INTRODUCTION

Erythropoiesis Stimulating Agent (ESA) therapy has transformed the management of CKD anaemia over the last couple of decades. Not only is the treatment highly effective, but it is one of the safest therapies that nephrologists use. Adverse effects are uncommon, and apart from occasional exacerbation of hypertension (which is usually easily managed), the treatment is remarkably well tolerated. There have been recent concerns about driving the haemoglobin up to too high a level following the publication of the CHOIR1 and CREATE2 studies, and the subsequent meta-analysis in the Lancet3, but again this is well within the capabilities of the attentive nephrologist.

ESA-associated pure red cell aplasia (PRCA), on the other hand, has in recent years been found to be a sporadic, unpredictable, and serious complication of anaemia therapy, and although this condition is extremely rare, its consequences can be catastrophic4. Patients suffering from this condition develop a rapid fall in haemoglobin concentration associated with a profound reticulocytopenia, and sparse or absent erythroblasts in the bone marrow5. The condition is mediated by antibodies against erythropoietin. These not only neutralise all currently available ESAs, but also the patient's own endogenous erythropoietin, thus obliterating any possible remaining erythropoietic activity in the bone marrow. There is no analytical technique available for identifying the trigger ESA drug.

Prior to 1998, a few isolated cases were reported in the literature, but following the publication of Nicole Casadevall’s case series in the New England Journal of Medicine in February 20026, increasing numbers of cases began to be reported, and there was much effort directed at elucidating the cause of this condition. More specifically, the reasons why some patients broke immune tolerance and developed antibodies against a naturally-occurring recombinant protein were investigated, and several pieces of the “pathogenesis jigsaw” came to light7.

POSSIBLE CONTRIBUTORY CAUSES TO ANTIBODY-MEDIATED PRCA

Early on in the investigations, it was apparent that the increase in reported cases was not simply attributable to increased patient exposure. The latter had been steadily rising from 1989 onwards, while the PRCA cases clearly developed after 1998 (Fig. 1). There was a clear preponderance of cases with epoetin alfa produced outside the US, and the link between this and the removal of human serum albumin from Eprex (mandated by the European Union in an attempt to control a feared outbreak of Creutzfeldt-Jakob disease) became a likely suspect7. Its replacement by polysorbate 80 was also implicated in the “micelles hypothesis”, which was based on the fact that this detergent orientated the recombinant protein in such a way as to render it more antigenic8. All cases of antibody-mediated PRCA reported since 1998 occurred with the use of the subcutaneous (SC) route of administration, and it is well-known that the SC route of administration is more immunogenic in man, due to the presence of Langerhans cells in the epidermis.
Concerns were also raised about possible breaks in the cold storage chain, leading to greater instability of the protein. Finally, the “rubber leachate hypothesis” was proposed as a major contributory factor. Eprex syringes containing both polysorbate 80 and rubber stoppers showed extra peaks on a chromatogram, and the chemical composition of these leachates from the rubber stoppers was determined. The final piece of the jigsaw was to show that these rubber leachates could act as an immune adjuvant, to intensify the immune response, and some in vitro data were generated to support this hypothesis.

Ortho Biotech reacted quickly to their concerns about the “rubber leachate hypothesis”, replacing all the Eprex syringes with teflon-coated stoppers. In addition, their scientists showed that syringes containing teflon-coated stoppers, even when polysorbate 80 was used as the detergent, did not generate any extra peaks on the chromatogram. Thus, the company believed that they had solved this mystery, and the next hurdle was to convince the EMEA that this was the case. The French health regulatory agency (AFSSAPS) was the first (May 2006) to feel that the data had some credibility, and granted Ortho Biotech a re-instatement of their subcutaneous license which had previously been removed. Portugal (INFARMED) followed suit in July. This renewal was, however, dependent on Ortho Biotech setting up a postmarketing surveillance registry to collect data on 20,000 patient years of exposure to all currently available ESAs. This postmarketing surveillance initiative (the PRIMS survey) is now underway.

Why is the mystery not completely solved?

Although the “rubber leachate hypothesis” may have explained the excess number of Eprex-associated cases in Europe, this cannot be the only explanation for antibody-mediated PRCA. This condition has been seen in patients who have received epoetin alfa prepara-
tions containing neither polysorbate 80 nor rubber stoppers, and also with the other currently available ESAs (epoetin beta and darbepoetin alfa). Thus, there is a low background incidence of antibody-associated PRCA which has not yet been explained, and new cases have appeared in Germany, the UK, and more recently Portugal, all within the last year. There is also concern that, with the impending arrival of biosimilar epoetins, there will be a further upsurge in cases of antibody-mediated PRCA. This concern led three French nephrology societies to produce a June 2006 position statement on the approval and use of biosimilars. We applaud this stance and feel more countries should work towards a national consensus on this issue.

**INVESTIGATION OF A SUSPECTED PRCA CASE**

The diagnosis of antibody-mediated PRCA associated with ESA therapy is not subtle. The patient usually experiences rapid onset of transfusion-dependence, along with a reticulocyte count <10x10^9/L. A bone marrow shows absence of erythroid progenitor cells, with the final criterion for the diagnosis of this condition being the detection of circulating antibodies in the serum of the affected patient. The latter is important in excluding other rare causes of PRCA, such as those associated with a thymoma or lymphoma, viral infections, or certain drugs. The vast majority of cases of a loss of response to ESA therapy will not be due to this cause, and other conditions such as bleeding, intercurrent infections, and haemolysis should be excluded first. The ERA-EDTA Anaemia Working Group devised detailed recommendations in 2004 on how nephrologists should proceed in the face of a suspected PRCA case. They also advised that a baseline serum sample be taken and stored prior to switching ESA brands, in order to ascertain more definitively which ESA brand might be responsible if PRCA were to develop.

**MANAGEMENT**

The critical first step in managing a patient who is suspected of having developed antibody-mediated PRCA is to stop the ESA therapy. Patients should not be switched to another ESA since the antibodies cross-react with all currently available agents, and attempts should then be made to suppress the antibody formation with immunosuppressant drugs. Several such agents have been used, including cyclosporin, prednisolone, cyclophosphamide, mycophenolate, and rituximab. The success of these various immunosuppressive regimens is variable but the best chance of remission appears to be with the use of cyclosporin or cyclophosphamide. Plasmapheresis has also been tried, but with disappointing results. Another approach which is currently being tested is to treat such patients with an erythropoietin receptor agonist which does not cross-react with anti-erythropoietin antibodies. This new agent, still in Phase II of its clinical trial programme, is called Hematide, a synthetic erythropoietin-mimetic peptide. Early results from this clinical trial appear promising, and we await the full publication of this study with interest.

**CONCLUSIONS**

Antibody-mediated PRCA is an extremely rare but nevertheless potentially devastating complication of ESA therapy. It is usually fairly obvious clinically, with well-defined characteristics. Its management at the present time consists of stopping all ESAs and instituting immunosuppressive therapy. Although rare, nephrologists should be aware of the features of this condition, in order that an early diagnosis may be made.

The first case of antibody-mediated PRCA in Portugal means that not even this blessed country is spared a visit from this spectre at the feast!

**Conflict of interest statement.**

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Dr Carrera is a scientific consultant, member of steering committees for international clinical trials and/or member of international advisory boards for the following companies: Amgen (Europe), Roche (International) and Shire (International).
References


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