Secular trends in recombinant erythropoietin therapy among the U.S. hemodialysis population: 1990–1996

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Background. Chronic anemia is a major cause of morbidity among the end-stage renal disease (ESRD) population. Recombinant erythropoietin (rHuEPO) has been recognized as a major advance in the treatment of anemia among the ESRD population. This study examines the secular trends in the use of and response to rHuEPO therapy among severely, moderately and mildly anemic hemodialysis patients.

Methods. We designed a cohort analytic study using seven years of claims data. The study population comprised all facility-based adult hemodialysis patients receiving rHuEPO therapy, who were initially reimbursed by Medicare in each of the first quarter of the calendar years 1990 through 1996 ($N = 64,957$).

Results. Between 1990 and 1996, the mean rHuEPO dose increased by 139% for the patient cohorts with a first observed hematocrit <0.25, 122% for the 0.25 to 0.29 cohorts, and 107% for the ≥0.30 cohorts, and produced a 0.02 to 0.03 increase in achieved hematocrit (A-Hct) over this time. Dosing of rHuEPO did not appear to be influenced by patient or provider characteristics, although African-Americans, the elderly, non-diabetics and persons receiving dialysis in a non-profit facility had a larger percent change in hematocrit compared to their counterparts ($P < 0.001$).

Conclusions. The results of the clinical use of rHuEPO seven years after FDA approval found in the general ESRD hemodialysis population have not equaled the results obtained in the initial clinical trials. Overall, our findings suggest that substantial increases in rHuEPO dose provided to anemic patients have resulted in only modest increases in hematocrit in the seven years since rHuEPO's introduction. Resistance to rHuEPO, prior rHuEPO treatment, inadequate use of supplemental iron, and policy and financial incentives may explain this finding.

Chronic anemia is a major cause of morbidity among the end-stage renal disease (ESRD) patient population, partic-

ularly among those who undergo hemodialysis therapy, a treatment that is provided to the vast majority of ESRD patients. Anemia primarily results from a relative or absolute deficiency of erythropoietin production by the kidneys. Based on clinical trial results, recombinant human erythropoietin (rHuEPO) was recognized as being beneficial for persons with anemia related to chronic renal failure and end-stage renal disease (ESRD) [1, 2]. In Phase I and II clinical trials, Eschbach et al reported that 25 patients had a baseline hematocrit (Hct) of 0.194 ± 0.027 and 12 of 25 patients were transfusion-dependent (receiving one or more transfusion per month) when rHuEPO therapy began [2]. Results of the combined Phase I and II clinical trial indicated that among the study population of hemodialysis patients with Hct of less than or equal to 0.25, a dose of 50 units per kilogram of body wt or higher thrice weekly resulted in a dose-dependent increase in Hct. In some cases, the average Hct doubled within four to five weeks during the clinical trials.

In the subsequent Phase III multicenter clinical trial that was designed to determine the overall effectiveness and safety of rHuEPO in a larger population of ESRD patients, rHuEPO was found to be effective for virtually all anemic patients (Hct <0.30) treated with hemodialysis [1]. Within 12 weeks, the baseline average Hct of 0.223 ± 0.002 increased to 0.35 ± 0.03 for 97% of all study patients using an average dose of 300 or 150 U/kg body wt. Eschbach et al also reported that as a group, the 333 Phase III patients received an average of 0.52 units of blood per patient per month before rHuEPO therapy. Patients became virtually transfusion-independent after rHuEPO therapy began during the clinical trial. More recently, the United States Renal Data System (USRDS) also reported that outpatient use of blood transfusions among the hemodialysis patients fell from a level of 15% prior to introduction of rHuEPO therapy to 5% by the last quarter of 1992 [3].

Medicare, which covers approximately 93% of all ESRD patients in the United States, began coverage for rHuEPO in June 1989. Medicare's coverage and reimbursement policy objectives were designed to encourage cost effective

rHuEPO therapy. For patients to qualify for Medicare coverage of rHuEPO therapy, the Health Care Financing Administration (HCFA) requires a patient's first observed Hct to be below 0.30. Once rHuEPO therapy has been initiated, the HCFA reimbursement policy established a target Hct range of between 0.30 and 0.33, despite the fact that the clinical trials used a much higher hematocrit target of 0.32 to 0.38, with an average achieved hematocrit of 0.36. Because of the narrowness of the target range selected by HCFA, its contractors allow the Hct to rise to 0.36 before initiating a medical review of rHuEPO claims. By implementing this rule, the HCFA, for the first time, required the reporting of a physiological parameter in its claims data. This decision facilitated clinical research on the census of ESRD patients regarding the effect of EPO dosing. In January 1991, Congress changed the Medicare reimbursement policy from a fixed "per administration" payment rate independent of the amount administered to a variable "total amount delivered" payment rate dependent on the amount administered. The rationale for this change was that "per administration" policy failed to encourage optimal rHuEPO therapy (or encouraged ineffective low rHuEPO doses), which resulted in many patients not achieving the desired target Hct range of between 0.30 and 0.33.

