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Epoetin-associated pure red cell aplasia: past, present, and future considerations

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Abstract

BACKGROUND—Since 1988, millions of patients have received epoetin products intravenously (IV) and subcutaneously. In 1998, epoetin-associated pure red cell aplasia (PRCA) was first reported and causation was attributed to formulations without human serum albumin (HSA), subcutaneous administration, and uncoated rubber stoppers.

STUDY DESIGN AND METHODS—Data on erythropoietin (EPO)-associated PRCA were obtained from the Food and Drug Administration (FDA), regulatory authorities in other countries, and the manufacturers of epoetin alfa, epoetin beta, and darbepoetin. The data included information on numbers of PRCA cases and estimated exposure-adjusted incidence rates by EPO product, anemia etiology, administration route, country of PRCA identification, and date reported.

RESULTS—In 1999, academicians in Paris identified 12 EPO-treated patients with antibody-mediated PRCA; 11 of these patients were on hemodialysis and had received subcutaneous Eprex (Johnson & Johnson). In 2002, authorities in Europe, Australia, Singapore, and Canada mandated Eprex by IV route to hemodialysis patients, and the relevant manufacturers added Teflon coating to prefilled syringes of Eprex; PRCA cases subsequently decreased by 90 percent. By 2003, 180 Eprex-associated PRCA cases were identified in Europe, Canada, Australia, and Asia, despite improvements in handling. Since 2002, FDA safety databases include information on 59 new cases of antibody-associated PRCA, primarily associated with subcutaneous epoetin alfa and darbepoetin that does not contain HSA.

CONCLUSION—Independent actions by regulatory authorities, manufacturers, and academic researchers identified significant numbers of PRCA cases between 1998 and 2003 and characterized the probable etiology. Today, antibody-mediated PRCA is an infrequent class toxicity occurring among some hemodialysis patients on EPOs.

Epoetin-associated pure red cell aplasia (PRCA) is characterized by severe anemia, low reticulocyte count, erythroblasts absence, epoetin nonresponse, and neutralizing antibodies

against erythropoietin (EPO).¹ From 1988 to 1997, three patients developed antibodies to EPO after treatment with the biologic product epoetin.²⁻⁴

In 1998 and 1999, Casadevall and coworkers⁵ unexpectedly identified three cases of epoetin-associated PRCA. Between 1999 and 2004, a total of 191 patients with epoetin-associated PRCA were identified in Australia, Canada, and certain countries of Europe and Asia, 95 percent of which were observed among hemodialysis patients who received several months of subcutaneous Eprex (Johnson & Johnson, New Brunswick, NJ), a particular formulation of epoetin alfa that contained polysorbate 80 as the stabilizer and marketed in countries outside of the United States.⁶ Pharmacovigilance efforts of academic researchers and manufacturers and safety guidance from regulatory authorities in mid-2002 in Europe and 2003 in Canada, Australia, and Singapore resulted in a greater than 95 percent decrease in the number of new cases of Eprex-associated PRCA.⁶ Since 2002, however, 59 cases of antibody-mediated PRCA have been reported worldwide in association with subcutaneous administration of epoetin beta, darbepoetin, and all formulations of epoetin alfa to chronic kidney disease patients. We outline the history, current understanding, and implications of identification of large numbers of cases of antibody-mediated PRCA after administration of erythropoietic products (Table 1).

