Long-term outcome of individuals with pure red cell aplasia and antierythropoietin antibodies in patients treated with recombinant epoetin: a follow-up report from the Research on Adverse Drug Events and Reports (RADAR) Project

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Since its introduction in 1988, recombinant human erythropoietin (epoetin) has been standard treatment for patients with anemia due to chronic kidney disease. From 1998 to 2004, nearly 200 epoetin-treated persons with chronic kidney disease developed antibodies to epoetin, resulting in pure red cell aplasia (PRCA). The majority of these patients received Eprex, an epoetin alfa product marketed exclusively outside the United States. Herein, we report on the long-term outcome of these individuals. For 170 chronic kidney disease patients who developed epoetin-associated PRCA and had 3 months or more follow-up information available, case reports from the Food and Drug Administration and epoetin manufacturers were reviewed for information on clinical characteristics of the patients, immunosuppressive treatments, epoetin responsiveness, and hematologic recovery. Overall, 64% of the PRCA patients received immunosuppressive therapy, including 19 who also underwent a renal transplantation. Thirty-seven percent experienced a hematologic recovery, with higher hematologic recovery rates among PRCA patients who received immunosuppressive therapy (57% vs 2%, $P < .001$). Among 34 patients who received epoetin after the onset of PRCA, 56% regained epoetin responsiveness. The highest rates of epoetin responsiveness were observed among persons whose antierythropoietin antibodies were undetectable when epoetin was administered (89%). Among chronic kidney disease patients with epoetin-associated PRCA, epoetin discontinuation and immunosuppressive therapy or renal transplantation is necessary for hematologic recovery. Reinitiation of epoetin therapy among individuals could be considered if antierythropoietin antibodies are undetectable. (Blood. 2005; 106:3343-3347)

Introduction

Epoetin-associated pure red cell aplasia (PRCA) is a recently identified syndrome characterized by anemia, low reticulocyte count, absence of erythroblasts on bone marrow examination, resistance to epoetin therapy, and neutralizing antibodies against erythropoietin (Table 1).[2-4] Antibodies obtained from individuals with epoetin-associated PRCA are cross-reactive with all forms of both endogenous and exogenous erythropoietin. From 1988 to 1998, 3 chronic kidney disease patients were reported to have developed this syndrome following long-term treatment with recombinant human erythropoietin.[5-7] In the mid-1990s, a shift from intravenous to subcutaneous epoetin administration occurred in many countries due to clinical and economic considerations.[8-11] In 1998, the formulation of the epoetin alfa product Eprex was changed, prompted by European concerns that human serum

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Table 1. Diagnostic criteria for epoetin-associated PRCA*

Criteria
Major criteria (each of the major criteria should be identified in all cases)
Treatment with epoetin for at least 3 weeks
Drop of hemoglobin level of about 1 g/L/day without transfusions *or* transfusion need of about 1 unit/week to keep hemoglobin level stable
Reticulocyte count less than 10×10^9/L
No major drop of white blood cell or platelet counts
Minor features†
Skin and systemic allergic features
Confirmational investigations
Bone marrow aspirate with normal cellularity and less than 5% erythroblasts with evidence of maturation block‡
Serum assay shows presence of antierythropoietin antibodies and evidence of neutralizing ability

*Casadevall et al.[1]

†Minor features provide suggestive evidence, which should be confirmed by bone marrow aspirate examination and serum assays for antibodies.

‡Although there is not international consensus, bone marrow biopsy should be considered to rule out lymphoproliferative disorders.

albumin could transmit variant Creutzfeldt-Jakob disease.[14,15] The reformulated Eprex contained the excipients polysorbate 80 and glycine.[4,14] Between 1998 and 2003, the exposure-adjusted incidence of PRCA was 27 per 100 000 person-years among chronic kidney disease patients receiving the human serum albumin–free formulation of Eprex via the subcutaneous route. The estimated incidence rates were 10-fold greater with the human serum albumin–free Eprex formulation in comparison to the epoetin beta formulation NeoRecormon and the epoetin alfa formulation Epogen (Procrit).[3] Worldwide, 191 individuals have been identified with this syndrome. These individuals all had chronic kidney disease and almost all had received the human serum albumin–free formulation of Eprex subcutaneously.[4] Herein, we provide long-term follow-up information on these individuals.

