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Changes in anemia management and hemoglobin levels following revision of a bundling policy to incorporate recombinant human erythropoietin

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In April 2006, Japan's health insurance system instituted a bundling policy that included recombinant human erythropoietin (rHuEPO) in outpatient hemodialysis therapy. To evaluate outcomes of this, we analyzed a prospective cohort of hemodialysis patients in the Japan Dialysis Outcomes and Practice Patterns Study, in 53 facilities using prevalent cross-sections of 1584 patients before and 1622 patients after the rHuEPO reimbursement change. Patient data included hemoglobin levels, iron management profiles, and anemia treatment with rHuEPO and intravenous iron. No significant differences were found in pre- or post-policy cross-sections for hemoglobin distributions or the percentage of patients prescribed rHuEPO. Among patients receiving rHuEPO, the mean dose significantly decreased by 11.8 percent. The percentage of patients prescribed intravenous iron over 4 months significantly increased; however, the mean dose of iron did not significantly change. Thus, this bundling policy was associated with reduced rHuEPO doses, increased intravenous iron use, and stable hemoglobin levels in Japanese patients receiving hemodialysis.

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Anemia of chronic kidney disease is mainly caused by relative deficiency of endogenous erythropoietin (EPO) production and is a very common complication of late-stage chronic kidney disease.[1] Therefore, the availability of recombinant human erythropoietin (rHuEPO) analogs, also known as erythropoietin-stimulating agents (ESAs), has had important implications for clinical practice. The introduction of rHuEPO in 1989 led to substantial rises in hemoglobin (Hb) levels among end-stage renal disease (ESRD) patients[2] and reduced the need for blood transfusions.[3] However, several large randomized clinical trials have demonstrated a trend toward increased mortality, or no difference in mortality, in either ESRD or chronic kidney disease patients receiving ESAs targeted to higher Hb levels ($\geqslant$13 g/dl) than those currently recommended in clinical guidelines.[4–8] Furthermore, some studies suggest that higher ESA doses may partially be responsible for the apparent elevation in mortality and morbidity risk associated with the higher Hb targets.[5,9]

Hemoglobin levels and doses of rHuEPO given to hemodialysis (HD) patients have both risen substantially since the introduction of rHuEPO.[10,11] The rHuEPO reimbursement policies in both Japan and the United States were, for many years, based on a fixed payment per dose. In the United States, rHuEPO now comprises nearly 10% of all Medicare costs for ESRD patients.[10] In Japan, rHuEPO payment was fixed per dose until 1 April 2006, and the annual expenditure on rHuEPO before this date was 6% of the total ESRD costs.[12] Thereafter, an rHuEPO bundling policy was initiated for outpatients, such that rHuEPO was not separately billable on a per-dose basis, but instead bundled within overall reimbursement for dialysis services.

In this study, we analyzed data from a representative cohort of HD patients in the Japan Dialysis Outcomes and

Practice Patterns Study (JDOPPS) to investigate the change in anemia treatment practice patterns—including rHuEPO dosing, intravenous (IV) iron use, and laboratory measures of iron stores—from before to after the newly introduced rHuEPO bundled reimbursement policy. We also evaluated practice changes according to different types of HD facility ownership.

RESULTS

Table 1 shows that patient characteristics were generally consistent across cross-sections. The mean age was 62.2 years in January 2006 and 63.0 years in January 2007. Mean HD vintage (duration of ESRD) increased from 8.3 to 8.4 years between the cross-sections. There was no marked change in the prevalence of 13 summary comorbidities over the cross-sections.

Patient Hb distributions by cross-section are shown in Figure 1. No notable differences were observed in the earlier versus later cross-sections for the mean Hb (10.39 g/dl in January 2006 vs 10.38 g/dl in January 2007; $P=0.80$) or median Hb (10.40 g/dl at both times). The overall distributions changed only slightly, with fewer patients having Hb $\geqslant$11 g/dl (from 32.4 to 29.5%; $P=0.06$), but slightly higher mean Hb for patients with Hb $\geqslant$11 g/dl (from 11.74 to 11.86 g/dl).