EPOETIN PRODUCTS

EPOs that are commercially available include epoetin alfa, epoetin beta (in Europe only), and darbepoetin (Table 1). Millions of patients with anemia secondary to chronic kidney disease, cancer, chemotherapy, or human immunodeficiency virus infection have now been treated with this drug.^{7,8} Eprex, an epoetin alfa formulation manufactured by Johnson & Johnson and marketed outside the United States, was the first epoetin to receive regulatory approval in Europe in 1988. Epogen, another epoetin alfa formulation, received regulatory approval in the United States in 1989 and is marketed in the United States by Amgen (Thousand Oaks, CA) for treatment of anemia in patients undergoing hemodialysis and by Johnson & Johnson, under the name of Procrit, through an agreement with Amgen for other indications. Neorecormon, an epoetin beta manufactured by Roche (Indianapolis, IN), received regulatory approval in Europe in 1990. Aranesp, a darbepoetin formulation manufactured by Amgen, received regulatory approval in the United States and other countries in 2001 and 2002. Changes in formulation and route of delivery of epoetin products to hemodialysis patients have occurred over time. For economic reasons, in the early 1990s, physicians outside of the United States adopted the subcutaneous route of administration of epoetin for hemodialysis patients.⁹ In 1998, the human serum albumin (HSA) stabilizer in Eprex was changed to a synthetic compound, polysorbate 80, because of theoretical concerns that albumin might transmit variant Creutzfeldt-Jakob disease. Subsequently, only HSA-free Eprex has been available in Europe.¹⁰ In Canada, Singapore, and Australia, both HSA-free and HSA-containing Eprex are available. Other epoetin products or darbepoetin products have not undergone formulation changes.

MATERIALS AND METHODS

Data on EPO-associated PRCA were obtained from the Food and Drug Administration (FDA), regulatory authorities in other countries, and the manufacturers of the three main recombinant formulations—epoetin alfa, epoetin beta, and darbepoetin. These data included information on numbers of cases and estimated exposure-adjusted incidence rates for antibody-mediated PRCA according to epoetin product, anemia etiology, administration route, country of use, and diagnosis date. Information on regulatory and manufacturer safety-related actions was obtained by reviewing Web site and published notifications for national regulatory authorities and the manufacturers of EPOs. Information on academic safety-related actions was obtained from

review of internal unpublished documents of the coauthors and published material identified in EmBASE and MedLine (MeSH terms epoetin, pure red blood cell aplasia).

RESULTS

Basic science findings

MacDougall and colleagues in England^{11,12} and Casadevall and colleagues⁵ in France established academic referral centers for evaluating serum samples for EPO antibodies among persons in Europe who developed severe anemia while receiving epoetin. Amgen scientists and Casadevall and colleagues reported that EPO antibodies produced in response to Eprex cross-reacted with other epoetin formulations and endogenous EPO.^{13,14} The antibodies are usually of subtype immunoglobulin (Ig)-G1 or IgG4 and are directed against the protein part of the EPO molecule. EPO antibodies are identified by either a radioimmune precipitation assay (RIPA) or an enzyme-linked immunosorbent assay (ELISA). Neutralizing effects of antibodies are confirmed in bioassays involving growth of primary marrow culture or an erythroleukemic cell line. In 2002, Roche scientists in collaboration with academic investigators developed an ELISA to detect EPO antibodies and Johnson & Johnson investigators reported that EPO antibodies formed in mice after exposure to rubber leachates. These leachates appeared to develop in prefilled Eprex syringes with uncoated rubber stoppers.^{15,16} Additional studies did not identify leachates when Teflon coating was added to the stoppers. Johnson & Johnson investigators felt that polysorbate 80 may have increased the immunogenicity of Eprex by eliciting the formation of epoetin-containing micelles or by interacting with leachates released by the uncoated rubber stoppers of prefilled syringes. They also reported that the polysorbate 80 formulation of Eprex has lower stability, making it more susceptible to stress conditions such as insufficient attention to the cold chain—a situation that could facilitate protein denaturation or aggregate formation. An EPO antibody-mediated PRCA rat model was recently developed by administering recombinant human EPO subcutaneously to rats three times weekly for 4 weeks. The rats that developed PRCA were rescued by a synthetic EPO receptor agonist in contrast to those receiving vehicle injections of EPO.¹⁷

