

ORIGINAL ARTICLE

Pure Red-Cell Aplasia and Epoetin Therapy

Charles L. Bennett, M.D., Ph.D., M.P.P., Stefano Luminari, M.D.,
Allen R. Nissenson, M.D., Martin S. Tallman, M.D., Stephen A. Klinge, B.A.,
Norene McWilliams, J.D., M.P.H., June M. McKoy, M.D., J.D., M.P.H.,
Benjamin Kim, M.D., E. Allison Lyons, B.A., Steve M. Trifilio, R.P.H.,
Dennis W. Raisch, Ph.D., Andrew M. Evens, D.O., Timothy M. Kuzel, M.D.,
Glen T. Schumock, Pharm.D., M.B.A., Steven M. Belknap, M.D.,
Francesco Locatelli, M.D., Jérôme Rossert, M.D., Ph.D.,
and Nicole Casadevall, M.D.

ABSTRACT

BACKGROUND

Between 1988 and 1998, antibody-associated pure red-cell aplasia was reported in three patients who had undergone treatment with recombinant human erythropoietin (epoetin). Between 1998 and 2000, 13 such cases were reported from France — 12 in patients who had received the Eprex formulation of epoetin alfa and 1 in a patient who had received Neorecormon (a formulation of epoetin beta); both are products that are marketed outside the United States.

METHODS

We obtained reports of epoetin-associated pure red-cell aplasia from the Food and Drug Administration and from the manufacturers of Eprex, Epogen (another formulation of epoetin alfa), and Neorecormon. The numbers of case reports and estimates of exposure-adjusted incidence were analyzed according to the product, the cause of anemia, the route of administration, the country in which pure red-cell aplasia was identified, and the date on which pure red-cell aplasia was reported.

RESULTS

Between January 1998 and April 2004, 175 cases of epoetin-associated pure red-cell aplasia were reported for Eprex, 11 cases for Neorecormon, and 5 cases for Epogen. Over half these cases had occurred in France, Canada, the United Kingdom, and Spain. Between 2001 and 2003, the estimated exposure-adjusted incidence was 18 cases per 100,000 patient-years for the Eprex formulation without human serum albumin, 6 per 100,000 patient-years for the Eprex formulation with human serum albumin, 1 case per 100,000 patient-years for Neorecormon, and 0.2 case per 100,000 patient-years for Epogen. After procedures were adopted to ensure appropriate storage, handling, and administration of Eprex to patients with chronic kidney disease, the exposure-adjusted incidence decreased by 83 percent worldwide.

CONCLUSIONS

After the peak incidence of Eprex-associated pure red-cell aplasia was reached in 2001, interventions designed in response to drug-monitoring programs worldwide resulted in a reduction of more than 80 percent in the incidence of pure red-cell aplasia due to Eprex.

From the Midwest Center for Health Services Research and Policy Studies, Jesse Brown Veterans Affairs Medical Center (C.L.B.); Division of Hematology and Oncology (C.L.B., M.S.T., A.M.E., T.M.K.), Division of Geriatrics (J.M.M.), and Division of General Internal Medicine (S.M.B.), all in the Department of Medicine (B.K.); and Institute for Health Services Research and Policy Studies (C.L.B., S.A.K., N.M., E.A.L.), Northwestern University, Feinberg School of Medicine; Robert H. Lurie Comprehensive Cancer Center of Northwestern University (C.L.B., M.S.T., A.M.E., T.M.K.); Department of Pharmacy, Northwestern Memorial Hospital (S.T.); and Center for Pharmacoeconomic Research, College of Pharmacy, University of Illinois at Chicago (G.T.S.) — all in Chicago; Dipartimento di Oncologia ed Ematologia, Università di Modena e Reggio Emilia, Modena, Italy (S.L.); Division of Nephrology, David Geffen School of Medicine at the University of California, Los Angeles (A.R.N.); Veterans Affairs Cooperative Study Program Clinical Research Pharmaceutical Coordinating Center, University of New Mexico, Albuquerque (D.W.R.); Department of Nephrology and Dialysis, A. Manzoni Hospital, Lecco, Italy (F.L.); and Department of Nephrology, Tenon Hospital, Pierre and Marie Curie University (J.R.); and Department of Hematology, Hôtel-Dieu, and INSERM Unité 352 (N.C.) — all in Paris. Address reprint requests to Dr. Bennett at the Midwest Center for Health Services and Policy Research, Jesse Brown Veterans Affairs Medical Center, 333 E. Huron St., Suite 277, Chicago, IL 60611, or at cbenne@northwestern.edu.

