrated. Inhibitors have also emerged in the Netherlands [7] and Belgium [8,9] after the introduction of new pasteurized factor VIII concentrates in haemophilia patients previously treated for long periods in 1990 and 1995. These 'outbreaks' were attributed to antigenic modifications of factor VIII during the additional step in the viral-inactivation processes.

Since 1989, plasma-derived products have been considered as medicinal drugs in the European Community (Council Directive 89/381). In 1993, the French Ministry of Health commissioned the Agence du Médicament to set up a prospective cohort of haemophilia patients treated, or likely to be treated, with factors VIII or IX. The Institut National de la Santé et de la Recherche Médicale (INSERM) acted as the Coordinating Centre. The main objective of this cohort, named *Suivi Thérapeutique National des Hémophiles* (SNH), was (i) to assess the long-

term safety of clotting factors used to treat haemophilia; and (ii) to conduct a 'health watch' in collaboration with the French national pharmacovigilance system to detect known adverse effects. In addition, through the creation of a sample bank, the SNH aimed to assess the theoretical risks of emerging infectious diseases. All hospital physicians involved in the treatment of haemophilia were invited to participate in the SNH. The first enrolments started in October 1994. This article describes the organization of the cohort and the characteristics of the patients so far included.

## Patients and methods

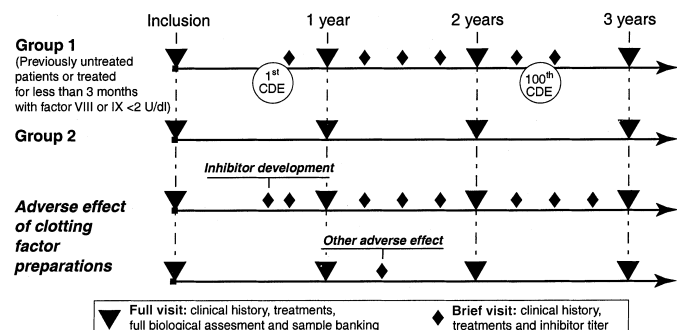
### Design and patients

SNH is a prospective multicentre cohort study with active direct follow-up. The criteria for inclusion are: (i) patients with haemophilia A or B, currently treated or qualifying for treatment with a clotting factor; and (ii) patients (or guardians if the patient is a minor) who are informed of the protocol and follow-up modalities and who have signed the consent form. Patients with a plasma activity of the deficient factor strictly below  $2 \text{ U dL}^{-1}$  (with two determinations), who have not previously been treated or whose first replacement therapy dates back less than 3 months compose Group 1 (Fig. 1). Group 2 comprises all other patients. The treatments received by the patients are unaffected by their enrolment in SNH. During the observation period covered by this report (1994–99), eight factor VIII preparations and three factor IX preparations were used.

### Enrolment and follow-up

During the enrolment visit, the family history of haemophilia and the personal disease history are recorded, i.e. history of inhibitors, previous viral

**Fig. 1.** Follow-up schedule. All patients have an enrolment visit then full follow-up visits yearly. In addition, brief visits are planned each trimester, in two cases: (1) group 1 patients after the first factor VIII or IX injection and until a figure of 100 cumulative days of exposure (CDE) is reached; and (2) when the occurrence of an inhibitor is confirmed, for as long as the inhibitor persists, and for at least 2 years after its complete disappearance.



infections, and vaccination status against hepatitis A and B. Events (e.g. bleeding events and surgery) occurring during the past year are described in detail, as are treatments received in the previous year, i.e. clotting factors (products, number of CDE and units, and batch numbers received); other plasma-derived products; labile blood products; desmopressin; and, if relevant, treatments for inhibitor. Weight and height are recorded, together with the blood cell count, serum transaminase activity, creatininaemia, lymphocyte subset counts (CD4 and CD8), serum immunoglobulin levels, the factor VIII or IX inhibitor titre (classical Bethesda assay), and serological tests for parvovirus B19 (IgG), HAV, HBV, HCV and HIV. Blood samples are sent to the centralized sample bank.