Epidemiologic estimates

A small number of studies from academic investigators and one study from the Swiss regulatory authority address epidemiologic findings for EPO-associated PRCA. In 2004, the Canadian PRCA Working Group reported that between 1998 and 2003, the exposure-adjusted PRCA incidence rate per 10,000 chronic kidney disease patients was 2.7 with subcutaneous HSA-free Eprex, 0.2 with subcutaneous epoetin beta or HSA-containing Eprex, and 0.06 with subcutaneous Epogen or Procrit.¹⁸ The RADAR group reported similar exposure-adjusted incidence rates per 10,000 chronic kidney disease patients: 0.2 for Epogen/Procrit, 0.2 for epoetin beta, and 4.5 and 2.0 for Eprex without HSA in 2002 and 2003, respectively; the exposure-adjusted incidence rate per 10,000 patient-years for Eprex-associated PRCA peaked at 4.5 in 2002 and decreased to 2.0 in 2003. Swiss Medic reported that before 2004, a total of 2300 Swiss chronic kidney disease patients had received epoetin alfa or epoetin beta and 5 patients had developed antibody-associated PRCA—resulting in an estimated PRCA incidence with epoetin beta of 0.14 per 10,000 patient-years versus 1.4 per 10,000 patient-years with Eprex.¹⁹

More recently, the manufacturers have reported estimated product-specific rates of EPO-associated PRCA. In 2005, incidence rates of Eprex-associated PRCA occurring between 1989 and April 2004 were reported by Johnson & Johnson.^{15,16} During this period, both uncoated and coated stopper formulations had been available. PRCA incidence rate for patients who received Eprex from syringes with polysorbate 80 and uncoated rubber stoppers was 3.4 per

10,000 patient-years versus 0.2 per 10,000 patient-years for products with polysorbate 80 and coated stoppers. After changes in the route of administration, formulation, and packaging of the Eprex formulation without HSA, Johnson & Johnson–sponsored studies (EPO-IMU-401 and EPO-IMU-402) identified 15 of 9,791 EPO-treated hemodialysis patients who had a loss of epoetin effect with epoetin therapy. All of these patients tested negative for the presence of EPO antibodies using a validated radioimmunoprecipitation assay.²⁰

In December 2005, EPO manufacturers reported exposure-adjusted incidence rates for antibody-mediated PRCA of 0.02 to 0.03 per 10,000 patient-years among patients who received prolonged subcutaneous Epogen, Procrit, darbepoetin, Eprex, or epoetin beta. These data suggest that antibody-mediated PRCA is now a rare class-related toxicity that occurs after extended periods of subcutaneous administration of EPOs to chronic kidney disease patients.

Clinical findings

Academic investigators have published most of the clinical details on EPO-associated PRCA. European investigations of cases of antibody-mediated PRCA began in 1996, when Casadevall and coworkers²¹ reported EPO antibody–mediated PRCA in a patient who had not received epoetin. In 1998 and 1999, her group identified 12 PRCA cases among epoetin-treated hemodialysis chronic kidney disease patients in Paris. By 2002, Casadevall and coworkers⁵ had evaluated 22 epoetin-associated PRCA cases. Twenty-one patients had received the Eprex product, suggesting that the toxicity was product-related. Tolman and colleagues²² in England also identified three clusters of hemodialysis patients who developed PRCA after subcutaneous administration of epoetin beta, raising concern of a class-related toxicity. In Singapore and Australia, regulatory authorities reported that in 2002, 12 and 10 cases of epoetin-associated PRCA, respectively, occurred among patients on hemodialysis.^{23,24} Furthermore, in 2002, FDA officials indicated that their safety database included 78 cases of epoetin-associated PRCA, almost all of which had received Eprex outside of the United States.²⁵ In 2004, Roche submitted reports to the European Committee on Proprietary Medicinal Products describing 13 chronic kidney disease patients who had received subcutaneous epoetin beta and developed antibody-mediated PRCA.⁶ These individuals had received epoetin products for a median of 20 months before PRCA onset versus 8 months for Eprex-associated PRCA cases. Mandreoli and coworkers²⁶ reported an 80-year-old hemodialysis patient who developed antibody-associated PRCA after 4 months of subcutaneous Eprex administration.²⁶ After four doses of rituximab and discontinuation of Eprex, serum samples from the patient revealed low-level epoetin antibodies. One year after the last rituximab treatment, the patient remained transfusion-independent with resumption of intravenously (IV) administered Eprex treatment.

