

Dialysis Facility Ownership and Epoetin Dosing in Hemodialysis Patients: A View From Europe

Together with the other articles in this section, the following is a commentary on Thamer M, Zhang Y, Kaufman J, Cotter D, Dong F, Hernan MA: Dialysis facility ownership and epoetin dosing in patients receiving hemodialysis. *JAMA* 297:1667-1674, 2007

Nephrologists in Europe who read the interesting report¹ by Thamer and colleagues published in the *Journal of the American Medical Association* in April 2007 may have been somewhat shocked at the findings in this paper and the allegations that followed its publication in the US press. The major conclusion from this study was that there is considerable variability in epoetin dosing among dialysis facilities in the United States, with significantly higher dosages used in for-profit dialysis chain facilities compared with not-for-profit facilities. The primary interpretation is that for-profit dialysis chains may be using epoetin as a means to enhance profits, whereas not-for-profit facilities are less liable to succumb to this motivation. The aim of this editorial is to discuss potential applicability of the *JAMA* paper to European practices, where the financial arrangements for erythropoiesis-stimulating agent (ESA) therapy are very different, and to provide some insight on reasons for these differences.

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES: WHAT IS THE EUROPEAN EXPERIENCE?

It is not surprising that there is variability in epoetin dosing across dialysis facilities within the United States; Dialysis Outcomes and Practice Patterns Study (DOPPS) data confirmed this finding several years ago.² However, financial incentives that engender these differences are alien to European nephrology practice. Although there is country-by-country variation in ESA therapy funding, the healthcare market in Europe is very sensitive to costs, as the manufacturers of ESA products are only too well aware. Thus, in

contrast to the United States, where epoetin therapy is reimbursed based on quantity administered, and the owner of a dialysis facility can use this reimbursement to enhance profits, epoetin therapy is not reimbursed based on quantity administered in Europe, so dialysis facilities in Europe will often do everything they can to reduce epoetin dosages and costs. This is particularly true in Eastern Europe where funding for ESA therapy is most restrictive, and where subcutaneous administration of epoetin to hemodialysis patients is highly prevalent due to the lower dosage requirements and cost compared with intravenous administration.^{3,4}

In some countries in Europe there is national contracting for ESA products, putting pressure on the ESA suppliers to offer competitive pricing. Until the outbreak of cases of pure red-cell aplasia associated with Eprex (epoetin alfa, Ortho Biotech) in 2002,^{5,6} dialysis facilities in the United Kingdom paid the list price for epoetin products. Following the removal of the subcutaneous licence for Eprex in Europe in 2002, the manufacturers of this particular epoetin product began negotiating discounts of up to 50% to 60% off the list price to compensate for the enforced use of the intravenous route of administration and to try to maintain their market share. Dialysis facilities in the United Kingdom then requested similar discounts from the other 2 ESA manufacturers in the United Kingdom, Amgen and Roche. Somewhat to their surprise, comparable discounts of around 50% to 60% were then offered by these companies.

Over the past several years in the United Kingdom, hospitals and/or dialysis facilities have formed consortia, with a view to contracting for ESA products with a larger volume of business. Recent consortium agreements include a West London contract, a contract for the entire region of Scotland, and a South London contract involving the 4 major hospitals in this region. For these regional consortia, contracts have been awarded to companies offering discounts in the region of