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ANTIBODY-MEDIATED PURE RED-CELL aplasia is a rare syndrome of anemia associated with a low reticulocyte count, an absence of erythroblasts in the bone marrow, resistance to recombinant human erythropoietin (epoetin) therapy, and neutralizing antibodies against erythropoietin.¹ Between 1988 and 1998, this syndrome was reported in three patients who had been treated with epoetin.²⁻⁴ By contrast, between 1998 and 2000, 13 patients with chronic kidney disease in France were found to have pure red-cell aplasia with neutralizing antierythropoietin antibodies after receiving epoetin administered subcutaneously¹; 12 patients had received the Eprex formulation of epoetin alfa and 1 Neorecormon (a formulation of epoetin beta), both products that are marketed outside the United States.¹

In response to the reports, the Food and Drug Administration (FDA) collected information on 82 patients worldwide, 78 of whom had received Eprex.⁵ In 2002, health authorities in France, Germany, Italy, Spain, and the United Kingdom concluded that the subcutaneous administration of Eprex should be considered contraindicated for treatment of anemia in patients with chronic kidney disease and mandated the intravenous administration of Eprex, which was thought to be less likely than subcutaneous administration to evoke an immune response.⁶⁻¹¹ In contrast, health authorities in Canada and Australia encouraged, but did not require, intravenous administration.^{12,13} Health officials worldwide also recommended adherence to new storage and handling procedures for Eprex.^{6,14} In 2003, nine cases of antibody-associated pure red-cell aplasia were reported worldwide in patients who had received epoetin.¹⁴⁻¹⁹ In this article investigators from the Research on Adverse Drug Events and Reports group review the international experience with epoetin-associated pure red-cell aplasia.²⁰

METHODS

The FDA's Adverse Event Reporting System receives adverse-event reports for epoetin alfa from drug-monitoring programs worldwide. We reviewed all the reports of cases of pure red-cell aplasia associated with the use of the epoetin alfa products Eprex (Johnson & Johnson; also marketed as Erypo) and Epogen (Amgen; also marketed as Procrit) received between January 1988 and April 2004. Eprex is manufactured in two formulations, one with human serum albumin and the other without human

serum albumin. The two types of Eprex were combined in the results for Eprex in our analysis, unless otherwise specified. Because the FDA does not receive adverse-event reports for epoetin beta, which is licensed outside the United States, adverse-event information for this same period for Neorecormon (Roche; also marketed as Recormon) was obtained from the manufacturer (Ruch R; personal communication).²¹ Estimates of the exposure-adjusted incidence of pure red-cell aplasia in the period from January 1, 2001, to December 31, 2003, were obtained from one of the manufacturers' Web sites, personal communications from the manufacturers of the three products, and a published survey.^{19,22}

The case definition of epoetin-associated pure red-cell aplasia included the use of epoetin and a diagnosis consistent with the syndrome (pure red-cell aplasia, anemia, loss of efficacy of the epoetin product, and drug-specific antibodies). The data reviewed included the reporting date and country where pure red-cell aplasia was identified; the patient's age and sex; the cause of the anemia; and information related to the patient's chronic kidney disease, including the use or nonuse of dialysis, dates of initiation and discontinuation of the use of epoetin, the route of administration, dose, and schedule, and the features of the pure red-cell aplasia. The epoetin product considered to be the cause of pure red-cell aplasia was the product administered when loss of efficacy of epoetin was reported, provided that only this one product had been administered prior to the onset of pure red-cell aplasia.