In 2004, investigators with the Research on Adverse Drug Events and Reports (RADAR) project in the United States, in collaboration with Professors Casadevall and Rossert from Paris and Locatelli from Italy, reported 191 hemodialysis patients with epoetin-associated PRCA, 95 percent having received the Eprex formulation via the subcutaneous route.⁶ The study indicated that the annual number of Eprex-associated PRCA cases reached its zenith in Europe in 2002 and in Canada, Australia, and Singapore in 2003—with cases almost exclusively occurring among chronic kidney disease patients who received Eprex subcutaneously. The median time to onset of PRCA was 9 months for PRCA associated with Eprex, 25 months for Epogen/Procrit-associated cases, and 18 months for epoetin-beta associated cases—and almost all of the cases were associated with subcutaneous epoetin administration to chronic kidney disease patients.

Several recently reported cases have identified patients with apparent early onset EPO-associated PRCA with marrow findings of erythroid hypoplasia and a reticulocyte count may not be as low as 20×10^9 per L. Amgen safety officials have received reports of nine patients who developed PRCA after use of Epogen or Procrit—seven had chronic kidney disease and

two had hepatitis C treated with interferon and ribavirin.²⁷ Furthermore, a recent case report describes a hepatitis C virus–infected liver transplant recipient who developed PRCA after several months of Epogen alfa (Procrit) administration and concomitant immunosuppressive agents.²⁸ The PRCA responded to discontinuation of epoetin and continuation of immunosuppressive therapy. RADAR investigators have found that since 2002, a total of 59 cases of EPO-associated PRCA, primarily occurring among hemodialysis patients receiving subcutaneous epoetin alfa or darbepoetin, have been reported to the FDA from the United States, Europe, Canada, and Asia. These findings support EPO-associated PRCA as a class toxicity.

Treatment of EPO-associated PRCA and long-term outcome

Case reports, two case series, and one consensus statement describe the treatment and outcome for EPO-associated PRCA. One case report describes a hemodialysis patient with Eprex-associated PRCA whose EPO antibodies became undetectable after corticosteroid therapy and who subsequently responded to a rechallenge with darbepoetin. Three months later, PRCA recurred when prednisone was discontinued.²⁹ Investigators from Germany, England, and France reported their experience with treatment of 47 patients with Eprex-associated PRCA. 12 Nine patients received no immunosuppressive treatment; none of these recovered. Of 37 patients who received immunosuppressive therapy, 29 (78%) recovered. All 6 patients who received a kidney transplant recovered within 1 month, and recovery rates were between 56 and 88 percent in patients treated with corticosteroids, corticosteroids plus cyclophosphamide, or cyclosporine. There was no relapse of PRCA after discontinuation of immunosuppressive therapy, but no patient was rechallenged with EPO. Academic investigators reported 3 patients with Eprex-associated severe PRCA who required frequent transfusions and were successfully rechallenged with different epoetin molecules;³⁰ 2 of these patients had received immunosuppression.

In 2005, a collaboration of investigators with the Canadian PRCA Focus Group, the European PRCA Working Group, and the RADAR project described long-term outcomes for 170 hemodialysis patients with epoetin-associated PRCA.³¹ Overall, 37 percent of these patients achieved hematologic recovery, with higher rates of recovery being associated with the use of immunosuppressive agents (57% vs. 2%, $p < 0.001$). Of 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%). Among 89 nontransplantation PRCA patients who received immunosuppressive therapies, 49 percent achieved hematologic recovery, with higher recovery rates being associated with cyclosporine. The highest rate of epoetin responsiveness was noted among those who had no detectable EPO antibodies at the time of epoetin administration (89%). Of 14 PRCA patients who were receiving immunosuppressive therapy and had detectable antibody levels at the time of rechallenge, 8 (57%) recovered epoetin responsiveness. Three of 11 PRCA patients who had detectable antibody levels and did not receive immunosuppression responded to epoetin rechallenge (27% response rate). In 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 reevaluated before death in the third patient. Of 15 PRCA patients who did not respond to epoetin retreatment, 3 died, 5 received additional immunosuppressive therapy and ultimately achieved hematologic recovery, 2 remained heavily transfusion-dependent, and long-term clinical follow-up was unavailable for 5 individuals. In an ongoing clinical trial (NCT00314795, <http://www.clinicaltrials.gov.com/>) EPO-associated PRCA cases are being treated with a pegylated peptide-based EPO receptor agonist that does not cross-react with EPO antibodies.^{32,33}

