The economic realities of erythropoiesis-stimulating agent therapy in kidney disease

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The administration of erythropoiesis-stimulating agents (ESAs) in the United States provides a classic example of how economics drive practice. When epoetin was first approved for the treatment of anemia in 1989, its use in hemodialysis patients was very conservative as long as it was reimbursed at a single capitated rate of $40 irrespective of dose. Once epoetin was reimbursed at a rate of $11 per 1000 U in 1991, its use skyrocketed. Despite two iterations of clinical practice guidelines recommending subcutaneous (SC) over intravenous (IV) epoetin administration in hemodialysis patients based on ample evidence that the former is significantly more effective, 95% of hemodialysis patients in the United States receive epoetin IV because epoetin is a profit center for dialysis providers and Medicare has been willing to pay for it. Although darbepoetin is about twice as expensive as epoetin for the same therapeutic effect in patients with chronic kidney disease, darbepoetin has achieved significant market penetration despite the higher cost burden for patients with co-pays and data demonstrating that comparable dosing intervals can be achieved in a majority of patients treated with epoetin. It is likely that increased attention to costs of medications by providers through reimbursement bundling models, payment for performance systems, and competition by newer therapeutic agents will have a significant impact on current practice patterns.

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The influence of economic realities on the erythropoiesis-stimulating agent (ESA) therapy for patients with kidney disease in the United States is undeniable. The most graphic demonstration of this phenomenon is illustrated in Figure 1.[1] Note that during the first year or so after epoetin was first released for use in hemodialysis patients, it was capitated at $40.00 per dose, irrespective of the number of units administered. As a result, use of the medication was quite conservative, averaging approximately 2700 U per patient three times weekly for the entire period. At the beginning of 1991, Medicare changed reimbursement policy for epoetin to $11.00 per 1000 U. This was followed by a rapid escalation of epoetin dosing over the next 3 years, which averaged approximately 4200 U per patient three times weekly by mid-1993.

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The Medicare reimbursement rate for epoetin was subsequently reduced to $10.00 per 1000 U for hemodialysis patients. Nonetheless, most hemodialysis providers could purchase epoetin for considerably less than this reimbursement rate, making epoetin a considerable profit center for dialysis providers in the United States. Therefore, the more epoetin dialysis providers administered, the more money they made. Despite the publication of the first set of clinical practice guidelines for the treatment of anemia in patients chronic kidney disease (CKD) by the National Kidney Foundation's Dialysis Outcomes Quality Initiative in 1997 which recommended the subcutaneous (SC) administration of epoetin in hemodialysis patients,[2] in 2004 only 5% of hemodialysis patients in the United States received their epoetin subcutaneously[3] as opposed to greater than 90% in Europe.[4] The revised clinical practice guidelines for the treatment of anemia in patients with CKD published by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative in 2001[5] also recommended that epoetin be administered SC to hemodialysis patients. Multiple studies and meta-analyses have shown that epoetin is 20–30% more effective when given SC versus intravenously (IV) with an annual cost savings of $1761 \pm $1080 per patient.[6] In 2004, the mean weekly epoetin dose for hemodialysis patients in the United States was 150 U/kg when administered SC versus 198 U/kg when administered IV.[3]

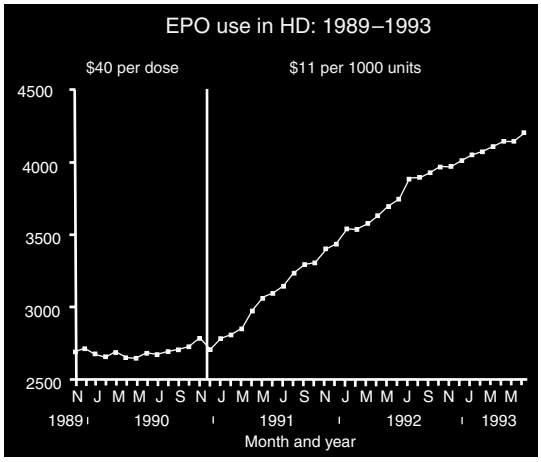

Figure 1 | EPO use in HD: 1989–1993.[1]