Figure 2 shows the distribution of rHuEPO doses in each cross-section. The percentages of HD patients prescribed rHuEPO were 81.9 and 82.2% in January 2006 and January 2007, respectively ($P=0.75$). Among patients prescribed rHuEPO, there were 93 patients whose average weekly dose was set to missing because of rHuEPO dose record or was out of the plausible dose range ($<$750 or $>$9000 U per week): $n=46$ (2.9%) and $n=47$ (2.9%) for January 2006 and January 2007, respectively. Those patients were not considered in calculation of the overall mean rHuEPO dose. The rHuEPO dose decreased from 5266 U per week in January 2006 to 4645 U per week in January 2007 (by 11.8%; $P<0.001$). When analyzed as categories of rHuEPO dose ($>$4500 U per week, 3000–4500 U per week, 750–2999 U per week, and not prescribed rHuEPO), the distribution of rHuEPO doses was also different ($P<0.001$) between the two cross-sections.

The distribution of IV iron dosing by cross-section is shown in Figure 3. The percentage of patients prescribed IV iron increased from 31.8% in January 2006 to 41.2% in January 2007 ($+9.4\%$; $P<0.001$). In addition, there were 29 patients prescribed IV iron who had an average monthly dose that was missing: $n=15$ (0.9%) and 14 (0.9%) for

Table 1 | Patient characteristics by cross-section

Patient characteristic	Mean (s.d.) or percentage	
	January 2006 (n=1584)	January 2007 (n=1622)
Demographics		
Age (years)	62.2 (12.2)	63.0 (12.0)
Male	60.7	61.3
Time on ESRD (years)	8.3 (7.1)	8.4 (7.3)
New to dialysis[a]	0.9	1.2
Comorbidities		
Coronary artery disease	40.6	40.1
Congestive heart failure	24.4	24.7
Other cardiac disease	32.9	31.9
Diabetes	32.3	33.5
Hypertension	73.2	74.7
Cerebrovascular disease	12.8	12.5
Peripheral vascular disease	17.6	16.6
Cancer (other than skin)	9.2	9.7
Lung disease	2.5	2.4
History of GI bleed	4.2	4.0
Neurological disease	9.1	7.8
Psychiatric disorder	3.4	3.4
Recurrent cellulitis/gangrene	4.4	3.2

Abbreviations: ESRD, end-stage renal disease; GI, gastrointestinal.
[a]Patients joining Dialysis Outcomes and Practice Patterns Study within 30 days of first-ever dialysis.

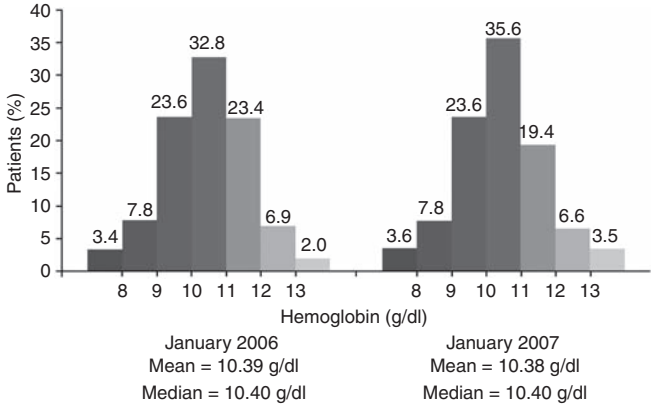

Figure 1 | Distributions of hemoglobin levels by cross-section. Intervals are $<$8, 8 to $<$9, 9 to $<$10, 10 to $<$11, 11 to $<$12, 12 to $<$13, and $\geqslant$13 g/dl.

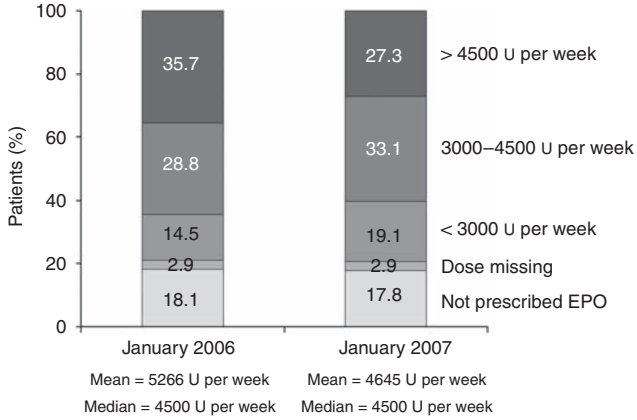

Figure 2 | Distributions of recombinant human erythropoietin (rHuEPO) doses by cross-section. Overall percentage of patients prescribed rHuEPO in January 2006 was 81.9% and in January 2007 was 82.2% ($P=0.75$). Among patients prescribed erythropoietin (EPO), the mean dose was 11.8% lower after bundling ($P<0.001$). The distribution of rHuEPO dose (as captured by the four categories in the figure) also differed between cross-sections ($P<0.001$).