Patients, materials, and methods

The Food and Drug Administration's Adverse Event Reporting System (AERS) receives adverse event reports from pharmacovigilance programs worldwide for epoetin alfa. All AERS reports of PRCA cases associated with the epoetin alfa products Eprex (also marketed as Erypo; Johnson and Johnson, New Brunswick, NJ) or Epogen (also marketed as Procrit; AMGEN, Thousand Oaks, CA) from January 1988 to April 2004 were evaluated, as were a small number of adverse event reports for the epoetin beta product NeoRecormon (also marketed as Recormon; Roche, Manheim, Germany) obtained from the product manufacturer (written personal communication, Rose Ruch, Roche Pharmaceuticals, April 24, 2004). The reports were reviewed by investigators with the Research on Adverse Drug events And Reports (RADAR) Project, a National Institutes of Health–funded collaboration of hematologists, oncologists, clinical pharmacologists, pharmacists, and statisticians.[15] Additional follow-up information was obtained in some cases from clinicians or case reports in the medical literature. Approval was obtained from the Northwestern University institutional review board for this study. Informed consent was provided in accordance with the Declaration of Helsinki.

The case definition included epoetin use and diagnoses consistent with the syndrome (PRCA, anemia, loss of efficacy of the epoetin product, and antierythropoietin antibodies). Data reviewed included reporting date and country; patient age and sex; cause of anemia; dates of initiation and discontinuation of epoetin; route of administration; features of the PRCA; treatments including immunosuppressive agents, renal transplantation, resumption of epoetin therapy; and hematologic outcomes. The epoetin product considered to be the cause of PRCA was the product administered during the 2 months prior to the loss of epoetin efficacy.

Hematologic recovery and recovery of response to epoetin were based on interpretation by 2 independent reviewers (C.L.B., K.R.C.) of the clinical status and laboratory findings included in the case report forms. Criteria used for determining hematologic recovery status were frequency of red blood cell transfusions ($\leq$ 1/mo), hemoglobin level ($\geq$ 80 g/L [$\geq$ 8 g/dL]), and reticulocyte count ($> 20 \times 10^9$/L). Recovery of epoetin response was defined as independence from red blood cell transfusions in patients with a stable hemoglobin level of at least 80 g/L (8 g/dL). Treatment follow-up was evaluated from the time of initiation of first immunosuppressive treatment to the date of the last available clinical report. For patients who did not receive immunosuppressive treatment, observational follow-up was measured from the time of PRCA diagnosis to the date of the last available clinical report. The relationship between hematologic recovery and treatment was assessed by optimal discriminant analysis.[16] Effects with generalized P less than .05 were considered statistically significant.

Results

Of 191 patients with epoetin-associated PRCA identified worldwide, follow-up information of 3 months or longer was available for 170 (89%). A median of 9 months of follow-up was available for these patients. European countries accounted for 61% of the cases associated with Eprex, all 9 of the cases associated with NeoRecormon, and all 6 of the cases receiving more than one epoetin formulation prior to the onset of PRCA. All 4 of the Epogen/Procrit-associated PRCA cases were from the United States. One hundred sixty-nine patients had received epoetin via the subcutaneous route, whereas one Epogen-treated patient had received epoetin intravenously.[4] Epoetin had been administered for a median of 9 months for the Eprex cases versus 18 months for the NeoRecormon cases and 24 months for the Epogen cases. The mean age of the patients was 62 years (standard deviation = 17 years), 53% were 65 years of age or older, and 66% were male.

PRCA treatment approaches varied over time, with 63% of the PRCA patients who never received immunosuppressive therapy experiencing a loss of epoetin efficacy in July 2002 or earlier. Overall, 37% of the patients achieved hematologic recovery, with markedly higher rates of hematologic recovery being associated with the use of one or more immunosuppressive agents (57% vs 2%, $P < .001$). Among 62 PRCA patients not receiving immunosuppressive therapy, only one achieved a spontaneous hematologic recovery. Of the 19 PRCA patients who received a renal transplant and subsequent administration of cyclosporine or tacrolimus, transfusion independence was obtained by all patients except 1 (95%).[17] Among 89 nontransplantation PRCA patients who received immunosuppressive therapies without transplantation, 49% achieved a hematologic recovery. Country-specific hematologic recovery rates ranged from 31% for patients in Spain to 100% for patients in Singapore. In Spain, corticosteroids and/or intravenous immunoglobulin administration were the predominant immunosuppressive treatments (for 11 of 13 patients). In contrast, 5 of the 6 patients in Singapore received cyclosporine-containing immunosuppressive regimens.