So the question arises why dialysis providers in the United States have resisted the recommendations of two iterations of clinical practice guidelines and the standard of care in other parts of the world by continuing to administer epoetin IV in 95% of hemodialysis patients. A number of rationalizations have been offered, including the fact that hemodialysis patients would prefer to avoid the sting of SC injections by receiving the medication IV and that SC erythropoietin carries a risk of pure red cell aplasia, but the reality is that dialysis providers in the United States administer epoetin IV because it makes them more money. Most dialysis providers have an extremely thin margin or actually lose money on the dialysis procedure itself, so they depend upon the profits from separately billable medications such as epoetin to stay in business. Thamer *et al.*[7] demonstrated that although mean hematocrit was not significantly different based on route of administration (34.4% for SC and 34.5% for IV users), the average weekly dose of epoetin was 14 143 U for SC users and 17 956 for IV users. Furthermore, patients were statistically significantly more likely to receive IV epoetin if they were treated in a freestanding for-profit dialysis facility, in a large non-chain facility, if the facility received greater than 11% of its payments attributable to injectables other than epoetin, if the patient resided in the Northeast part of the United States, and if the patient was dialyzed using a catheter. Although it may be difficult to explain the independent regional variation in IV epoetin administration, it is not difficult to suggest that the largest for-profit dialysis chains and non-chain facilities, accountable to their stockholders and Wall Street analysts, are more likely to augment their bottom line by increasing their epoetin use through IV administration. The economic irresponsibility related to the widespread use of IV epoetin in the United States has led to the public questioning of the responsibility and credibility of American nephrologists by a Canadian counterpart.[8]

Understanding the perverse economic incentives that have resulted from the profitability of separately injectable drugs and the unprofitability of the composite rate for hemodialysis treatments in the United States, Medicare in 2005 changed its policy to reimburse separately billable drugs in dialysis at a much less profitable average selling price (ASP) plus 6%, and to add the profit margin that was previously attributable to separately billable drugs to the dialysis composite payment so that total expenditures would be budget neutral. In 2006, this drug profit margin component increased the dialysis composite rate by 14.5%. Although this policy change may be a step in the right direction to economically discourage the excessive use of injectable drugs in dialysis patients, the ASP plus 6% reimbursement rate for epoetin will still make the drug profitable for most providers, encouraging the use of larger doses by IV administration. Eventually, after the completion of a demonstration project, all injectable drugs administered in the hemodialysis unit will be bundled into a case mix adjusted composite rate, at which time these medications will become a cost center rather than a profit center for the provider. At that time, at least two competitors to epoetin, darbepoetin and continuous erythropoietin receptor activator, may have made significant penetration into the hemodialysis market. Both of these newer agents are equally effective when administered IV or SC. As there is no dosing penalty for these newer agents when administered IV, it is likely that IV administration will predominate in the hemodialysis environment irrespective of a bundled composite payment. However, for providers continuing to use epoetin in a bundled payment environment, the dosing penalty of IV administration will inevitably drive an increase in SC use.

On 1 April 2006, Medicare changed its reimbursement policy for ESAs administered to hemodialysis patients. Any ESA claim for a patient with a hematocrit greater than 39% (hemoglobin greater than 13 g/dl) should have a dose reduction of 25% which would be noted using a modifier GS code. ESA claims for patients with a hematocrit greater than 39% without this modifier will have the payment reduced by 25%. This 25% reduction in Medicare payment for ESA administration is based on a month-to-month change in total ESA administered, not a treatment-to-treatment change before and after the dosage reduction has occurred. Therefore, many providers are waiting until the end of the calendar month to reduce the ESA dose in patients with a hematocrit greater than 39%, even though a hematocrit value earlier in the month would have otherwise triggered such a dose titration according the facility's own protocol. This practice results in the excessive use and cost for the ESA during the balance of the month when a dosage reduction might have otherwise occurred, and may increase the potential risks to the patient that are attributable to an elevated hematocrit level.

Another provision of the 1 April 2006 change in Medicare ESA reimbursement policy is that any dose of epoetin greater than 500 000 U or darbepoetin greater than 1500 mcg per month will not be paid at all as this is a 'medically unbelievable error'. The ASP for epoetin in the first quarter of 2006 was $9.027 per 1000 U. Therefore, at the reimbursement