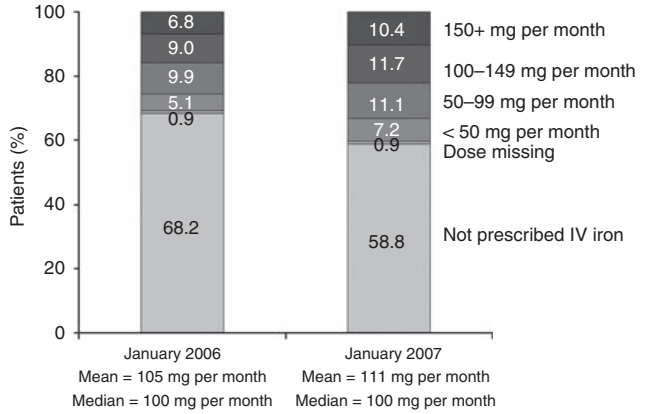

Figure 3 | Distributions of intravenous (IV) iron doses by cross-section. Overall percentage of patients prescribed IV iron in January 2006 was 31.8% and in January 2007 was 41.2% ($P<0.001$). Among patients prescribed IV iron, mean doses rose 6 mg/month ($P=0.15$). The distribution of IV iron prescription (as captured by the five categories in the figure) also differed between cross sections ($P<0.001$).

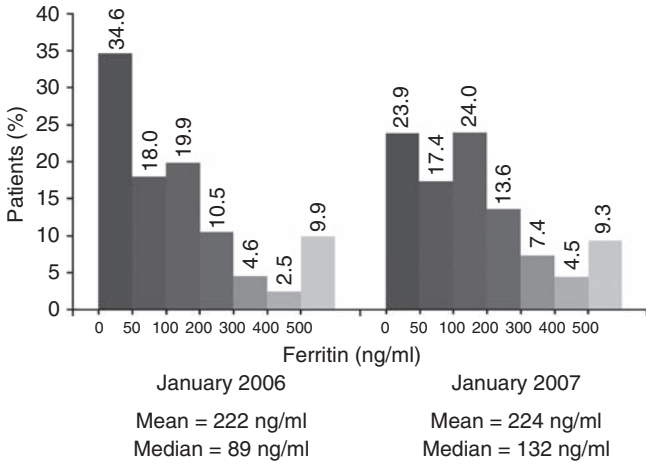

Figure 5 | Distributions of ferritin by cross-section. Intervals are <50, 50 to <100, 100 to <200, 200 to <300, 300 to <400, 400 to <500, and $\geqslant 500$ ng/ml.

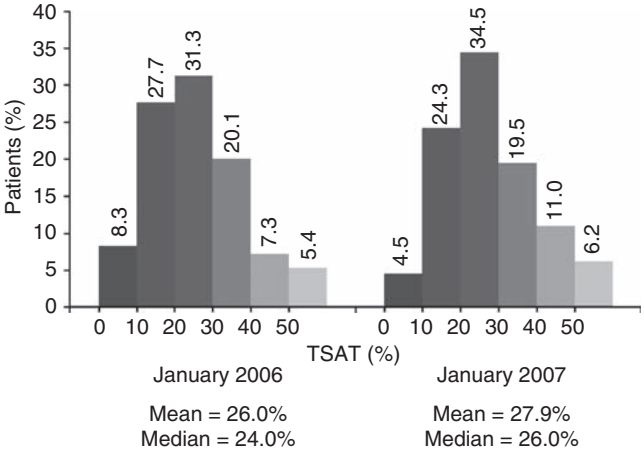

Figure 4 | Distributions of transferrin saturation (TSAT) by cross-section. Intervals are <10, 10 to <20, 20 to <30, 30 to <40, 40 to <50, and $\geqslant 50\%$.

January 2006 and January 2007, respectively. The overall mean IV iron dose among HD patients prescribed IV iron did not differ substantially in the two cross-sections (105 mg per month in January 2006 vs 111 mg per month in January 2007; $P=0.15$). However, the IV iron dose distribution differed ($P<0.001$) between the cross-sections when treated as a categorical variable ($\geqslant 150$ mg per month, 100–149 mg per month, 50–99 mg per month, 1–50 mg per month, and not prescribed IV iron).