Manufacturer safety notifications and actions

Since 2001, Johnson & Johnson officials have disseminated periodic PRCA updates; the first notifications were warnings placed on the regulatory authorities' Web sites in the United Kingdom, France, Germany, Italy, Spain, and Canada describing rare instances of epoetin-associated PRCA.^{34–38} In 2002, recognizing the fact that the Eprex formulation was implicated in most of the EPO-associated PRCA cases, Johnson & Johnson suggested that breaches in product handling practices might be occurring. Quality control programs were implemented, yet reports of PRCA among hemodialysis patients continued. Next, the company reported that subcutaneous administration of Eprex to hemodialysis patients appeared to enhance immunogenicity. In Canada, Johnson & Johnson revised the product monograph indicating that if IV access is available, hemodialysis patients should receive Eprex IV.³⁹ Otherwise, providers of patients receiving Eprex subcutaneously were directed by the monograph to inform these patients that the risk of PRCA developing, although small, was slightly greater than that with IV administration.

In 2002, Roche reported that PRCA due to epoetins was unlikely to be a class effect. They based this statement on several observations: Eprex and epoetin beta had different carbohydrate structures, basic isoforms, and the type, concentration, and number of stabilizing agents; changes in the Eprex formulation had occurred in 1998 while the epoetin beta formulation had never been changed; and the epoetin beta formulation had always included a Teflon-coated rubber stopper, while the Eprex formulation packaging had switched to this type of stopper in 2003.

In 2002, Amgen revised package inserts for darbepoetin and Epogen to include recommendations that hemodialysis patients with antibody-mediated PRCA not be given other epoetins. Amgen and Johnson & Johnson issued “Dear Doctor” letters in 2006 in the United States indicating that following the FDA’s definitional revision of PRCA (anemia associated with neutralizing antibodies includes both PRCA and severe anemia, with or without a decrease in white blood cells or platelets associated with neutralizing antibodies), rare instances of PRCA with long-term use of Epogen, Procrit, or darbepoetin had been identified.^{40–42} Package inserts now indicate that for hemodialysis patients, the IV rather than subcutaneous route of administration of darbepoetin or epoetin alfa is preferred. If EPO antibody-associated anemia is suspected, the package insert advises physicians to withhold the prescribed drug and contact the manufacturer who will perform assays for binding and neutralizing antibodies. If anemia associated with neutralizing antibodies is confirmed, the prescribed drug should be permanently discontinued. The inserts also indicate that for hemodialysis patients, the IV route of administration is preferred.

Regulatory notifications

In 2001, national regulatory authorities in European Union countries disseminated the first recommendations about epoetin-associated PRCA. These letters advised physicians to suspect epoetin-associated PRCA if chronic kidney disease patients experienced loss of response to epoetin and to discontinue epoetin if the diagnosis was confirmed.^{34–38} In 2001 in Canada, where HSA-free single use and HSA-containing multiuse Eprex vials have been available since 1998, the Canadian Therapeutics Products Directorate recommended IV Eprex administration to hemodialysis patients.⁴³ For economic reasons, many hemodialysis patients continued receiving epoetin subcutaneously and new cases of Eprex-associated PRCA continued to be reported. In December 2002, regulatory authorities in Europe advised that subcutaneous administration of Eprex to patients on hemodialysis was contraindicated. Switzerland, a non-European Union member, acted independently. Swiss Medic reported in 2002 that regulatory authorities in European Union countries mandated IV Eprex administration to chronic kidney disease patients. In mid-2002, Health Canada advised physicians to report suspected PRCA

cases to Health Canada.⁴³ A “Black Box” was added describing PRCA and the importance of Eprex discontinuation if it developed. In 2004, faced with continuing reports of Eprex-associated PRCA cases among hemodialysis patients, Health Canada advised that HSA-free Eprex be administered IV and that if HSA-containing multiuse Eprex vials were used, IV administration was preferred.⁴⁴ Since 2004, only two patients with Eprex-associated PRCA have been identified in Canada.

