see original article on page 340

Anemia management under a bundled payment policy for dialysis: a preview for the United States from Japan

Jay B. Wish[1]

The goal of a bundled payment policy for dialysis is to decrease overall expenditures and shift financial risk from the payer to the provider. The primary target for cost reduction is invariably erythropoiesis-stimulating agents (ESAs), because of their large costs and potential for dose sparing. Japan succeeded in reducing ESA doses and maintaining stable hemoglobin levels through modest increases in intravenous iron administration. Dialysis providers in the United States have this and other strategies available.

Kidney International (2011) **79,** 265–267. doi:10.1038/ki.2010.459

Given the upcoming 2011 bundling of payments for separately reimbursable drugs such as erythropoiesis-stimulating agents (ESAs) and intravenous (IV) iron into the dialysis payment in the United States, the report by Hasegawa *et al.*[1] (this issue) of Japan's experience with anemia management practices following a similar reimbursement change is particularly timely and relevant. Although the major driving force for reimbursement bundling in the United States was the cost of ESAs, which constitute 10% of Medicare costs for end-stage renal disease (ESRD) patients, it is interesting to note that Japanese policymakers identified a similar economic imperative despite that ESAs constituted only 6% of total costs for ESRD treatment and that reimbursement for ESAs for ESRD patients is capped at 9000 units per week in Japan as opposed to 400,000 units per month in the United States. Nonetheless, the change in Japanese reimbursement policy appears to have had its desired effect of decreasing ESA use while maintaining constant hemoglobin (Hb) levels, largely associated with an increase in IV iron use. It is anticipated that a similar scenario will occur in the United States after January 2011, although in the United States there is also a secular trend of decreasing ESA doses[2] and Hb levels,[3] which began after the publication of the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study[4] in 2006 and was sustained by changes in ESA reimbursement policy in 2008. A secular trend of increased IV iron use in the United States since 2006 has not yet been identified, because of the discontinuation of the ESRD Clinical Performance Measures Project, which previously collected such data, and the lag time for claims data reported in the US Renal Data System Annual Data Report.

Following the publication of the CHOIR study[4] in 2006, which demonstrated increased mortality among patients treated with ESAs to higher target Hb levels, Congress began to apply pressure on Medicare to implement a bundled payment system for dialysis, and a timeline was established in the Medicare Improvements for Patients and Providers Act (MIPPA) of 2008. In September 2009, a proposed rule was released by the Centers for Medicare and Medicaid Services, which was finalized in July 2010 for implementation in January 2011. MIPPA mandated a 2% decrease in overall expenditures for the ESRD program with the onset of bundled payment (as opposed to the targeted reduction of 4% in Japan) but did not specify how that reduction would occur at the provider level. It has been argued that the cost savings of ESAs in a bundled payment environment could be as high as 50% and that these savings should be passed on to Medicare through greater reductions in payment to facilities.[5] This would be achieved by conversion to subcutaneous (SC) ESA administration, more aggressive IV iron use,[6] lowering of Hb targets within the range of 10–12 g/dl, and more conservative use of ESAs in resistant patients.[7]

Despite considerable evidence regarding the potential ESA dose and cost savings of SC versus IV ESA administration,[8] providers in Japan continued to administer ESAs IV in a bundled payment environment, largely because of concerns regarding pure red cell aplasia (PRCA). Whether this will be the case in the United States remains to be seen. PRCA is extremely rare in the United States, perhaps because of consistency of the manufacturing process from a single vendor. Nephrologists in the United States typically administer ESAs SC to anemic patients with chronic kidney disease who are not on dialysis (CKD-ND) and those receiving peritoneal dialysis (CKD-PD), so the SC route of administration is clearly acceptable. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for anemia management in patients with kidney disease recommend IV ESA administration for patients on hemodialysis and SC administration for CKD-ND and CKD-PD patients;[9] this double standard would make it appear that PRCA is not truly a concern and that the major goal is to avoid the sting of SC administration in patients receiving hemodialysis who have an alternate route of ESA administration readily available. The role of patient comfort and

[1]*Division of Nephrology, University Hospitals Case Medical Center, Cleveland, Ohio, USA*
Correspondence: *Jay B. Wish, Division of Nephrology, University Hospitals Case Medical Center, 11100 Euclid Avenue, Cleveland, Ohio 44106, USA. E-mail: jaywish@earthlink.net*

satisfaction in US dialysis facilities has been emphasized by the Medicare requirement that providers administer and respond to patient quality-of-life and experience-of-care instruments on an annual basis. The push-back by patients that may occur, as well as a potential marketing disadvantage, if ESA administration is switched from the IV to the SC route may be enough to give US providers pause in making this change in 2011.