Worldwide, 506 reports of epoetin-associated red cell aplasia were identified. Pure red-cell aplasia was the most common adverse event associated with the use of epoetin therapy in the database of the FDA's Adverse Event Reporting System.

The most common reasons for exclusion from the study were the absence of documentation of epoetin-associated antibodies (208 cases), the use of multiple epoetin products (44 cases), duplicate reports (34 cases), and features inconsistent with the diagnosis of pure red-cell aplasia (29 cases). The remaining 191 case reports and estimates of exposure-adjusted incidence were analyzed according to the product, cause of anemia, route of administration, country, and reporting date.

RESULTS

The number of cases of epoetin-associated pure red-cell aplasia varied according to product, cause of anemia, route of administration, country, and re-

porting date (Table 1). Drug-monitoring programs in France, Canada, Spain, and the United Kingdom reported 52.3 percent of the total number of 191 cases. The median age of the patients was 67 years for the 175 cases associated with the use of Eprex, 47 years for the 5 cases associated with the use of Epogen, and 51 years for the 11 cases associated with the use of Neorecormon. Most of the patients were male and were undergoing hemodialysis or peritoneal dialysis, nearly all had chronic kidney disease, and nearly all had received epoetin administered by the subcutaneous route. The median duration of treatment with epoetin before pure red-cell aplasia was diagnosed was 9.1 months for patients receiving Eprex, 24.8 months for patients receiving Epogen, and 18.0 months for patients receiving Neorecormon. Before receiving the diagnosis of pure red-cell aplasia, six patients had allergic reactions at the injection sites, which recurred despite changes in the product, the route of administration — from subcutaneous to intravenous — or both. The number of cases per 100,000 patient-years was 18.0 for the Eprex formulation without human serum albumin, 6.0 for the Eprex formulation with human serum albumin, 1.0 for Neorecormon, and 0.2 for Epogen.²²

Temporal trends and geographic variations were most notable for cases associated with Eprex (Fig. 1 and 2). The greatest number of case reports were from Canada, France, the United Kingdom, and Spain. The number of cases reported annually increased in France, the United Kingdom, and Spain until 2001 and in Canada until 2002, and afterward decreased by more than 90 percent in France, the United Kingdom, and Spain and by 80 percent in Canada (Fig. 1). A similar pattern was noted for the exposure-adjusted incidence, which peaked in the United Kingdom, France, and Spain in 2001 and in Canada in 2002 (at more than 60 per 100,000 patient-years in these countries) and decreased in each country by 90 percent in the next year (data not shown). In contrast, between 1998 and 2003, 14 cases were reported in Germany and Italy. Throughout Europe, the estimated exposure-adjusted incidence increased through the end of 2001 and decreased thereafter (Fig. 2).¹⁹

DISCUSSION

Worldwide, the number of cases and the exposure-adjusted incidence of epoetin-associated pure red-cell aplasia began to increase in 1998 and reached

Table 1. Characteristics of 191 Cases of Antibody-Positive Epoetin-Associated Pure Red-Cell Aplasia.*

Characteristic	Epoetin Alfa		Epoetin Beta
	Eprex (N=175)	Epogen (N=5)	Neorecormon (N=11)
Age (yr)			
Median	67	47	51
Range	17–86	11–77	19–74
Male sex (%)	70	40	73
Anemia from chronic kidney disease (%)	97	100	100
Subcutaneous administration (%)	100	60	100
Dialysis (%)			
Any	75	60	82
Hemodialysis	51	0	82
Peritoneal	20	40	0
Unknown type	4	20	0
None	20	20	18
Unknown	6	20	0
Country (%)†			
Canada	16	0	0
France	14	0	9
United Kingdom	13	0	27
Spain	11	0	9
Australia	8	0	0
Germany	4	0	18
Italy	4	0	0
United States	0	100	0
Other European countries	9	0	27
Asia, Africa, and South America	19	0	9
Unknown	1	0	0
Time to initial identification of pure red-cell aplasia (mo)			
Median	9.1	24.8	18.0
Range	0.3–82	3–50	5–54

