Nephrol Dial Transplant (2004) 19: 2121–2125
DOI: 10.1093/ndt/gfh307

Nephrology Dialysis Transplantation

Brief Report

High prevalence in Switzerland of pure red-cell aplasia due to anti-erythropoietin antibodies in chronic dialysis patients: report of five cases

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Abstract

Background. Pure red-cell aplasia (PRCA) after erythropoietin (Epo) administration due to the appearance of neutralizing anti-Epo antibodies has been reported in over 200 cases between 1998 and 2002. However, large intercountry disparities were observed in the occurrence of this syndrome.

Methods. On behalf of the Swiss Society of Nephrology, a survey was conducted in all the dialysis units of Switzerland in order to collect information on the occurrence, diagnostic and evolution data of the cases observed. A questionnaire was send to the nephrologists in charge of each of the 69 dialysis units in January 2003. The clinical and biological data of the suspected cases were analysed and compared with the data provided to health authorities and pharmaceutical companies.

Results. A total of five cases were identified as true PRCA with demonstrated positive anti-Epo antibodies. They occurred between November 1998 and February 2002, were all treated by haemodialysis and had received Epo subcutaneously. The median appearance time of refractory anaemia after Epo initiation was 10 months (range: 7–54 months). Two cases had been treated exclusively with epoietin-α, one solely with epoietin-β and the two others with a combination of both. With five cases out of a total of about 2500 dialysis patients and 2300 Epo-treated dialysis patients or an exposure rate to Epo of 9900 dialysis patient-years during a 4.3 year period, this prevalence is among the highest of those reported in European countries.

Conclusions. The prevalence of PRCA after Epo administration in dialysis patients appears particularly high in Switzerland. Among the potential explanations, the most plausible are the high percentage of dialysis patients treated with Epo, the almost exclusive subcutaneous administration, the larger market distribution of the epoietin-α brand, the eventual disruption of the cold chain and the setting-up of a systematic national survey.

Keywords: anti-erythropoietin antibodies; chronic dialysis; chronic kidney failure; end-stage renal disease; erythropoietin; pure red-cell aplasia; renal anaemia

Introduction

The gene for human erythropoietin (Epo) was cloned and expressed in 1985 [1,2] and recombinant human Epo was approved for marketing in 1987 in the United States and in 1988 in Switzerland. During the 1990s, despite the liberal use of Epo in clinical practice, only three cases were reported worldwide in which anti-Epo antibodies (Ab) were detected after Epo administration [3–5].

However, in February 2002, Casadevall *et al.* [6] published a series of 13 patients on chronic dialysis who developed pure red-cell aplasia (PRCA) due to neutralizing anti-Epo Ab while receiving Epo therapy. By now, over 200 cases of PRCA occurring after Epo administration have been reported, most often to the manufacturers and/or health authorities [7–9]. The presence of anti-Epo Ab was not documented in all of them. This occurrence has now led to important changes in the determination of Epo type and mode of administration (www.swissmedic.ch/cgi7news) [10,11].

When the first two cases were observed in Switzerland by one of the authors (C.S.), the Swiss Society of Nephrology asked through its Dialysis Committee, with the help of the Swissmedic

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Pharmacovigilance Section, for the setting up of a systematic survey of the observed cases among dialysis patients. We report here the results of this investigation.

Subjects and methods

A questionnaire was set up and sent in January 2003 to the nephrologist in charge of each of the 69 dialysis units in Switzerland (among which are three paediatric units). We asked about the occurrence of past or present cases of end-stage renal disease patients with suspected or proven diagnosis of PRCA due to anti-Epo Ab. The period of survey extended between 1998 and June 2002, since during summer 2002, due to the occurrence of the syndrome, important changes in Epo administration were introduced. In addition, information on the number of patients treated by dialysis at the end of 2002 was also requested. The dialysis staffs of the centres that did not respond or returned incomplete data were interviewed directly by telephone.

The clinical, diagnostic and therapeutic data of the suspected cases were collected and compared with the information already obtained by the Swissmedic Pharmacovigilance Section and by the national branches of the manufacturers. Only cases with positive anti-Epo Ab were considered for analysis. The antibody tests had been performed by either radioimmunoprecipitation or enzyme-linked immunosorbent assays in different laboratories (Service d'Hématologie Clinique, Hôpital Hôtel-Dieu, 75181 Paris, France; CLIA Laboratory, Immunochemistry Dept, PPD Development, 2244 Dabney Road, Richmond, VA 23230, USA; MDS, Pharma Services, 2350 rue Cohen, Saint-Laurent, Montreal, Quebec, H4R 2N6 Canada).

Just the Epo-α and -β brands were available during the survey period, since darbepoietin only became available in Switzerland in September 2002. According to different sources, the α brand constituted 70% and the β brand 30% of the total sales for dialysis patients during the observation period.

Results

All the 69 Swiss dialysis centres participated in the survey. A total of five cases of confirmed PRCA with a positive test for neutralizing anti-Epo Ab were identified. Their characteristics and clinical evolution are summarized in Table 1.