The distributions of serum transferrin saturation (TSAT) and ferritin levels by cross-section are presented in Figures 4 and 5. Mean TSAT rose from 26.0% in January 2006 to 27.9% in January 2007 ($+1.9\%$). The percentage of patients with TSAT $<20\%$ decreased from 36.0 to 28.8% (-7.2%), whereas the percentage with TSAT $\geqslant 40\%$ increased from 12.7 to 17.2% ($+4.5\%$). Mean serum ferritin levels were nearly unchanged between the cross-sections (222 ng/ml in January 2006 vs 224 ng/ml in January 2007). However, the percentage of patients with ferritin <100 ng/ml decreased from 52.6 to 41.3% (-11.3%) and the median ferritin levels increased from 89 to 132 ng/ml, suggesting an overall increase in iron repletion of HD patients due to additional iron provision after implementation of the rHuEPO bundling policy.

Table 2 provides trends of anemia treatment and iron management profiles according to Hb strata of <11 and $\geqslant 11$ g/dl. Similar reductions of rHuEPO doses were observed in the higher and lower Hb groups. The mean dose of rHuEPO decreased from 4455 U per week to 4125 U per week ($+7.4\%$; $P=0.01$) in the higher Hb stratum and from 5579 U per week to 4803 U per week ($+13.9\%$; $P<0.001$) in the lower Hb stratum. Among patients with Hb <11 g/dl or $\geqslant 11$ g/dl, the percentage of patients prescribed IV iron increased over the cross-sections (from 30.6 to 41.9% ($+11.3\%$; $P<0.001$) and from 34.1 to 40.6% ($+6.5\%$; $P=0.02$), respectively). The percentages of patients with TSAT $<20\%$ and ferritin <100 ng/ml decreased similarly in the higher and lower Hb groups.

In Table 3, we show change in rHuEPO and IV iron dosing from January 2006 to January 2007 by the type of facility ownership (private clinics, private hospitals, and public hospitals). The change in the percentage of HD patients on rHuEPO differed by type of ownership: the percentage on rHuEPO decreased in the private clinics (-1.5%; $P=0.13$) and public hospitals (-1.5%; $P=0.14$), but increased in private hospitals ($+5.2\%$; $P=0.03$). The mean doses of rHuEPO decreased consistently in each facility ownership type over the cross-sections: by 12.1% in the private clinics ($P<0.001$), by 13.7% in the private hospitals ($P<0.001$), and by 8.8% in the public hospitals ($P=0.002$). The percentage of patients prescribed IV iron increased across facility type,

Table 2 | Trends of anemia treatment and iron management profiles, overall and by Hb levels

	Overall		Hemoglobin <11 g/dl		Hemoglobin ⩾11 g/dl	
Measure	2006	2007	2006	2007	2006	2007
Number of patients[a]	1584	1622	1054	1133	504	473
rHuEPO use						
Patients on rHuEPO (%)	81.9	82.2	89.0	89.9	68.8	65.5
Mean dose (U per week)	5266	4645[b]	5579	4803[b]	4455	4125[c]
Percentage change in dose		−11.8%		−13.9%		−7.4%
IV iron use						
Patients on IV iron (%)	31.8	41.2[b]	30.6	41.9[b]	34.1	40.6[c]
Mean dose (mg per month)	105	111	95	109[c]	123	117
Measures of iron stores						
TSAT (mean, %)	26.0	27.9[b]	25.1	27.7[c]	27.7	28.5
TSAT <20% (%)	36.0	28.8[c]	38.2	28.8[c]	32.0	29.1
Ferritin (mean, ng/ml)	222	224	240	238	182	187
Ferritin <100 ng/ml (%)	52.6	41.3[b]	52.3	39.0[b]	53.0	47.2[d]

Abbreviations: Hb, hemoglobin; IV, intravenous; rHuEPO, recombinant human erythropoietin; TSAT, transferrin saturation.
[a]Patient numbers by Hb levels does not equal overall number because of missing Hb values ($n=26$ and 16 for January 2006 and January 2007, respectively).
[b]$P\leqslant 0.001$ vs January 2006 value.
[c]$0.001<P\leqslant 0.05$ vs January 2006 value.
[d]$0.05<P\leqslant 0.10$ vs January 2006 value.