* Numbers of cases are the numbers of antibody-positive cases in patients who received only one epoetin product. Epogen is also marketed as Procrit, and Neorecormon as Recormon. Percentages may not total 100 because of rounding. † Country denotes the country where cases of pure red-cell aplasia were identified.

a maximum in 2001. The incidence of the syndrome varied according to the product and the route of administration of epoetin, the country, and the reporting date. Eprex, which is marketed outside the United States, accounted for 92 percent of the cases. Almost all cases involved patients with chronic kidney disease who had received subcutaneous injections of epoetin. Beginning in 2002, after improvements were made in the storage and handling of Eprex and in its administration to patients

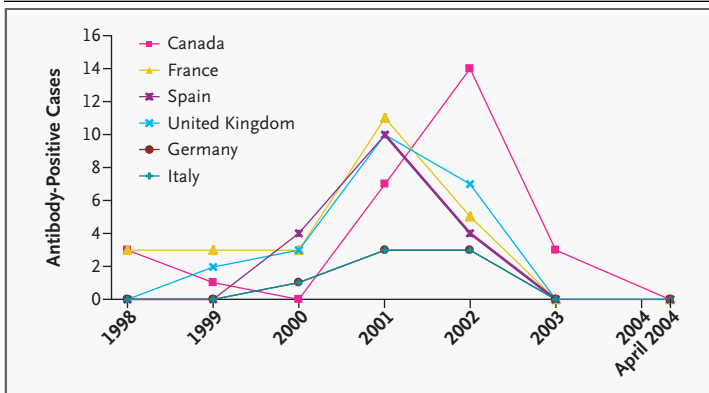


Figure 1. Cases of Antibody-Positive, Eprex-Associated Pure Red-Cell Aplasia Identified in the Database of the Adverse Event Reporting System of the Food and Drug Administration between January 1998 and April 2004.

In Germany and Italy there were the same number of case reports within each year.

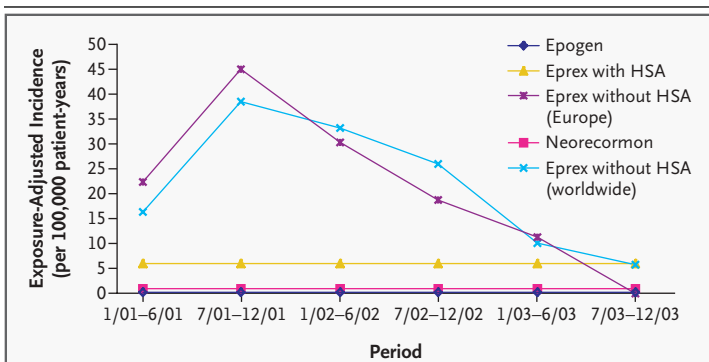


Figure 2. Estimates of the Worldwide Exposure-Adjusted Incidence of Epoetin-Associated Pure Red-Cell Aplasia According to the Product, between January 1, 2001, and December 31, 2003.

HSA denotes human serum albumin. Epogen is also marketed as Procrit, and Neorecormon as Recormon.

of epoetin to subcutaneous administration for patients with chronic kidney disease occurred in many countries, because subcutaneous administration was thought to be more cost-effective and because it avoided the need for intravenous access.^{23,24} As has been noted with other proteins, subcutaneous administration of epoetin, particularly self-administration, with the attendant problems in the storage and handling of the product, has the potential to induce antibody formation.²⁵