In addition to the positive anti-Epo Ab test, a bone marrow biopsy was compatible with PRCA in all cases and other causes of PRCA had been excluded on clinical, biological and serological grounds. All were treated by chronic haemodialysis for ≥9 months and developed refractory anaemia after a median of 10 months (range: 7–54 months) of Epo therapy.

According to our information, only Epo-α had been used in two cases, one patient had received Epo-β exclusively and in the two remaining cases both α and β brands had been administered. In those last two cases, Epo-α had been given first at doses increasing from 7500 to 12 000 U/week for 2 and 5 months, respectively, and then replaced by Epo-β at 7000 to 20 000 U/week for 5 and 7 months, respectively, before the diagnosis of PRCA was made.

The clinical evolution was interesting in several aspects: in two cases a remission occurred spontaneously 3 and 6 months after Epo withdrawal without any immunosuppressive therapy; in another case PRCA persisted clinically after kidney transplantation, requiring blood transfusions for ≥6 months, however, the anti-Epo Ab are still positive, despite immunosuppressive therapy, 3 years after transplantation and 3.5 years after Epo withdrawal. Cases 2 and 3 are reported in detail elsewhere [12,13].

Since all the dialysis units responded to this survey, the prevalence of PRCA due to anti-Epo Ab in Switzerland could be calculated. With 69 dialysis units in a country of 7.3 million inhabitants, Switzerland has a high density of dialysis centres. During 2002, the incidence and prevalence of chronic dialysis patients were 115 and 343 per million inhabitants, respectively. According to our survey, at the end of 2002, a total of 2555 patients were treated by chronic dialysis: 2237 by haemodialysis (among which 27 were haemodialyzed at home) and 318 by peritoneal dialysis. These numbers had been increasing only slowly over the preceding 4 years. This means that with five cases for around 2500 dialysis patients, Switzerland has a higher prevalence (1/500) than its surrounding countries: France with 33 cases out of 28 000 chronic dialysis patients (1/848), Germany with six out of 58 000 (1/9666) and Italy with four out of 36 000 (1/9000) [8,14].

Those diverse prevalences can be explained, at least partly, by the varying uses of Epo in the different countries and their administration mode [10]. According to our survey, during the first part of 2002, ~90% of the total dialysis population was treated with Epo, among which 79.4% were treated subcutaneously (s.c.) and 20.6% intravenously (i.v.). Based on those results it appears that, when considering the two Epo brands together, the five cases were observed in a weighted chronic dialysis population of 2500, in an Epo-treated dialysis population of around 2300 patients or in about 9900 dialysis patient-years of exposure to Epo during a 4.3 year period. According to various sources, during the survey period the α brand constituted 70% of the sales to the chronic dialysis units in Switzerland. When restricted to the pure cases, this prevalence becomes 1/1150 for only Epo-α-treated patients and 1/2300 for only Epo-β patients.

Discussion

The present survey identified five cases of PRCA occurring during Epo therapy in chronic dialysis patients in Switzerland. Some of our observations shed additional light on the clinical evolution of Epo-related PRCA: while, so far, a spontaneous remission appears exceptional [8], in our cases 4 and 5, a remission of the syndrome occurred spontaneously without any immunosuppressive therapy, respectively,

Table 1. Characteristics and clinical evolution of the PRCA cases due to anti-Epo Ab during Epo administration in chronic dialysis patients in Switzerland

Case no.	1	2	3	4	5
Year of birth	1915	1975	1925	1936	1961
Gender	Male	Female	Male	Male	Male
Kidney disease	Unknown aetiology	MPGP	Nephroangiosclerosis	Glomerulonephritis	MPGP on HCV
Date HD started	July 1998	April 1998	May 1994	April 2001	July 1999
Date Epo started	April 1998	April 1998	May 1994	April 2001	June 1999
Brand of Epo given	α	α + β	β	α + β	α
Route of Epo administration	s.c	s.c	s.c	s.c	s.c
Date of PRCA occurrence	Nov. 1999	Jan. 1999	Nov. 1998	Feb. 2002	March 2000
Time from Epo start to RA (months)	18	9	54	10	9
Date of anti-Epo Ab test	01/00	12/00	9/02	11/01	1/01
Date of bone marrow evaluation	12/99	2/99	2/99	2/02	6/00
Minimal Hb value (g/l)	65	42	76	53	54
Transfusion requirements (no. units)	44	151	65	16	55
Date Epo stopped	March 2000	March 2000	Not stopped	March 2002	March 2001
Time from Epo stop to TI (months)	7 (till patient death)	11	TI since Nov. 2000	3	6
Immunosuppressive therapy	CsA (2.5 months)	Kidney transplant Sept. 2000; corticoids, CsA ATG, thymectomy	ATG CsA	No treatment	No treatment
Outcome	Died Oct. 2000 (dialysis withdrawn at patient request)	TD (14 units Sept. 2000–March 2001); no transfusions since, but low Hb and Epo Ab remain	Died Sept. 2002 (pulmonary neoplasia)	Kidney function partially restored (GFR 30 ml/min) HD stopped May 2002 Hb stable 11.5 g/dl	Transfusion requirements increased during interferon therapy for HCV; since Dec. 2001 Hb stable 9 g/dl kidney transplantation June 2002

MPGP, membranoproliferative glomerulopathy; HCV, chronic hepatitis C; HD, haemodialysis; RA, refractory anaemia; TI, transfusion independence; CsA, cyclosporin A; ATG, anti-thymocyte globulin; TD, transfusion dependent; Hb, haemoglobin; GFR, glomerular filtration rate.