At each follow-up visit, events and treatments since the last SNH visit and the inhibitor titre are recorded. In addition, at the yearly visits, a biological review similar to that done at enrolment is undertaken (except for previously positive serological tests).

#### *Description of adverse events*

All confirmed adverse events potentially related to clotting factor administration are immediately notified to the Coordinating Centre and to the national pharmacovigilance system. Until 1998, inhibitor development was defined by an elevated titre (> 0.6 Bethesda units [BU]) in two different samples, or an elevated titre and reduced *in vivo* recovery. Gradually, the participating centres have adopted the Nijmegen modification of the Bethesda assay for factor VIII inhibitors [10].

#### *Centralized sample bank*

Samples of serum, plasma and peripheral blood mononuclear cells (PBMC) are stored in a centralized sample bank (International Sample Bank, Annemasse, France). Tubes of whole blood (one 6-mL vacuum tube without anticoagulant, and four 4.5-mL citrated vacuum tubes) are addressed to the sample bank by express mail on the day the visit takes place. The number of citrated tubes can be reduced if the patient is less than 5 years of age. Within 24 h after sampling, the samples are distributed into 500- $\mu$ L sterile straws and stored in liquid nitrogen ( $-196^{\circ}\text{C}$ ).

#### *Monitoring and data quality*

The investigators complete and mail a form at each visit. The forms are checked by monitors (physicians)

of the Coordinating Centre within 5 days following their receipt. If necessary, a request for further information is sent to the investigator. Double data entry is performed with a computerized database. Periodically, logical verification programs are executed and hitherto unnoticed adverse events are identified. In keeping with Good Clinical Practice recommendations [11], monitors regularly visit each participating centre and check that the data noted on the forms match those in the patients' clinical files (source data).

#### *Committees, ethical guarantees and confidentiality*

A Coordinating Committee including eight clinicians from haemophilia treatment centres was set up. An independent Scientific Committee supervises the SNH, especially concerning research projects and use of the sample bank. Each year, an update on the SNH is provided to the French Haemophilia Association.

The SNH protocol was approved by the Necker-Enfants Malades Ethics Committee and the French computer watchdog body. Patients are identified by an anonymous number, guaranteeing the confidentiality of the information forwarded to the Coordinating Centre and sample bank. Access to the SNH database is protected by passwords.

#### *Budget*

The extra burden of work generated by participation in the SNH was estimated at 4 h per patient per year. On this basis, assistance proportional to the number of patients was made available to each centre after 1997. The Coordinating Centre comprises one coordinator, one statistician, 2.4 monitors and 0.5 secretarial staff. In addition, the centralized sample bank cost 80 000 euros per year (including transport, straw preparation and storage).

## **Results**

#### *Enrolment phase*

The first enrolments were made in October 1994 in five pilot centres. Beginning in April 1995, the SNH protocol was proposed to all clinicians treating haemophilia in France (Fig. 2). The results presented here concern 1208 patients whose full forms have been received; 85.1% have haemophilia A, 14.9% have haemophilia B, and 53.6% have severe haemophilia ( $< 1 \text{ U dL}^{-1}$ ). At enrolment, 50.2% of patients were under 15 years of age, and the

number of CDE was below 50 in 35.1% of cases (Table 1). Table 2 describes patients at risk, at enrolment, for the main known adverse effects of current factor VIII and IX preparations (inhibitors and infection by nude viruses), and patients at risk of HBV, HCV or HIV infection. One thousand and 72 patients (88.7%) were at risk of developing an inhibitor, of whom 88 were particularly at risk (severe haemophilia A patients with fewer than 50 CDE).

*Follow-up*

As of 31 December 1999, 3480 follow-up visits had been made (Fig. 2). The cumulative observation period (between enrolment and the last follow-up visit) was 2729 person-years (median: 26.9 months per patient). During this observation period there were 135 947 days of exposure to factor VIII or IX (median: 31 days), corresponding to 211 million units of factor VIII or IX (median: 48 430 units). A total of 54 000 samples had been stored in the centralized SNH sample bank (median: 44 straws).