Of note, in 2005 and 2006, Australia and Canada, respectively, became the first countries to reauthorize subcutaneous administration of the HSA-free formulation of Eprex, after the addition of a Teflon coating to the rubber stopper.⁴⁵ It is not known if more cases of Eprex-associated PRCA in these countries will be identified.

DISCUSSION

Epoetin-associated PRCA is one of the first examples where manufacturers, academic researchers, and national regulatory authorities investigated an emerging international adverse drug reaction (Table 2 and Table 3). Each group investigated unique aspects of pharmaceutical safety.

Manufacturers focused on disseminating safety warnings and evaluating etiologic hypotheses. Initially, Johnson & Johnson suggested that epoetin-associated PRCA was due to a class effect or improper product handling. Subsequently, they reported that EPO antibodies formed after exposure to rubber leachates in HSA-free Eprex syringes that contained uncoated rubber stoppers, although proof of the role of leachates remains elusive.¹⁵ Despite the importance of rapidly controlling the increasing number of new cases of epoetin-associated PRCA and sharing emerging safety findings, representatives from each of the three manufacturers attended no joint meetings.

Regulatory authorities took the lead on risk management, although they too did not coordinate these responses. Safety notifications from European Union regulatory authorities' responses were timely, mandating in late 2002 that Eprex be administered to hemodialysis patients IV with a resultant 90 percent decrease in the annual number of Eprex-associated PRCA cases and the exposure-adjusted incidence rates in these countries. Faced with uncertainty that the subcutaneous administration route was indeed the cause of Eprex-associated PRCA, and concerned about high costs of IV administration and the frequent absence of IV access among nondialyzed chronic kidney disease patients, regulatory authorities in Canada, Singapore, and Australia did not mandate this change; additional Eprex-associated PRCA cases were subsequently identified in these countries. In 2003 and 2004, regulatory authorities in these countries finally mandated administration of Eprex IV to hemodialysis patients or switching to subcutaneous darbepoetin for nondialyzed chronic kidney disease patients. Since this change in 2004, only six cases of Eprex-associated PRCA have been reported.

Academic researchers investigated the epidemiology and clinical and basic laboratory findings of epoetin-associated PRCA (Table 2). While these investigations initially occurred independently, international collaborations rapidly developed. French investigators identified the first 12 cases.⁵ The RADAR group collated clinical information on an additional 179 PRCA patients.⁶ The Canadian PRCA Focus Group and the RADAR group simultaneously reported estimates of the exposure-adjusted incidence rates.^{6,18} International collaborations in 2004 and 2005 facilitated collaborative reporting of consensus diagnostic criteria, treatment recommendations, and long-term follow-up assessments.^{5,46} A European PRCA Working Group indicated that immunosuppression or renal transplantation was required to diminish transfusion dependency among hemodialyzed chronic kidney disease patients with PRCA and cautioned against rechallenge with epoetin products. Academic investigators also served as

informal liaisons for exchanging important clinical and laboratory findings among the three manufacturers and regulatory authorities.

These findings have implications for the emerging field of follow-on biologic products—referred to as biosimilars. The European Medicines Agency (EMA) issued draft guidance in 2005 and made final recommendations in 2006 about these products, operationally defined as synthetic peptides of less than 40 amino acids, monoclonal antibodies, and therapeutic recombinant DNA drug proteins.⁴⁷ A central issue is whether to mandate large safety studies focused on identifying rare instances of antibody formation as a premarketing or postmarketing safety assessment requirement. In March 2006, an appendix document from the EMA indicated that safety assessments conducted alongside two double-blind clinical trials that demonstrated efficacy of a follow-on EPO product could provide necessary preapproval documentation required to assess safety.⁴⁸ After regulatory approval, postmarketing pharmacovigilance will be required to prospectively identify any case of PRCA that occurs among patients who receive the biosimilar product. The FDA has discussed these concerns with advisory groups, but has not yet issued guidance.⁴⁹ In Eastern Europe, a biosimilar recombinant epoetin has been recently developed and approved for marketing in Poland.⁵⁰ Nonclinical safety testing was carried out before the 2006 publication of EMA guidelines on biosimilars. More recently, nonclinical testing was extended to take into account the 2006 EMA guidelines. Regulatory authorities will need to prospectively and diligently look for clinical cases of antibody-mediated PRCA cases when large numbers of patients receive follow-on erythropoietic products in Europe in the coming years.