3 and 6 months after Epo withdrawal. In contrast, while kidney transplantation is reported to cure PRCA syndrome within a few weeks [6–8], in our case 2, PRCA persisted clinically, necessitating blood transfusions during 6 months after an otherwise successfully functioning kidney transplant and the anti-Epo Ab still remain positive 3 years after transplantation, with haemoglobin levels oscillating spontaneously between 64 and 82 g/l [13].

The most interesting observation of this survey is the high prevalence of PRCA due to anti-Epo Ab observed in Switzerland: five cases for a chronic dialysis population receiving Epo of 2300 and an exposure rate of 9900 patient-years during a 4.3 year period. Even if this total population remains low when compared with other countries, it has to be noted that in France, despite the initial report by Casadevall *et al.* [6] and the subsequent increased awareness, a lower prevalence is observed [10]. The prevalence is also much lower in other neighbouring countries, such as Germany and Italy. It is presently estimated that the incidence of PRCA due to anti-Epo Ab is one to two per 10 000 dialysis patients receiving Epo by the s.c. route [11]. Due to the changes in the manufacturing, handling and prescription mode introduced for the Epo-α brand during summer 2002, the occurrence of new cases seems to be decreasing.

The national discrepancies appear multifactorial. In France, the patient has to go to the pharmacy in person to obtain the product with a subsequent greater risk of cold-chain disruption, while in Germany and Italy, Epo is routinely administered by the dialysis staff and much more often by the i.v. route. In Switzerland, Epo is generally ordered and stocked directly by the dialysis unit or hospital pharmacy and administered most often s.c., directly by the dialysis staff.

Several factors can be put forward to explain the high frequency of PRCA cases due to anti-Epo Ab observed in Switzerland:

(i) Since in our country Epo was admitted and reimbursed very early for chronic dialysis patients, it could be prescribed without financial or administrative constraints, which explains why ~90% of chronic dialysis patients received Epo.

(ii) On the basis of a national multicentre study [15] and the, by then, existing guidelines [11], s.c. administration was – until summer 2002 – used in the vast majority of Swiss dialysis patients (up to 94% in the Suisse romande centres during a quality evaluation survey conducted in 2001 in the 21 dialysis units of western Switzerland [16]: 92.4% of this chronic dialysis population ($n = 617$) received Epo and among those, 94.4% received Epo by the s.c. route); subsequently, this route was demonstrated to put the patients at greater risk of PRCA [8,11].

(iii) Among the two different brands of Epo available, the α formulation was used in almost 70% of the Swiss patients during the observation period. Since that time, the α brand has been shown to represent a greater risk, which led the manufacturer to forbid its s.c. use in December 2002 (www.swissmedic.ch/cgi7news).

(iv) The possibility of a ruptured cold-chain was first suggested by the fact that two of the five cases were observed in the same dialysis centre, but they occurred in a 2 year time interval and the handling of the medication was repeatedly investigated by the hospital pharmacist, who ruled out this possibility; moreover, in none of the five cases was self-administration practised at home, which makes this hypothesis less likely.

It must also be added that due to the mandatory declaration to Swiss health authorities of any clinical syndrome suspected of PRCA during Epo administration and the simultaneous 100% response rate of the present survey, the prevalence reported here corresponds to the real prevalence, which is not necessarily the case in other countries.

Indeed, a recent Editorial proposed the setting up of a dedicated independent registry devoted to the Epo-induced PRCA syndrome, in order to obtain a clearer view of its occurrence and outcome [11]. Our survey appears as an original step in this direction and seems to indicate that the prevalence might be underestimated at present.

In conclusion, the prevalence of PRCA after Epo administration in dialysis patients appears particularly high in Switzerland. Among the potential explanations, the most plausible are the large use of Epo in dialysis patients, the almost exclusive s.c. administration, the larger market distribution of the Epo-α brand, the eventual disruption of the cold chain and the setting up of a systematic national survey.

Acknowledgements. The authors wish to thank the staff of all the Swiss dialysis units who participated in this investigation. The help of the Swissmedic Pharmacovigilance Unit (Dr R. Stoller) and of the national branches of the Janssen-Cilag and Roche companies for the collection and/or verification of part of the data is also appreciated.

Conflict of interest statement. Several authors participated in experts meetings and/or multicenter studies financed by Janssen-Cilag or Roche; the present study did not receive any financial support.

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Received for publication: 17.3.04
Accepted in revised form: 16.4.04