Most of the larger dialysis providers in the United States are already preparing for the bundled payment system by testing ESA and iron protocols to determine which are the most cost-effective. The ability of a provider to achieve consistent Hb levels will be paramount, not only for patient safety (avoiding high Hb levels) and quality of life (avoiding low Hb levels), but also to maximize reimbursement, as Medicare will reward providers financially for keeping patients' Hb levels within the 10- to 12-g/dl range starting in 2012. More consistent application of anemia management algorithms and delegation of protocol-driven ESA and IV iron dose titration to an 'anemia management nurse' within a dialysis facility may be responsible for the decrease in the Hb standard deviation from 1.49 to 1.35 g/dl between 2006 and 2008.[3] It is likely that such anemia management algorithms will cap the ESA dose well below the 400,000 units per month currently reimbursed by Medicare, both to decrease costs and to respond to concerns that such high doses may be associated with adverse patient outcomes.[10] Whether studies raising the latter concern are confounded by indication bias remains controversial, but recent actions by the US Food and Drug Administration to better inform patients regarding the risks of ESA therapy will certainly contribute to a more ESA-conservative culture. It is likely that many patients previously receiving large doses of ESAs to maintain Hb levels in the 10- to 12-g/dl range will experience a decline in Hb to less than 10 g/dl as ESA doses are curtailed. However, it is unclear whether this will lead to poorer outcomes, as the risk interplay of Hb level and ESA dose has yet to be fully elucidated. Some patients may be better off with lower Hb doses and Hb levels less than 10 g/dl. If that proves to be the case, Medicare must reevaluate its anemia payment incentive program to adjust for case mix in such patients.

Under bundling, Japan achieved most of its ESA dose reduction through increased iron dosing.[1] Japan was and continues to be very conservative regarding IV iron therapy because of the higher incidence of hepatitis C and the long dialysis vintage in that country. IV iron is administered on an as-needed intermittent basis when transferrin saturation is less than 20% or serum ferritin less than 100 ng/ml. Unlike in the United States, maintenance IV iron protocols are discouraged. In the United States there has recently been a tendency to liberalize IV iron administration as an ESA-sparing strategy, especially since the publication of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) study and its subsequent analyses.[6] Many US dialysis facilities continue to use a maintenance IV iron protocol of 50–100 mg/wk for patients with transferrin saturation less than 50% and serum ferritin less than 800–1200 ng/dl, and some are administering additional doses of IV iron to maintain transferrin saturation between 30 and 50%. Any additional opportunity for ESA dose and cost sparing with more aggressive IV iron management will probably occur in facilities that have historically been more conservative in their iron administration practices because of concerns regarding IV iron safety. The 2006 National Kidney Foundation KDOQI anemia practice guidelines[9] provided modest guidance on this issue, and further studies are clearly needed to establish the optimal targets for IV iron therapy with respect to both short-term outcomes (Hb level and ESA dosing) and long-term outcomes (safety and mortality).

Although the economic drivers behind bundling of dialysis payment are the same in Japan and the United States, namely, cost savings primarily through reduction in ESA use, the options available to achieve that goal are somewhat different. Japan succeeded through an increase in IV iron use, although still very conservative in comparison with doses used in the United States. SC ESA administration was not an option, because of concerns regarding PRCA, and as the weekly ESA dose was already capped at 9000 units by Japanese reimbursement policy, there was no opportunity to reduce ESA doses in very high users of the drug. In the United States there is already a secular trend toward decreased ESA use based on concerns regarding the safety of high ESA doses and Hb levels, reimbursement policies, and evidence

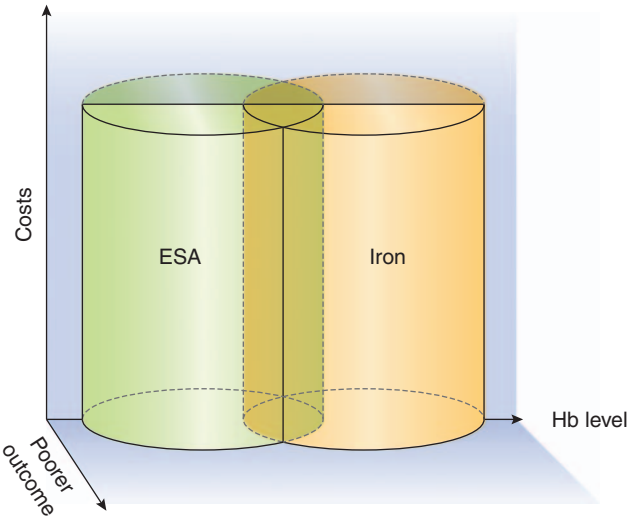

Figure 1 | A conceptual model of the interplay among ESA and IV iron doses, costs, Hb level, and outcomes. The intersection between the ESA and iron cylinders represents the ESA-sparing effect of IV iron. Changing the doses of these drugs changes the size of the cylinders in all dimensions. The height of the cylinders corresponds to costs. The size of the footprint of the cylinders on the horizontal plane correlates with Hb level and potential toxic effects of the drugs, which may affect patient outcomes. The cylinders can move on the horizontal plane depending on the level of ESA resistance. In patients with more ESA resistance (low Hb levels despite high ESA doses), the cylinders move forward and to the left. ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IV, intravenous.

supporting more aggressive IV iron use as being safe and effective. This will no doubt accelerate under a bundled payment system, but it is extremely unlikely that ESA use will decline by the 25–50% predicted by some observers.[5] Although PRCA is not as much a concern in the United States as in Japan, it is not likely there will be a massive shift to SC ESA administration under a bundled payment system; the overall decrease in ESA dose is likely to be similar to that in Japan, in the 10–20% range. It will take many years for Medicare and other analysts to determine whether dialysis patients in the United States are better off with the lower ESA and higher IV iron doses that will inevitably result from efforts at cost conservation. The interplay among ESA dosing, iron dosing, Hb achieved, cost containment, and long-term outcomes (survival) is extremely complex and will require sophisticated models to elucidate (Figure 1). It is hoped that the Centers for Medicare and Medicaid Services and the National Institutes of Health will exploit this unique opportunity to perform a structured analysis of the effects of this radical change in dialysis reimbursement on anemia management processes and outcomes to inform policy makers and providers as US health care attempts to transition to a culture of comparative effectiveness.