The diffusion of rHuEPO among the ESRD population was rapid, growing from 3.9% of ESRD beneficiaries in July 1989 to 53.0% in only eleven months [4, 5]. Studies of rHuEPO practice patterns in the early years of its availability describe a low dosing regimen with concomitant low achieved Hct, relative to clinical trial results [4, 6, 7]. In subsequent years, after Congress changed HCFA's reimbursement policy from a fixed rate to a variable rate, a dramatic increase in the amount of rHuEPO administered relative to the original first year dosing recommendations occurred [8]. Financial reasons as well as target Hct levels imposed by HCFA have been implicated in the increased dosing of rHuEPO [9, 10]. Expenditures for rHuEPO are substantial; in 1996, $1.2 billion was spent by Medicare for rHuEPO therapy among the ESRD dialysis population [11].

This study examines changes in rHuEPO dosing from 1990 to 1996 and the resultant impact on the Hct level, adjusting for the changing patient case-mix during this period. Unlike other published research, this study also investigates whether moderately and mildly anemic patients—who comprise an increasingly large majority of the Medicare-reimbursed ESRD population—respond to rHuEPO therapy in the same way as the severely anemic patients studied in the clinical trials.

METHODS

Data source

Data for the study were obtained from HCFA's ESRD Program Management and Medical Information System (PMMIS) database, HCFA's Quarterly EPO Billing File, and the annual ESRD Facility Survey. HCFA data are obtained from dialysis providers and include information on patient demographics, modality of dialysis, dates of dialysis treatments, dates of kidney transplantation, date of death, and the identity of dialysis providers. Information related to patients whose claims are new to the PMMIS (that is, the first time Medicare pays for rHuEPO services for a particular beneficiary) during the first quarter for each of the years 1990 through 1996, and all claims for the succeeding four months were extracted from these databases. Claims data represent the record of services delivered that is a necessary requirement for the payment of services. All patients in the study were at least 18 years old and received both rHuEPO and hemodialysis therapy on an outpatient basis at a dialysis facility during the four-month observation period.

Variables

The three key variables in this study are the following: (*1*) mean rHuEPO dose per day (EPO Dose), defined as the total dose of rHuEPO administered to a patient over the study period divided by the outpatient days-of-risk based on days-of-service reported in the claims; (*2*) the first observed incident Hct (I-Hct), defined as the Hct reading taken prior to the last administration of rHuEPO for the first billing period in which Medicare paid for rHuEPO therapy; and (*3*) achieved Hct (A-Hct), defined as the Hct reading taken prior to the last administration of rHuEPO on the last bill occurring in the patient's final month of the observed period. A mean rHuEPO dose for each study month was used because individual observations for each rHuEPO therapy session are not available using claims data. Additional variables of interest examined as predictors or confounders of EPO Dose, I-Hct, A-Hct, and the relationship between these variables are: age, race, sex, provider type (for-profit, not-for-profit, or government), number of dialysis sessions, and the primary disease causing ESRD. EPO Dose, I-Hct, A-Hct, and the number of dialysis sessions were derived from HCFA's Quarterly EPO Billing File. The PMMIS Enrollment File was the source for information regarding age, race, and sex. The underlying disease causing ESRD was obtained from the PMMIS Medical Evidence File and provider status was extracted from ESRD Facility Survey files.

Patient selection

Using seven years of outpatient claims data that comprised all Medicare-entitled ESRD hemodialysis patients in the U.S. for the years 1990-1996, seven cohorts incident to rHuEPO therapy reimbursed by Medicare during the first quarters of the years 1990 to 1996 were identified. Based on previous research regarding exposure to rHuEPO [1, 6], each cohort was followed for a minimum of three months and a maximum of four months starting in the first quarter

of each calendar year. Exposure to rHuEPO for 12 weeks or more was deemed necessary to ensure a stable A-Hct. The variability in follow-up periods results from the reporting of a total rHuEPO dose and a single A-Hct on a calendar monthly basis, despite the fact that a person may have initiated Medicare reimbursed treatment at any point during the month.