Table 3 | Trends of anemia treatment and iron management profiles, by facility ownership type

	Private clinics (*n*=27 facilities)		Private hospitals (*n*=14 facilities)		Public hospitals (*n*=12 facilities)		
Measure	2006	2007	2006	2007	2006	2007	*P*-value for interaction[a]
Number of patients (*n*)	824	837	440	464	320	321	—
Hemoglobin (g/dl)	10.40	10.33	10.58	10.49	10.13	10.36[b]	0.01
rHuEPO use							
Patients on rHuEPO (%)	80.5	79.0	78.4	83.6[b]	90.3	88.8	0.01
Mean dose (U per week)	4879	4287[c]	5347	4615[c]	6063	5528[b]	0.65
Percentage change in dose		−12.1%		−13.7%		−8.8%	
IV iron use							
Patients on IV iron (%)	28.9	37.5[c]	34.1	48.7[c]	35.9	40.2	0.10
Mean dose (mg per month)	113	119	95	104	102	108	0.92

Abbreviations: IV, intravenous; rHuEPO, recombinant human erythropoietin.
[a]*P*-values for interaction between changes in each measure and ownership type.
[b]$0.001<P\leqslant 0.05$ vs January 2006 value.
[c]$P\leqslant 0.001$ vs January 2006 value.

but was more remarkable in the private clinics (+8.6%; $P<0.001$) and hospitals (+14.6%; $P<0.001$) than in the public hospitals (+4.3%; $P=0.24$). The change in mean monthly IV iron dose was similar across facility types.

DISCUSSION

The Japanese government introduced an rHuEPO bundling policy for outpatient HD patients in April 2006 with the aim to curtail overall dialysis payments by 4%. With this rule, outpatient ESA reimbursement changed from a fixed payment per units of administered rHuEPO to a payment that included rHuEPO independent of its dose (bundling).

Payment for each dialysis treatment was increased by 2900 yen (~30 US dollars), irrespective of rHuEPO use. In this study, using two cross-sections of HD patients in JDOPPS, we investigated the shift in anemia treatment practice patterns before versus after the April 2006 change in outpatient ESA reimbursement. Data from the cross-sections before and after the change in rHuEPO reimbursement indicate that the distribution of Hb levels was essentially unchanged (Figure 1). Although the percentage of patients on rHuEPO did not change appreciably, the overall mean rHuEPO doses among the 82% of patients treated with rHuEPO decreased by 11.8% (Figure 2). The overall percentage of patients prescribed IV iron increased by 9.6% between the cross-sections (Figure 3).

Longitudinal trends in anemia management practices in Japan before the new ESA reimbursement policy of April 2006[13] need to be considered when comparing data from January 2006 with that from January 2007. Akizawa *et al.*

described that mean Hb level rose from 9.7 g/dl (1999) to 10.1 g/dl (2002) to 10.4 g/dl (2006) ($P<0.0001$). That change was likely, in part, due to the clinical guidelines for renal anemia of ESRD patients released by the Japanese Society for Dialysis Therapy (JSDT) in 2004.[14] Our data indicate that the mean Hb level had stabilized before implementation of the bundle in 2006 (mean Hb = 10.5 g/dl in 2005). The percentage of patients prescribed rHuEPO and IV iron were 83 and 32%, respectively, and both remained constant in the 7-year (1999–2006) observation period. Similarly, mean rHuEPO doses did not change substantially during the years preceding the policy change (5176 U per week in 2002 to 5231 U per week in 2006).[13] Thus, the observed trends from pre- to post-policy change do not appear to be explained by continuation of a prior trend in anemia management.

We looked for concurrent changes in case mix and observed no difference in mean patient age or comorbidity burden among Japanese HD patients over the cross-sections in this investigation (Table 1). Therefore, the decrease in mean rHuEPO dose and increase in percentage of patients prescribed IV iron were likely mostly attributable to the newly introduced rHuEPO reimbursement policy.