DISCLOSURE

JBW has been a consultant to Affymax and Sanofi-Aventis, and has been on scientific advisory boards for Affymax, AMAG, and Sanofi-Aventis and on speaker bureaus for AMAG and Amgen.

REFERENCES

1. Hasegawa T, Bragg-Gresham JL, Pisoni RL *et al.* Changes in anemia management and hemoglobin levels following revision of a bundling policy to incorporate recombinant human erythropoietin. *Kidney Int* 2011; **79**: 340–346.
2. United States Renal Data System. *2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health: Bethesda, MD, 2009, p 340.
3. Spiegel DM, Khan K, Krishnan M *et al.* Changes in hemoglobin level distribution in US dialysis patients from June 2006 to November 2008. *Am J Kidney Dis* 2010; **55**: 113–120.
4. Singh AK, Szczech L, Tang KL *et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; **355**: 2085–2098.
5. Cotter D, Thamer M, Narasimhan K *et al.* Translating epoetin research into practice: the role of government and the use of scientific evidence. *Health Aff* 2006; **25**: 1249–1259.
6. Pizzi LT, Bunz TJ, Coyne DW *et al.* Ferric gluconate treatment provides cost savings in patients with high ferritin and low transferrin saturation. *Kidney Int* 2008; **74**: 1558–1595.
7. Wish JB. Past, present and future of chronic kidney disease anemia management in the United States. *Adv Chronic Kidney Dis* 2009; **16**: 101–108.
8. Besarab A, Reyes CM, Hornberger J. Meta-analysis of subcutaneous versus intravenous epoetin in maintenance treatment of anemia in hemodialysis patients. *Am J Kidney Dis* 2002; **40**: 439–446.
9. National Kidney Foundation. KDOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis* 2006; **47**(Suppl 3): S1–S145.
10. Kilpatrick RD, Critchlow CW, Fishbane S *et al.* Greater epoetin alfa responsiveness is associated with improved survival in hemodialysis patients. *Clin J Am Soc Nephrol* 2008; **3**: 1077–1083.

see original article on page 288

Fueling the fire in acute kidney injury: endothelial cells collect their Toll

Timothy A. Sutton[1] and Pierre C. Dagher[1]

Chen *et al.* demonstrate endothelial expression of Toll-like receptor 4 (TLR4) in the outer medulla of the kidney early in the course of ischemic acute kidney injury. Furthermore, they provide data that support the hypothesis that activation of endothelial TLR4 in the early extension phase of AKI by damage-associated molecular pattern molecules released from injured tubules results in endothelial activation. This activation can serve to amplify inflammation and tubular damage.

Kidney International (2011) **79,** 267–269. doi:10.1038/ki.2010.456

There is a long-standing appreciation that altered vascular function contributes to decreasing glomerular filtration rate during acute kidney injury (AKI). Although overall renal blood flow is only transiently diminished following an inciting insult to the kidney, there is a more persistent and profound (relative to the cortex) decrease in outer medullary blood flow that is implicitly linked to the complex interplay among tubular injury, inflammation, and endothelial alteration.[1] This interplay not only serves to adversely impact glomerular filtration rate but can also promote further tubular-cell injury beyond the initial insult by extending tissue hypoperfusion. Activation of inflammation is an important component of both the initiation and the extension of injury in ischemic AKI, and enhancement of leukocyte–endothelial interactions is a salient feature of this process. Interruption of the leukocyte–endothelial interaction has been an attractive target for therapeutic intervention; however, the mechanisms of endothelial activation in AKI are poorly defined. Chen *et al.*[2] (this issue) shed light on this area by providing evidence that incriminates endothelial Toll-like receptor 4 (TLR4) in the initiation of endothelial-cell activation and further implicates the innate immune system (Figure 1) in the pathophysiology of ischemic AKI.[3]

The recognition of TLR4 as the receptor for endotoxin more than a decade ago revolutionized the fields of innate immunity and infectious diseases. TLR4 is one of more than a dozen receptors belonging

[1]*Division of Nephrology, Department of Medicine and the Indiana Center for Biological Microscopy, Indiana University School of Medicine, Indianapolis, Indiana, USA*
Correspondence: *Timothy A. Sutton, Division of Nephrology, Department of Medicine, Indiana University School of Medicine, 950 West Walnut Street, R-2, 202, Indianapolis, Indiana 46202, USA. E-mail: tsutton2@iupui.edu*