Seventeen patients had no follow-up visits during the 2 years preceding the analysis and are considered potentially lost to follow-up. Forty-one patients moved home and are currently being followed in another centre participating in the SNH protocol. Follow-up was interrupted in 22 cases: two children's parents withdrew their consent and 20 patients died; 12 of these 20 patients were not infected by HIV and died of intracranial haemorrhage (*n* = 4), primary liver cancer (*n* = 2), suicide (*n* = 2), myocardial infarction (*n* = 1), cardiac insufficiency (*n* = 1), colon cancer (*n* = 1) or bladder cancer (*n* = 1).

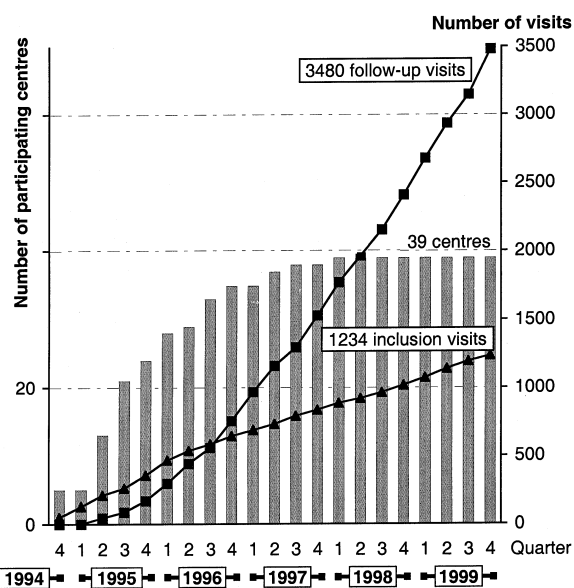


Fig. 2. Number of participating centres and visits since October 1994. As of 31 December 1999, 39 centres were participating in the SNH and 1234 patients had been enrolled.

**Discussion**

Since the late 1970s, several national blood product-monitoring systems were set up in Europe and North America. In 1976, the Directors of Haemophilia Centres in the United Kingdom decided to collect information on all known patients with haemophilia, including those who had not received treatment, and also on carriers and patients with von Willebrand's disease treated at haemophilia centres [12]. In 1988,

Table 1. Patients' characteristics at enrolment.

	Haemophilia A				Haemophilia B				Total	
	Severe*		Mild/moderate		Severe*		Mild/moderate		n	%
	n	%	n	%	n	%	n	%		
<b>Age years</b>										
0-4	117	20.9	68	14.6	14	16.3	14	14.9	213	17.6
5-14	196	34.9	143	30.6	25	29.1	30	31.9	394	32.6
Over 15	248	44.2	256	54.8	47	54.7	50	53.2	601	49.8
<b>Number of cumulative days of exposure to factor VIII or IX</b>										
0	9	1.6	48	10.3	2	2.3	5	5.3	64	5.3
1-49	95	16.9	198	42.4	15	17.4	52	55.3	360	29.8
50-99	33	5.9	80	17.1	11	12.8	12	12.8	136	11.3
Over 100	424	75.6	141	30.2	58	67.4	25	26.6	648	53.6
<b>Enrolled patients</b>	561	100.0	467	100.0	86	100.0	94	100.0	1208	100.0

\* Severe, < 1 U dL<sup>-1</sup>.

**Table 2.** Patients at risk at enrolment of developing inhibitors to factor VIII or IX, or parvovirus B19, hepatitis A, B or C virus or human immunodeficiency virus (HIV) infection.

	Haemophilia A				Haemophilia B				Total	
	Severe*		Mild/moderate		Severe*		Mild/moderate			
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
<b>Patients at risk of inhibitor development†</b>										
All	452	80.6	442	94.6	84	97.7	94	100.0	1072	88.7
< 50 CDE	88	15.7	242	51.8	17	19.8	57	60.6	404	33.4
= 50 CDE	364	64.9	200	42.8	67	77.9	37	39.4	668	55.3
<b>Patients at risk of viral infection‡</b>										
Parvovirus B19	101	18.0	96	20.6	12	14.0	15	16.0	224	18.5
Hepatitis A virus	150	26.7	135	28.9	19	22.1	26	27.7	330	27.3
Hepatitis B virus	26	4.6	43	9.2	3	3.5	6	6.4	78	6.5
Hepatitis C virus	257	45.8	255	54.6	36	41.9	49	52.1	597	49.4
HIV	447	79.7	434	92.9	75	87.2	84	89.4	1040	86.1
<b>Enrolled patients</b>										
	561	100.0	467	100.0	86	100.0	94	100.0	1208	100.0