In 1998, the formulation of Eprex with human serum albumin that was marketed in Europe was changed in response to concern that human serum albumin could transmit a variant of Creutzfeldt-Jakob disease.²⁶ The reformulated Eprex and the epoetin beta product Neorecormon contain different vehicles (polysorbate 80 and glycine in Eprex, and polysorbate 20, glycine, calcium chloride, urea, and a 5-amino-acid complex in Neorecormon), and different procedures for handling the product are suggested by each manufacturer. In the United States, Epogen, an epoetin alfa product, and the second-generation epoetin product darbepoetin alfa (Aranesp, Amgen) have always included human serum albumin as a stabilizer, whereas in Europe and Canada, darbepoetin alfa is formulated with polysorbate 80 at a lower concentration than in the polysorbate Eprex formulation (0.005 percent vs. 0.03 percent); in Europe, Neorecormon has always included polysorbate 20 as a stabilizer.²² Organic compounds leached by polysorbate 80 from the rubber plungers used in the prefilled syringes of Eprex may also have had a role in the product's immunogenicity.²² In mid-2003, the manufacturer of Eprex replaced the rubber plungers with Teflon-coated plungers. Another potential cause of increased immunogenicity is the use of silicone oil as a lubricant in the prefilled syringes of Eprex, which was introduced in 1994.²²

Between 1998 and 2003, the exposure-adjusted incidence was low and few cases were reported in Italy and Germany. In contrast, between 1998 and 2001, the highest exposure-adjusted incidence and the greatest number of cases had been reported in France and Canada. These four countries receive Eprex from Swiss factories, but there may be important differences in administration, storage, and handling among the countries.^{27,28}

The absence of reports of patients with cancer and epoetin-associated pure red-cell aplasia may be due to chemotherapy-associated immunosuppression. In thrombocytopenia due to the neutral-

with chronic kidney disease, the exposure-adjusted incidence of Eprex-associated pure red-cell aplasia decreased by 83 percent worldwide, dropping nearly to pre-1998 levels.¹⁹

A confluence of factors related to the production, handling, and route of administration of epoetin may account for the increased incidence of Eprex-associated pure red-cell aplasia beginning in 1998. Processes (such as freeze-drying) and formulations that facilitate the oxidation or aggregation of protein can enhance immunogenicity. In the mid-1990s, a shift from intravenous administration

izing antibodies that are evoked by subcutaneous administration of recombinant megakaryocyte-derived growth and development factor, the exposure-adjusted incidence was 30 times higher among healthy volunteers than among patients with cancer who were receiving chemotherapy.²⁹ About two thirds of the cases of Eprex-associated pure red-cell aplasia occurred in male patients, a finding that suggests that sex-related differences may have a role in this syndrome. In patients with chronic kidney disease who do not have permanent vascular access, epoetin continues to be administered subcutaneously^{30,31}; regulatory authorities recommend a specific route of administration only when such patients receive Eprex in the formulation without human serum albumin.

On the basis of the reports, the clinical manifestations of the syndrome of epoetin-associated pure red-cell aplasia were severe. Its onset was characterized by rapid decreases in hemoglobin levels in patients receiving subcutaneous injections of epoetin. In the absence of immunosuppressive treatment, neutralizing antibodies persisted, and patients required frequent red-cell transfusions. Of 37 patients reported to have this syndrome in Germany, the United Kingdom, and France, three quarters responded to treatment with corticosteroids, cyclophosphamide, cyclosporine, or intravenous immune globulin, which resulted in the diminution of antibodies and of the need for transfusions.³² Among the 191 patients identified by worldwide drug-monitoring programs as having epoetin-associated pure red-cell aplasia, several have been successfully retreated with epoetin after receiving immunosuppressive therapy (data not shown). Twenty of these patients also underwent renal transplantation.