ABBREVIATIONS

PRCA, pure red cell aplasia; RIPA, radioimmune precipitation assay.

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TABLE 1

Available types or brands and formulations of EPO (with or without albumin)

Formulation	Pharmaceutical company	Countries where sold	Albumin content
Epogen (epoetin alfa)	Amgen	United States only	With albumin
Procrit (epoetin alfa)	Amgen	United States only	With albumin
Eprex (epoetin alfa)	Ortho Biologics LLC	Outside United States only	With albumin (with or without albumin after 1998)
Aranesp (darbepoetin alfa)	Amgen	United States, Europe, Canada, and Australia	With albumin (or polysorbate)
NeoRecormon (epoetin beta)	Roche Pharmaceuticals	Europe	With albumin

TABLE 2

Investigative collaborations among academic investigators, epoetin manufacturers, and national regulatory authorities

Principal investigators	French investigators: Casadevall, Rosert⁵	Canadian investigators: Cournoyer, Messner¹⁸	United States investigators: Bennett, Tallman, Nissenson⁶
Date of first publication (number of PRCA patients)	February 14, 2002 (n = 13)	September 30, 2004 (n = 172)	September 30, 2004 (n = 191)
Primary collaborative work-group (funding source)	European PRCA Work Group (grants, Amgen, Johnson & Johnson)	Canadian PRCA Focus Group (Johnson & Johnson)	Research on Adverse Drug Events and Reports (grants)
Primary focus	Clinical, basic science	Epidemiology	Clinical, epidemiology
Participation in additional work groups (sponsor)	Ad Hoc Working Group for Diagnostic Criteria (Johnson & Johnson)	Ad Hoc Working Group for Diagnostic Criteria (Johnson & Johnson)	None
Participation in manufacturers' advisory boards	Global Safety Advisory Board (Amgen), Immunology Advisory Board (Johnson & Johnson)	None	Global Safety Advisory Board (Amgen)
Primary data sources	Samples and clinical details sent from clinicians in England, France, Germany, and other European countries	Epoetin manufacturers data—worldwide experience	Epoetin manufacturers data and the FDA—worldwide experience
Countries where coinvestigators reside	France, Germany, United Kingdom, Italy	Canada	United States, Italy, Canada, France, Singapore
Presentation to regulatory authorities and manufacturers	1999	2004	2004
Collaboration with the other investigative groups	2003	2004	2003

TABLE 3

Research and risk management activities of the three major epoetin manufacturers

	Johnson & Johnson	Amgen	Roche
Epoetin products manufactured by each company	Eprex—worldwide except for the United States (1998)	Epogen/Procrit (1999)—United States; darbepoetin (Aranesp)—worldwide (2001)	Neorecormon—Europe (1990)
Primary causation theories	Class effect (2001); breaches in cold storage and handling (2001); leachates (2002) uncoated rubber stopper on prefilled HSA-free Eprex syringe (2003)	None reported	Micelles (2002)
Primary research focus	Animal models, epidemiology, technical studies focused on the rubber stopper as a causative factor for leachates	Antibody assays	Antibody assays, micelles
Established internal work groups	2000	2000	2000
Established external advisory groups	Immunology Advisory Board	Global Safety Advisory Board	None
Provided unrestricted grants to academic investigators	Yes	Yes	Yes
Advisory issued not to switch to other epoetins	In 2001	In 2001 and 2003	No
Collaborated with regulatory authority to indicate that subcutaneous Eprex administration was contraindicated	European Union—2002; not done in Singapore, Australia, Canada, or Switzerland	Not applicable	Not applicable
Disseminated risk management advisories in conjunction with warnings from national regulatory authorities	Yes, beginning in 2001; European Union, World Health Organization, Singapore, Australia, Canada	No	No