\* Severe, < 1 U dL<sup>-1</sup>. †Patients with no previous history of inhibitors to factor VIII or IX and no inhibitors (titre < 0.6 BU) at enrolment (CDE = cumulative days of exposure to factor VIII or IX). ‡Patients with no previous history of infection or vaccination (anti-HAV or anti-HBV) and no specific antibodies at enrolment.

the Italian National Registry of Patients with Congenital Coagulation Disorders was created by AIDS Operational Centres at the *Istituto Superiore di Sanita*, the Italian Haemophilia Foundation and haemophilia care centres nationwide [13]. In 1988, the Canadian Hemophilia Registry was created by the Association of Hemophilia Clinic Directors of Canada [14]. In the United States from 1987 to 1996, the Seroconversion Surveillance Project has been conducted by the National Hemophilia Foundation with support from the Food and Drug Administration and in collaboration with the Centers for Disease Control (CDC) [15]. In 1995, an active haemophilia surveillance system (HSS) was developed by the CDC to identify all residents with haemophilia in six US states [16]. In 1999, a Universal data collection system with serum storage in a national sample bank was performed by the CDC for surveillance of joint and infectious disease complications on all known persons with haemophilia and related congenital blood clotting disorders in the US [17]. All these national surveillance systems involved patients with clotting disorders (UK, Italy, US) or solely patients with haemophilia A and B (Canada). They were aimed at covering the entire eligible population from the outset. Systems set up in the 1970s and 80s provided information on the nationwide prevalence of haemophilia, viral infections (especially HIV and HCV) and causes of death in the haemophiliac population.

In the 1990s, mainly because of difficulties in comparing the incidence of inhibitors in studies

according to the product used, several authors recommended prospective observational cohorts studies [18] coordinated by an agency that is independent of the factor VIII manufacturers [19], in which large numbers of haemophiliacs are routinely screened for known side-effects and the data routinely collected [20–23]. The French surveillance system, launched in this context, require enough haemophilia patients at risk to be enrolled to fulfil its main objectives. Its follow-up schedule was not optimized for the study of a particular risk (viral infections, for example), but is simple and compatible with long-term follow-up of a large number of patients. The results show that the investigators tended to include patients at risk, i.e. young children free of infection and patients with severe haemophilia. The total population of haemophiliacs in France can be estimated from the documented prevalence in other countries. With a mean prevalence in the total male population of 14 cases per 100 000 [14,16,24,25] and a male population of 29 million, the estimated number of haemophilia patients in France is 4060. Five years after the beginning of enrolment, it can therefore be roughly estimated that a third of all haemophiliacs living in France were being monitored within the SNH cohort. The proportion would be higher if one considered only treated haemophiliacs or only those with severe deficiencies.

The large centralized sample bank is the most original aspect of the SNH approach. Stored samples can be used to confirm an alert or to contribute to

validating a hypothesis on an adverse effect if a suitable biological test is available [17]. For example, transmission of the agent responsible for new variant Creutzfeldt–Jakob disease by blood products is today only a theoretical risk [26,27]. Should a validated blood test become available, it will be possible to use the most suitable sample (serum, plasma or PBMC) stored in the framework of the SNH to look for the agent in haemophiliacs. Given their chronic exposure to high cumulative doses of plasma-derived or recombinant products, haemophiliacs are a population at risk of developing ‘emergent infectious diseases’. If a new agent transmissible by these products is discovered, close monitoring of haemophilia patients can therefore benefit all individuals exposed to plasma-derived or recombinant products. This national prospective cohort is the first pharmacoepidemiological survey of its type in France. In addition to its sentinel role, information on patients followed in the SNH provides a base for clinical research projects.

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## Appendix

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\*No longer active in the clinical centre.