Some limitations of our study should be acknowledged. First, cases were included if epoetin

antibodies were identified with the use of either binding assays or bioassays. It is reassuring that in one quarter of the cases, neutralizing antibodies were identified at a single reference laboratory. The antibodies inhibited erythroid-colony formation by normal bone marrow cells *in vitro*. Also, although we excluded patients who had received more than one brand of epoetin before the onset of epoetin-associated pure red-cell aplasia, our findings were quantitatively similar to results that would have included these cases. Delayed or incomplete case reporting and the accuracy of incidence estimates are matters of concern. However, follow-up queries in April 2004 to the FDA and the manufacturers of the epoetin products identified only one additional case, which had occurred during the last quarter of 2003. Despite these limitations, our findings suggest that, since the peak incidence of epoetin-associated pure red-cell aplasia reported in 2001, the subsequent collaboration among national health authorities in conjunction with the manufacturers of epoetin has resulted in a decrease of more than 80 percent worldwide in the incidence of this severe syndrome.

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REFERENCES

- Casadevall N, Nataf J, Viron B, et al. Pure red cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 2002;346:469-75.
- Bergrem H, Danielson BG, Eckardt KU, Kurtz A, Stridsberg M. A case of antierythropoietin antibodies following recombinant erythropoietin treatment. In: Bauer C, Koch KM, Scigalla P, Wiecek L, eds. *Erythropoietin: molecular physiology and clinical applications*. New York: Marcel Dekker, 1993: 265-73.
- Peces R, de la Torre M, Alcazar R, Urra JM. Antibodies against recombinant human erythropoietin in a patient with erythropoietin-resistant anemia. *N Engl J Med* 1996; 335:523-4.
- Prabhakar SS, Muhlfelder T. Antibodies to recombinant human erythropoietin causing pure red cell aplasia. *Clin Nephrol* 1997; 47:331-5.
- Gershon SK, Luksenburg H, Cote TR, Braun MM. Pure red-cell aplasia and recombinant erythropoietin. *N Engl J Med* 2002; 346:1584-6. [Erratum, *N Engl J Med* 2002; 347:458.]
- Intravenous administration required when using Eprex/Erypo (epoetin alfa) in chronic renal failure patients. *Johnson & Johnson News*. December 2, 2002. (Accessed July 30, 2004, at http://www.jnj.com/news/jnj_news/20021202_143150.htm.)
- Agence Francaise de Securite Sanitaire des Produits de Sante. Les lettres aux prescripteurs: Eprex: information importante de pharmacovigilance, 17 decembre 2002. (Accessed July 30, 2004, at <http://agmed.sante.gouv.fr/htm/10/filltrpsc/lp021201.htm#>.)
- Arzneimittelkommission der Deutschen Arzteschaft, Erypo/Eprex (Epoetin alfa). *Art der Anwendung – nur intravenose Applika-*