These rHuEPO doses and Hb levels are markedly lower in Japan than in Western countries, as shown by the Dialysis Outcomes and Practice Patterns Study (DOPPS).[15–17] Differences are largely because of Japanese practice guidelines, the rHuEPO package insert, and the reimbursement policy. The 2004 JSDT guideline is most relevant to the current publication, as the guideline was next updated in 2008 (after the study period). The 2004 JSDT guideline for renal anemia in HD patients recommended a target Hb of 10–11 g/dl for most HD patients and 11–12 g/dl for relatively younger active HD patients.[14] It indicated that rHuEPO should be injected (IV) through the dialysis circuit because of concerns about the onset of pure red cell aplasia. Until these guidelines were released, Japanese physicians had generally adhered to the targeted Hb level according to the rHuEPO package insert in Japan ($\sim$10 g/dl). The maximum dose of rHuEPO has been limited to 9000 U per week for HD patients by the Japanese package insert and (until April 2006) by Japanese reimbursement policy. Additionally, Akizawa *et al.*[13] reported that >90% of pre-dialysis session blood samples in Japan were drawn in the supine position and at the first dialysis session of the week, and that these may partly account for the lower reported Hb levels than that observed in the other DOPPS participating countries.

Japanese HD patients were also least likely to be prescribed IV iron among the 12 DOPPS countries.[15–17] The 2004 JSDT recommendation for the target iron profiles are more conservative (TSAT >20%, serum ferritin >100 ng/ml) than some other countries' guidelines.[18,19] The criteria for starting iron administration was TSAT <20% or serum ferritin <100 mg/ml, with iron preparation IV injected. The recommended iron administration regimen is as follows: iron preparation of 40 mg is administrated for a total of 13 consecutive dialysis treatments or once weekly for 3 months. The JSDT guideline does not set the upper limit of iron indices. It recommends transient, rather than continuous ('maintenance'), administration only in the presence of iron deficiency, considering the risk of iron overload more sensitively in the Japanese setting such as greater prevalence of patients with hepatitis C and with longer HD vintage compared with other countries, etc. This may be one of the barriers to more liberal IV iron use in Japan. Despite these conservative management practices for renal anemia, the mortality rate of HD patients in Japan has been the lowest among the 12 DOPPS countries.[20,21]

The hypothesis that the anemia management response to bundling differed by the type of HD facility ownership was partly supported by this study. Whereas the mean rHuEPO dose fell similarly in all three facility types, the percentage of patients treated with rHuEPO increased in private hospitals and decreased in other facility types. The increase in the proportion of HD patients on IV iron was somewhat larger in private clinics and private hospitals than in public hospitals over the cross-sections. No international data on similar policy changes are currently available; however, practice differences by type of HD facility ownership have been described in the United States. The US Renal Data System data has shown large variations in rHuEPO doses among HD facilities, and that large for-profit chain facilities prescribed higher rHuEPO doses with higher achieved Hb levels than non-profit facilities.[22] Similarly, exceeding the target Hb levels recommended by National Kidney Foundation–Kidney Disease Outcomes Quality Initiative guidelines in 2006[23] (11 to <13 g/dl) was more common in for-profit facilities than in non-profit ones.[24] However, in general, for-profit healthcare providers are prohibited in Japan. Japanese dialysis facilities are divided into public hospitals (for example, national hospitals, municipal hospitals, or semipublic entities such as universities or the Red Cross Society), private hospitals, and solo practice (private) clinics. Some private hospitals and clinics are owned and operated by large dialysis chains in Japan, but they are not 'truly for profit' entities. Therefore, it is difficult to compare the differences in practice patterns among provider types between Japan and the United States.

The clinical impact of changes in anemia management over this time period in Japan remains unknown. Beyond regulation of red blood cell production, pleiotropic effects of ESAs have been identified as possible explanations for potential benefit or harm of supraphysiological ESA dosing. With respect to IV iron, several past studies have shown that its use can reduce average rHuEPO dose.[25,26] Moreover, recent investigations indicated that IV iron therapy raised Hb levels and improved rHuEPO responsiveness in HD patients with low TSAT, even when serum ferritin was elevated.[27,28] Meanwhile, avoiding iron overload may be necessary to prevent potential adverse effects such as exacerbation of infection[29] including hepatitis C.[30] Although the possibility of increased risk with increased IV iron therapy merits

additional study, the observed increase of IV iron given, as well as the rise in serum TSAT and ferritin levels, were relatively small in this observation period.