Of 34 patients who received epoetin after the onset of PRCA, 56% recovered epoetin responsiveness (Table 2). The highest rate of epoetin responsiveness was noted among those who had no detectable antierythropoietin antibodies at the time of epoetin administration (89%). Of 14 PRCA patients who were receiving immunosuppressive therapy and had detectable antibody levels by enzyme-linked immunosorbent assay (ELISA) or radioimmunoprecipitation assay (RIPA) at the time of rechallenge, 8 (57%) recovered epoetin responsiveness. However, results of antierythropoietin antibody–neutralizing assays were not reported for any of

Table 2. Epoetin rechallenge cases (n = 34 individuals) and development of epoetin responsiveness

Case no.*	RIPA or ELISA antibody status at rechallenge	RIPA or ELISA antibody assay	Concomitant immunosuppression	Neutralizing assay results at time of rechallenge	Epoetin responsiveness
Group 1					
1	−	RIPA	+	Unknown	+
2	−	RIPA	+	−	+
3	−	RIPA	+	−	+
4	−	RIPA	−	−	+
5	−	ELISA	−	Unknown	−
6	−	ELISA	−	−	+
7	−	Unknown	+	Unknown	+
8	−	Unknown	+	Unknown	+
9	−	Unknown	−	Unknown	+
Group 2					
10	+	RIPA	+	Unknown	−
11	+	RIPA	+	Unknown	−
12	+	RIPA	+	Unknown	−
13	+	RIPA	+	Unknown	+
14	+	RIPA	+	Unknown	+
15	+	RIPA	+	−	+
16	+	RIPA	+	−	+
17	+	ELISA	+	Unknown	−
18	+	Unknown	+	Unknown	+
19	+	Unknown	+	Unknown	+
20	+	Unknown	+	Unknown	+
21	+	Unknown	+	Unknown	−
22	+	Unknown	+	−	+
23	+	Unknown	+	+	−
Group 3					
24	+	RIPA	−	Unknown	−
25	+	RIPA	−	Unknown	−
26	+	RIPA	−	Unknown	−
27	+	RIPA	−	Unknown	−
28	+	RIPA	−	Unknown	−
29	+	RIPA	−	Unknown	−
30	+	RIPA	−	Unknown	−
31	+	RIPA	−	Unknown	+
32	+	RIPA	−	Unknown	+
33	+	RIPA	−	−	+
34	+	ELISA	−	Unknown	−

The 3 groups were defined as follows: Group 1, no evidence of antierythropoietin ELISA or RIPA antibody at the time of rechallenge; Group 2, antibodies detected and concomitant immunosuppression was administered; Group 3, antibodies detected and concomitant immunosuppression was not administered.

*The percentage epoetin responsive were 89% for Group 1, 57% for Group 2, and 27% for Group 3.

these 8 individuals. Three of the 11 PRCA patients who had detectable antibody levels and did not receive immunosuppression responded to epoetin rechallenge (27% response rate). In each of these 3 cases, antibodies confirming the diagnosis of epoetin-associated PRCA were detected using the RIPA method. No neutralizing activity was detected in one patient, a repeat RIPA was borderline positive in the second patient, and antibodies were not re-evaluated prior to death in the third patient. Of the 15 PRCA patients who did not respond to epoetin retreatment, 3 died, 5 received additional immunosuppressive therapy and ultimately achieved a hematologic recovery, 2 remained heavily transfusion dependent, and long-term clinical follow-up was unavailable for the remaining 5 individuals.

Discussion

We have reported on the treatment and long-term follow-up of patients worldwide with epoetin-associated PRCA, 86% of whom had received Eprex. Hematologic recovery rates were 2% without immunosuppressive treatment, 52% following immunosuppressive treatment(s) outside of the renal transplantation setting, and 95% following renal transplantation. About one fifth of these individuals were re-treated with epoetin, one half of whom regained epoetin responsiveness. In interpreting our findings, a number of factors should be considered.