- tion bei Patienten mit Nierenversagen & Erinnerungshinweis betreffend Lagerung – bei 2-8° C aufbewahren, 11 Dezember 2002. (Accessed July 30, 2004, at http://www.akdae.de/20/40/Archiv/2002/95_20021211.pdf.)
9. Ministero della Salute. Note informative importanti-Epoetina alfa, Gentile Dottore/Dottoressa, 11/12/2002. (Accessed July 30, 2004, at http://www.ministerosalute.it/medicinali/resources/documenti/note_informative/ddl_eprex.pdf.)
10. Agencia Espanola del Medicamento. Nota Informativa Epoetina Alfa: Contraindicacion de la Administracion por via Subcutanea en Pacientes con Insuficiencia Renal Cronica, 2 de diciembre de 2002. (Accessed July 30, 2004, at http://www.agemed.es/documentos/notasPrensa/csmh/2002/cont_epoetina_dic02.htm.)
11. Medicines Control Agency. Eporex (epoetin alfa) and pure red cell aplasia — contraindication of subcutaneous administration to patients with chronic renal disease. (Accessed July 30, 2004, at <http://www.mca.gov.uk/ourwork/monitorsafequalmed/safetymessages/eprex121202.pdf>.)
12. Therapeutic Goods Administration. Epoetin alfa and pure red cell aplasia. Australian Adverse Drug Reactions Bulletin. Vol. 21. No. 3. August 2002. (Accessed July 30, 2004, at <http://www.tga.health.gov.au/adr/aadrb/aadr0208.htm#4>.)
13. Therapeutic Products Directorate. Important safety information: Eporex (epoetin alfa) sterile solution: revised prescribing information for patients with chronic renal failure. (Accessed July 30, 2004, at http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/eprex3_hpc_e.html.)
14. Epoetin alfa: subcutaneous administration and PRCA. World Health Organization Pharmaceuticals Newsletter, 2003. (Accessed July 30, 2004, at <http://www.who.int/medicines/library/pnewslet/1news2003.pdf>.)
15. Epogen (epoetin alfa) prescribing information. (Accessed July 30, 2004, at <http://www.epogen.com/patient/pi.html>.)
16. Procrit (epoetin alfa) full prescribing information, revised September 2003. (Accessed July 30, 2004, at http://www.procrit.com/common/prescribing_information/PROCRIIT/PDF/ProcritBooklet.pdf.)
17. Neorecormon (epoetin beta) brief prescribing information, March 2003. Accessed July 30, 2004, at <http://www.roche-oncology.net/wclc/NeoRecormonSmpc.pdf>.)
18. Information for healthcare providers, February 25, 2004. (Accessed July 30, 2004, at <http://www.amgen.fi/clinicians/prca.html>.)
19. Summary of PRCA case reports. Johnson & Johnson News. January 20, 2004. (Accessed July 30, 2004, at http://www.jnj.com/news/jnj_news/1021024_095632.htm.)
20. Ladewski L, Belknap SM, Nebeker JR, et al. Dissemination of information on potentially fatal adverse drug reactions for cancer drugs from 2000 to 2002: first results from the Research on Adverse Drug Events and Reports Project. *J Clin Oncol* 2003;21:3859-66. [Erratum, *J Clin Oncol* 2004;22:1169.]
21. Swissmedic. Pure red cell aplasia. March 26, 2003. (Accessed July 30, 2004, at http://www.swissmedic.ch/en/industrie/overall.asp?theme=0.00097.00002&theme_id=509&news_id=2588&page=1.)
22. Locatelli F, Aljama P, Barany P, et al. Erythropoiesis-stimulating agents and antibody-mediated pure red-cell aplasia: where are we now and where do we go from here? *Nephrol Dial Transplant* 2004;19:288-93.
23. Kaufman JS, Reda DJ, Eye CL, et al. Subcutaneous compared with intravenous epoetin in patients receiving hemodialysis. *N Engl J Med* 1998;339:578-83.
24. Hynes DM, Stroupe KT, Greer JW, et al. Potential cost savings of erythropoietin administration in end-stage renal disease. *Am J Med* 2002;112:169-75.
25. Porter S. Human immune response to recombinant human proteins. *J Pharm Sci* 2001;90:1-11.
26. Locatelli F, Del Vecchio L. Pure red cell aplasia secondary to treatment with erythropoietin. *Artif Organs* 2003;27:755-8.
27. Rossert J, Casadevall N, Eckardt KU. Anti-erythropoietin antibodies and pure red cell aplasia. *J Am Soc Nephrol* 2004;15:398-406.
28. Locatelli F, Pisoni RL, Combe C, et al. Anaemia in haemodialysis patients of five European countries: association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2004;19:121-32.
29. Li J, Yang C, Xia Y, et al. Thrombocytopenia caused by the development of antibodies to thrombopoietin. *Blood* 2001;98:3241-8.
30. Knauss MD, Walton T, Macon EJ. Switching from intravenous to subcutaneous epoetin in hemodialysis patients. *Am J Health Syst Pharm* 2002;59:1783-4.
31. Kaufman JS. Subcutaneous erythropoietin therapy: efficacy and economic implications. *Am J Kidney Dis* 1998;32:Suppl 4:S147-S151.
32. Verhelst D, Rossert J, Casadevall N, Kruger A, Eckhardt KU, Macdougall IC. Treatment of erythropoietin-induced pure red-cell aplasia: a retrospective study. *Lancet* 2004;363:1768-71.

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