All study patients met the following clinical and billing-related criteria: initial reimbursement by Medicare for rHuEPO therapy occurring during the first calendar quarters of 1990 through 1996; be at least 18 years old; receive rHuEPO on an outpatient in-center basis; be treated with hemodialysis; not receive a kidney transplant during the observation period; have both an I-Hct and A-Hct less than 0.60, but not below 0.10; and have at least one outpatient bill for rHuEPO services during the third or fourth calendar month after Medicare initiated payment for rHuEPO services. A total of 64,957 patients met these study population selection criteria between 1990 and 1996.

Since hospitalization could interrupt dosing of rHuEPO, all analyses were conducted with and without the 1,216 patients who were hospitalized at some point during the study period. There was no statistically significant difference after including a dummy variable for hospitalization in the response to rHuEPO based on I-Hct. Using a number of interaction terms between hospitalization and patient characteristics, only race and hospitalization were significant between groups ($P = 0.03$). Therefore, hospitalization was not used as an exclusion criteria. Finally, persons receiving transfusions of one or more blood units were not excluded from the study population. Blood units administered are identifiable in claims data only if the provider charges for the blood units, a practice that varies across states. Furthermore, Eschbach reported that receipt of blood was not used as an exclusion criteria in earlier clinical trials [1].

In summary, seven unique patient cohorts, one for the first quarter of each calendar year, were identified. These cohorts were disaggregated into three groups based on their I-Hct: less than 0.25, severely anemic; between 0.25 and 0.29, moderately anemic; and equal to or greater than 0.30, mildly anemic. Each patient in the study population was observed for approximately 97 days [standard deviation (SD), 21 days], during which time the patients received approximately 34 rHuEPO administrations (SD, 11 administrations).

Statistical methods

Differences in patient demographics, clinical characteristics and facility characteristics were tested using Pearson's chi-square statistic. Differences in the change in Hct across the seven years and between patient and provider characteristics were tested using an ANOVA model. Individual comparisons between years were tested using the Tukey method of multiple comparisons. Finally, a multivariate regression was modeled using the A-Hct as the dependent variable predicted by the I-Hct, rHuEPO dose per day and various patient and provider characteristics. We did not employ multivariate regression techniques for this study since: (*1*) individual rHuEPO therapy session data are not available; and (*2*) critical variables required to explain the variability in A-Hct are not available from the claims data (such as, iron supplementation and patient weight). All differences with a *P* value less than or equal to 0.05 were considered to be significant.

RESULTS

The demographic and clinical characteristics of the hemodialysis study population are presented in Table 1. The ESRD population incident to Medicare-reimbursed rHuEPO was largest in 1990 as a result of the large number of anemic patients who initiated treatment soon after the introduction of rHuEPO in June 1989. The overall population using rHuEPO increased during the following six calendar years (1991 to 1996), reflecting both the wider use of rHuEPO and the increasing size of the ESRD population in the U.S. ($P < 0.05$). Except for 1990, there were more men incident to rHuEPO therapy in the Medicare program in each subsequent study year compared to women. The age distribution of the study population remained relatively constant from 1991 to 1996, with the majority of patients over the age of 65 years. More than half of the racial composition of the study population was classified as white, one-third or more as African-American and the remainder was classified as other (primarily Asian or Native American). The proportion of African-Americans initiating rHuEPO therapy reimbursed by Medicare decreased during the seven year period from 39.1% in 1990 to 31.5% in 1996. The proportion of all patients with diabetes as an underlying cause of ESRD increased notably from 30% of the population in 1990 to 42% in 1996 ($P < 0.05$). Hypertension as an underlying cause of ESRD decreased across the study period; similarly, the proportion of patients with glomerulonephritis and other interstitial kidney diseases decreased from 16% to 12% ($P < 0.05$). Almost two-thirds of the study population received both hemodialysis and rHuEPO services in for-profit facilities, while the remaining one-third were treated in non-profit facilities.

The proportion of patients by I-Hct category incident to rHuEPO therapy reimbursed by Medicare shifted dramatically over the course of the study period (Table 1 and Fig. 1). In 1990, 33.2% of the study population were severely anemic, 42.5% were moderately anemic and one-fourth were mildly anemic. Over the seven-year study period, the proportion of patients incident to rHuEPO reimbursed by Medicare with severe anemia decreased notably; by 1996, only 10.2% had severe anemia, while 54.9% had only mild anemia ($P < 0.05$).