Many of the initial patients with epoetin-associated PRCA remained undiagnosed for long periods of time because the disease entity had not been well described prior to 2002. Once PRCA was diagnosed, immunosuppressive treatment was frequently not initiated due to concerns about the tolerability of immunosuppressive treatment in patients with chronic kidney disease and other comorbid illnesses. Over time, the PRCA diagnosis was confirmed more reliably and reports of hematologic recovery following immunosuppressive therapy were published. Most of the more recently diagnosed patients received immunosuppressive regimens consisting of prednisone, intravenous immune globulin (often with prednisone), cyclophosphamide (often with prednisone), or cyclosporine. Doses and schedules commonly used were similar to those that had been used for individuals with other immune-mediated cytopenias (Table 3). As no randomized clinical trials of alternative immunosuppressive therapies can be conducted, there are insufficient data to provide guidance on the preferred immunosuppressive agents or treatment regimen.[18] However, for a subset of 47 PRCA

Table 3. Immunosuppressive regimens used for treatment of epoetin-associated pure red cell aplasia

Immunosuppressive reatments	Dose range	Route	Observed recovery, %*
Cyclophosphamide + prednisone	50–100 mg/day + 1 mg/kg/day	Oral	87
Cyclosporine	100 mg twice/day or 5–8 mg/kg/day	Oral	67
Prednisone	1 mg/kg/day	Oral	56
Intravenous immunoglobulin*	2 g/kg over 2 to 5 days	Intravenous	11

Hemoglobin level, reticulocyte counts, and transfusion interval should be monitored over a 4- to 8-week interval. If no hematologic response occurs within 3 to 4 months with initial therapy, a therapeutic trial of a second-line therapy should be considered.

*Recovery rates are based on long-term follow-up reported by the European PRCA Study Group for 47 patients with complete follow-up data.[18]

patients from England, France, and Germany who had virtually complete follow-up information, the European PRCA Study Group[19] reported that hematologic recovery rates were highest with cyclophosphamide and corticosteroids (87%) and lowest with intravenous immune globulin (11%). Hematologic responsiveness was noted in these patients after a median of 3 months of immunosuppression (Table 3). In Canada and Europe in 1999 and 2000, several patients diagnosed with epoetin-associated PRCA were empirically treated with renal transplantation after failing multiple immunosuppressive regimens. These individuals experienced rapid hematologic responses, after which policy makers in several countries made chronic kidney disease patients with epoetin-associated PRCA a higher priority on the waiting lists for renal transplantation procedures.

The European PRCA Study Group reported that the majority of the PRCA patients who achieved a hematologic recovery had antierythropoietin antibody levels below the lower limit of detection in the referral laboratory of one of the coauthors (N.C.).[18] For those PRCA patients who do not clear the antierythropoietin antibodies with immunosuppression alone, renal transplantation appears to be a viable treatment option. Several epoetin-associated PRCA patients, after failing to recover epoetin responsiveness after administration of multiple immunosuppressive agents, developed a reticulocytosis one day after renal transplantation and a complete hematologic recovery shortly thereafter.[19,20] Hematologic recovery occurred for all but one of the renal transplant recipients with epoetin-associated PRCA. Small antigenic differences between endogenous erythropoietin and recombinant epoetins may exist in vivo, accounting for the high rates of recovery following renal transplantation and the resumption of natural erythropoietin production. Recently, small peptide molecules without sequence homology with epoetin and nonpeptidic erythropoietin mimetics that bind to the erythropoietin receptor have been developed.[21,22] Antibodies to these agents are unlikely to inhibit the pharmacologic activity of epoetin and, conversely, antierythropoietin antibodies are unlikely to inhibit their erythropoietic effects. It is possible that erythropoietin mimetics will be successful in treating those individuals who have persistent epoetin-associated PRCA despite multiple immunologic therapies.

Our findings have implications for rechallenging PRCA patients with epoetin following immunosuppressive therapy. Physicians have been advised that epoetin therapy should not be administered to individuals with epoetin-associated PRCA.[23-26] However, faced with ongoing and frequent red blood cell transfusion requirements, recent case reports describe individuals with epoetin-associated PRCA who recovered responsiveness to the same or different epoetin product following immunosuppressive therapy.[27-33] Worldwide, 19 of the 34 individuals who received epoetin after the onset of epoetin-associated PRCA regained epoetin responsiveness. The highest recovery rates (89%) were among individuals who received epoetin when antierythropoietin antibody levels were undetectable.