As a potential limitation, JDOPPS dialysis facilities may not perfectly reflect national data. However, JDOPPS prospectively collected data using stratified random selection of facilities to be nationally representative and random selection of patients within facilities to reduce data collection burden. Of the 60 facilities selected, 88% (53 facilities) contributed data for the time frame of these analyses. Although the secular trends that we have observed are likely attributable to bundling, we cannot rule out other causes of change in clinical practice. It is also possible that additional changes in response to the April 2006 rHuEPO bundling policy will occur beyond our median follow-up date of January 2007. Moreover, we suggest caution when applying the findings in Japan to predict changes in practice and Hb levels in other countries (for example, in response to ESA bundling in the United States, which is anticipated in 2011), because Hb values and ESA and iron dosing are notably lower in Japan than in other countries.

In conclusion, in this short-term observational study among representative Japanese HD patients following a new ESA reimbursement policy that bundled rHuEPO into the outpatient dialysis services payment since April 2006, rHuEPO doses decreased and IV iron use increased, while mean Hb values remained stable. Although the patterns differed slightly by type of HD facility, the overall directions of change (lower rHuEPO dose, greater IV iron use) were consistent across facility type. Evaluation of the impact of these changes in practice on clinical outcomes will require longer-term follow-up. The need remains to identify ESA and iron dosing strategies that optimize patient outcomes and cost effectiveness.

METHODS

Data sources

The DOPPS is an observational study of HD patients randomly selected from nationally representative facilities in 12 industrialized countries. Detailed information on the sampling plan and study methods has been described.[31,32] Data for this analysis came from JDOPPS3 (2005–2008). All patients were at least 18 years of age at study enrollment.

Data collection

A total of 53 HD units from Japan were included for analysis. These units had data from prevalent cross-sections of patients before and after the date of change in rHuEPO reimbursement (1 April 2006). The first cross-section had a median date of January 2006 (range 1 November 2005 to 27 February 2006) and included 1584 patients. The second cross-section had a median date of January 2007 (range 1 November 2006 to 27 February 2007) and included 1622 patients. Patients who were in the first cross-section, but had left the study before the second cross-section, were replaced by randomly selected patients new to the dialysis facility since the time of the first cross-section. Patient information was collected without identifiers in order to maintain patient anonymity. Informed consent was obtained for each sampled patient as required from local or national ethics committees or institutional review board. Patient data on rHuEPO dosing, IV iron dosing, and laboratory values were abstracted from patient records every 4 months by a nurse coordinator in each HD unit. To simplify analysis, only patients prescribed IV rHuEPO (Epoetin alfa or Epoetin beta) were included in this study. Seven HD patients (0.2%) who were prescribed subcutaneous rHuEPO and two HD patients on Darbepoetin alfa (a long-acting ESA approved for use in Japan in July 2007) were excluded. The rHuEPO use was defined as any use (yes/no) over the most recent month. The rHuEPO dose (U per week) was calculated as the average weekly dose over the most recent 4-week period. IV iron use was defined as any use (yes/no) over the last 4 months. IV iron dose (mg per month) was calculated as the average monthly dose over the most recent 4 months.

The plausible rHuEPO dose range was set at 750–9000 U per week, with 9000 U per week as the upper limit, because this is the restricted maximum dose of rHuEPO in the Japanese system. A total of 24 and 11 patients had rHuEPO doses either <750 or >9000 U per week, respectively. These patients were prescribed rHuEPO, but their rHuEPO doses were set to missing, and they were not used in the calculation of average weekly dose. For patients missing reported TSAT, the measure was calculated as 100 $\times$ serum iron/total iron binding capacity, when these values were reported.

Trends from the first to second cross-section of Hb levels, serum ferritin and TSAT levels, and treatment with rHuEPO and IV iron were analyzed. Patient characteristics examined at each cross-section included age, sex, HD vintage, and the 13 summary comorbidities listed in Table 1. A patient was considered new to (incident) dialysis if he or she entered the study within 30 days of their first-ever dialysis treatment. Types of facility ownership considered in the analysis were private clinics, private hospitals, and public hospitals.

Statistical analysis

Descriptive statistics at each cross-section were used to report differences over time in treatment and laboratory values. Linear mixed models were used to test for differences in continuous variables (for example, Hb levels) between the cross-sections, and accounted for the correlation between patients present in both cross-sections. Ratios (for example, percentage medication use) were compared between the cross-sections using a χ^2-test. All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC).

DISCLOSURE

SF is an Advisor of Quality of Life on a valuation and epidemiology study for Kyowa Hakko Kirin and receives consulting fees from Kyowa Hakko Kirin. TA is a consultant and has grants with Kirin and Chugai.

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