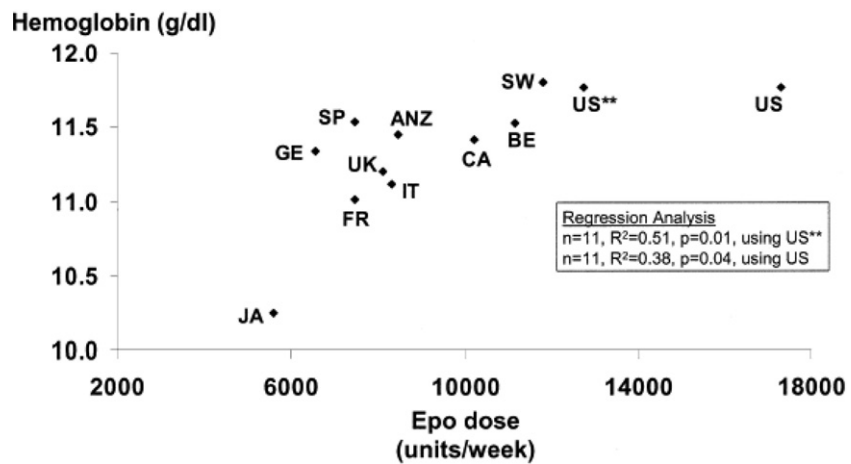
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Figure 1. Unadjusted weekly epoetin (Epo) dose and mean hemoglobin level in prevalent hemodialysis patient by country as seen in 12 countries contributing data to the Dialysis Outcomes and Practice Patterns Study (DOPPS) II in 2002-2003. **US, data for patients excluding those administered >36,000 units per week of epoetin to account for skewed data. Abbreviations: ANZ, Australia/New Zealand; BE, Belgium; CA, Canada; FR, France; GE, Germany; IT, Italy; JA, Japan; SP, Spain; SW, Sweden; UK, United Kingdom. Reprinted with permission from Pisoni et al.²



60% to 70% off the list price. In the United Kingdom at least, nephrologists and dialysis providers recognized that they had been fuelling large profit margins for the ESA manufacturers and used negotiating power to change this trend. Of course, some of these profit margins have been recycled in the promotion of various educational activities, symposia, guideline development, etc.

Nephrologists in the United States, accustomed to the Medicare-reimbursed system, may be inexperienced with the capitation system of the United Kingdom. In the United Kingdom, most dialysis facilities are attached to hospitals. These hospitals have a pharmacy budget for all therapeutic agents, and this budget is set in relation to the number of patients dialyzing. Part of the job of a renal pharmacist in the United Kingdom is to set the budget for the following year, predicting the number of patients requiring treatment as well as the expenditure for increasingly high-cost drugs. This system presents challenges for manufacturers of new ESAs; because the original products have such a good efficacy-safety profile, there is little incentive for dialysis facilities to pay even a small cost premium for novel ESAs that offer slight advantages such as less-frequent dosing.

Another finding in the *JAMA* paper deserves comment. It has been recognized for over a decade that epoetin doses are higher in the United States than in Europe and much of the rest of the world. This was clearly demonstrated in DOPPS,² where mean epoetin doses varied from 5,297 units per week in Japan to 17,360 units per week

in the United States. Although Japan had slightly lower achieved hemoglobin concentrations, the variability in epoetin doses across countries achieving similar hemoglobin levels to the United States was still marked (Fig 1).² There are many reasons for this variability, including practice patterns (arteriovenous fistula use versus dialysis catheter use, intravenous iron utilization, etc) and also socioeconomic factors that relate to epoetin funding and reimbursement. The latter certainly accounts for the disparity in epoetin administration between Western and Eastern Europe, with lower achieved hemoglobin levels and lower epoetin use in the latter region.⁴

The issue of Medicare reimbursement and for-profit dialysis facilities using higher epoetin dosages likely does not fully explain the considerably higher epoetin dosages in the United States compared to Europe, as even the not-for-profit facility in the Thamer article still used a mean dose of epoetin of 17,832 units per week.¹ For a similar achieved hemoglobin level (a mean of 11.7 g/dL) at a similar time period, the mean epoetin dose was 9,570 units per week (median 8,000 units per week) in the United Kingdom (Fig 2).⁷ Lower utilization of arteriovenous fistulas, greater prevalence of comorbid conditions including diabetes, and higher levels of obesity in the United States only partly account for these differences, leaving many unanswered questions.