Geographic variations in PRCA treatment and outcomes exist. Six countries (Canada, France, England, Australia, Spain, and Switzerland) accounted for almost 70% of the cases we report. These countries had the highest rates of subcutaneous use of the human serum albumin–free formulation of Eprex and the highest exposure-adjusted incidence rates.[4] Overall, Switzerland had the highest PRCA prevalence with 1 case per 460 epoetin-treated chronic kidney disease patients.[34] Spain had the lowest hematologic recovery rates and the highest rates of intravenous immunoglobulin use as immunosuppressive therapy, whereas all 6 of the Singapore PRCA patients recovered, 5 of whom had received cyclosporine for immunosuppression. A published case series from Thailand described 4 epoetin-associated PRCA patients who failed to recover epoetin responsiveness after immunosuppressive therapy initially but recovered epoetin responsiveness shortly after undergoing renal transplantation.[20] These patients all displayed HLA DR B1*9, an allele present in 8.7% of the general Thai population. Considering the low incidence of epoetin-associated PRCA and the identification of HLA B1*9 in these patients, the authors speculated that there may be a role for major histocompatibility complex–encoded proteins that relates to immune recognition and production of antibodies to recombinant epoetins.[20] This should be interpreted with caution, however, since there have been no further studies supporting this observation.

In the future it is likely that few individuals will develop this serious syndrome. Two factors hypothesized to contribute to the development of antierythropoietin antibodies are the subcutaneous administration of the human serum albumin–free formulation of Eprex and leachates from the rubber stopper of prefilled syringes of this Eprex formulation.[4,35] Coinjection of leachates and either epoetin alfa or ovalbumin results in increased antibody production in BDF-1 mice, demonstrating purportedly adjuvant activity of leachates.[35] In mid-2003, a Teflon coating was added to the rubber stopper of prefilled syringes of human serum albumin–free Eprex. Subsequently, the exposure-adjusted incidence rate decreased 13-fold when this product was administered intravenously to chronic kidney disease patients.[36] However, the relative impact of the Telflon coating of the rubber stopper versus the change to intravenous administration is unclear. Of note, the formulation of the human serum albumin–free Eprex product has not changed since 1998.

The limitations of this study should be identified. First, the diagnosis of epoetin-associated PRCA should be based on results of clinical information, bone marrow examination, and the demonstration of antierythropoietin antibodies (Table 1).[1] Presence of antierythropoietin antibodies has been assessed using several different methods that vary in sensitivity and specificity.[37] At referral labs in Europe, a first set of immunoglobulin assays (RIPA, ELISA, or surface plasmon resonance) are used to identify binding antibodies in patients who are being evaluated for suspected epoetin-associated PRCA. Then, an in vitro bioassay is used to identify the neutralizing ability of the antibodies.[37-42] In the patients reported herein, antibodies were evaluated primarily by radioimmunoassay with only a minority

of the case reports including information on neutralizing antibody assay results. Second, the majority of our cases were obtained from voluntary reports of variable quality submitted by health professionals to government regulatory authorities. A systematic approach to obtain long-term follow-up information could not be pursued.[1] Moreover, median follow-up in this study was 9 months and follow-up information after initial reporting of hematologic recovery was frequently not available. Due to the relatively limited follow-up periods in our database, mortality-related information could not be reported herein. In contrast, the European PRCA Study Group prospectively obtained comprehensive clinical and laboratory information for many patients and was able to report findings on long-term clinical and laboratory information for 47 patients with epoetin-associated PRCA in France, England, and Germany.[18] These patients were identified through collaboration of senior investigators in France and England and following solicitation from the German Society of Clinical Nephrology. The conclusions derived from these 2 studies are reasonably congruent with respect to hematologic recovery rates, whereas Verhelst et al[18] did not report results of PRCA patients who subsequently were re-treated with epoetin products.

In conclusion, review of the worldwide experience with epoetin-associated PRCA indicates that either immunosuppressive therapy alone or renal transplantation is generally necessary for hematologic recovery. Serum from patients with suspected epoetin-associated PRCA should be sent to referral laboratories for comprehensive investigations of possible antierythropoietin antibodies. Epoetin rechallenge could be considered in epoetin-associated PRCA patients with no detectable antierythropoietin antibodies.

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