Use of higher epoetin doses in the United States extends beyond the dialysis population to the population with chronic kidney disease stage 3 to 4, as reported in the Correction of Anemia

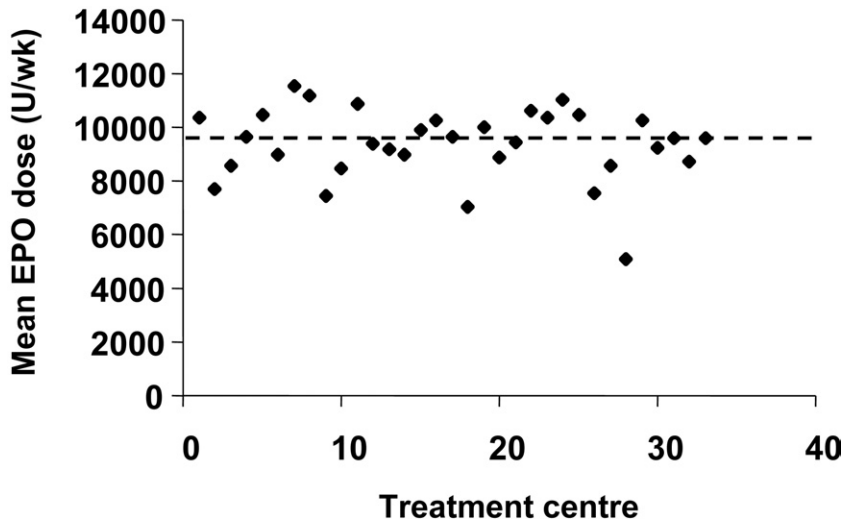


Figure 2. Mean epoetin dose by hemodialysis treatment center in the United Kingdom (data extracted from the UK Renal Registry, Eighth Annual Report, December 2005, p. 144).⁷

with Epoetin Alfa in Chronic Kidney Disease (CHOIR)⁸ and Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia (CREATE)⁹ studies. In the US-based CHOIR study, the mean epoetin dose was 10,694 to 12,884 units per week for the higher target hemoglobin group and 6,057 to 11,098 units per week for the lower target hemoglobin group,⁸ compared with a median of 5,000 units per week for the higher target hemoglobin group and 2,000 units per week for the lower target hemoglobin group for a similar patient population in the European-based CREATE study.⁹

WHAT SHOULD PHYSICIANS DO?

These major differences in epoetin dosages between the United States and Europe have not only economic implications, but may also have effects on morbidity or even mortality. In an observational cohort study, Zhang and colleagues¹⁰ showed that for every given level of achieved hemoglobin, the dosage of epoetin predicted subsequent mortality, and these data, coupled with those from the 3 randomized controlled trials published in the *New England Journal of Medicine* (the US Normal Hematocrit Trial,¹¹ CHOIR,⁸ and CREATE⁹) suggest that it is short-sighted to examine hemoglobin without knowledge or consideration of the epoetin doses used to achieve this. It is still too soon to suggest that the higher epoetin dosages used in the for-profit dialysis facilities in the *JAMA* paper may

increase the risk of death, but this question is certainly worthy of further study. At this time, we do not have a biological explanation for why high dosages of epoetin may be harmful, if indeed this is the case. What we do know is that the circulating plasma levels of erythropoietin associated with epoetin therapy may be at times 100 to 1,000 times greater than the physiological levels in healthy individuals with normal hemoglobin levels.¹² Adverse effects on the endothelium and enhanced thrombogenicity are among possible pathophysiological mechanisms that could be implicated.

In addition to the discrepancy between epoetin dosages in the United States and Europe, there have been tangible differences in the reactions to the publication of the CHOIR and CREATE studies in November last year. The US National Kidney Foundation Kidney Disease Outcomes Quality Initiative Anemia Work Group was reconvened in February 2007, the US Food and Drug Administration announced a black box warning in March 2007, and stringent efforts have been made by many US nephrologists not to target a hemoglobin concentration greater than 12 g/dL. For better or for worse, none of this panicked reaction has been evident in Europe; thus, at the time of writing, the European Renal Association-European Dialysis and Transplant Association has not recalled the European Best Practice Guideline Anaemia Work Group, the European Medicines Agency have not yet publicized an

opinion on this matter, and many nephrologists remain comfortable with hemoglobin levels up to, but not exceeding, 13 g/dL.

Although the main conclusion of the Thamer et al paper is that higher epoetin usage may generate profits for dialysis facilities, many European nephrologists will regard this report as simply highlighting the differences in anaemia management between the United States and Europe, not to mention Australia, Canada, and the rest of the world. Understanding the thinking behind these differences may be useful in optimizing ESA use on both sides of the Atlantic.

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