The mean I-Hct for the study population, disaggregated

Table 1. Demographic and clinical characteristics of ESRD patients incident to rHuEPO therapy reimbursed by Medicare during the first quarter of 1990–1996

Covariate	1990	1991	1992	1993	1994	1995	1996
N	11,722	7,346	7,938	8,780	9,077	9,781	10,339
			Percentage				
Gender							
Male	49.3	52.0	52.1	52.4	52.8	52.6	53.0
Female	50.7	48.1	48.0	47.6	47.2	47.4	47.0
Age *years*							
18–34	9.0	7.8	6.6	7.2	6.9	6.2	5.1
35–64	45.7	41.0	40.1	39.8	39.1	39.0	39.4
65+	45.3	51.2	53.3	53.0	54.0	54.8	55.6
Missing	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Race							
White	53.1	55.9	58.7	59.6	59.6	60.4	60.7
Black	39.1	36.2	33.9	33.7	34.0	32.1	31.5
Other	6.1	6.3	5.9	5.7	5.9	6.9	7.2
Missing	1.7	1.7	1.5	1.0	0.5	0.6	0.6
Primary cause of ESRD							
Diabetes	30.0	33.9	36.5	37.1	37.0	39.0	42.3
Hypertension	29.4	30.9	31.2	30.0	30.6	28.1	25.2
Glomerulonephritis[a]	18.8	16.1	15.3	13.8	14.4	13.0	13.8
Other[b]	10.6	9.9	9.3	9.5	8.6	7.5	8.2
Unknown/unspecified	4.4	4.8	4.5	4.8	4.8	4.8	7.4
Missing	6.8	4.4	3.2	4.8	4.7	7.7	3.2
Provider status							
Profit	62.8	60.1	62.0	61.6	62.5	63.4	64.9
Non-profit	32.8	35.2	33.5	33.5	32.7	32.7	30.8
Government	4.4	4.6	4.3	4.6	4.5	3.7	3.7
Unknown/other	0.1	0.1	0.2	0.4	0.3	0.3	0.6
Initial Hct							
<0.25	33.2	26.4	21.6	18.3	14.9	12.7	10.2
0.25–0.29	42.5	44.9	44.7	41.8	40.1	36.9	34.9
0.30+	24.3	28.7	33.6	39.9	45.0	50.4	54.9

[a] Includes other interstitial kidney diseases such as kidney infections and polycystic disease
[b] Other includes systemic lupus erythematosus, multiple myeloma, congenital, metabolic disorders and sickle cell anemia

by severe, moderate and mild anemia, across the study period is presented in Figure 2A. RHuEPO dosing increased dramatically across the seven-year study period and was associated with a small increase in A-Hct in each subsequent year (Fig. 2 B, C and D). For example, for each of the three anemia cohorts, the percentage increase in mean rHuEPO dose per day between 1990 and 1996 was 139% for the severely anemic cohort, 122% for the moderately anemic cohort, and 107% for the mildly anemic cohort, corresponding to a 10%, 8% and 7% increase in A-Hct for each anemia cohort, respectively ($P < 0.05$). In terms of a realized improvement in the A-Hct level, the increase in dose resulted in a 0.028, 0.023 and 0.02 increase in A-Hct across the seven-year study period in each cohort, respectively. For severely anemic patients initiating rHuEPO therapy, the average rHuEPO dose increased from 1,750 units to 2,285 units per day, while the average A-Hct increased from 0.27 to 0.30 from 1990 to 1996 ($P < 0.05$).

RHuEPO dose and both I-Hct and A-Hct across the study period were analyzed based on age, gender, and race (Fig. 3 A and B, 3 C and D, and 3 E and F, respectively).

While the rHuEPO dose administered was not statistically different based on race, African-Americans had both a lower I-Hct and A-Hct than whites in all study years ($P < 0.05$). The increase in A-Hct in Figure 3A parallels the increase in the I-Hct for the population between 1990 and 1996, suggesting the improvement in A-Hct may be influenced by the fact that the study population is increasingly less anemic. Persons under age 65 received similar rHuEPO doses compared to persons over age 65 and both age cohorts had similar I-Hct values across the study period. Unexpectedly, the elderly population had a 0.01 higher A-Hct in each study year. Males and females received similar doses of rHuEPO therapy across the study period. Similarly, the improvement in A-Hct by gender during this time appears to parallel the increase in I-Hct among each group. Diabetes as an underlying cause of ESRD did not appear to influence rHuEPO dosing or I-Hct or A-Hct values (data not shown). Finally, there was a difference in dosing of rHuEPO in 1990, 1991 and 1992 based on provider status, that is, for-profit facilities initially provided lower rHuEPO doses compared to non-profit facilities (data not shown, $P < 0.05$). After 1992, however,
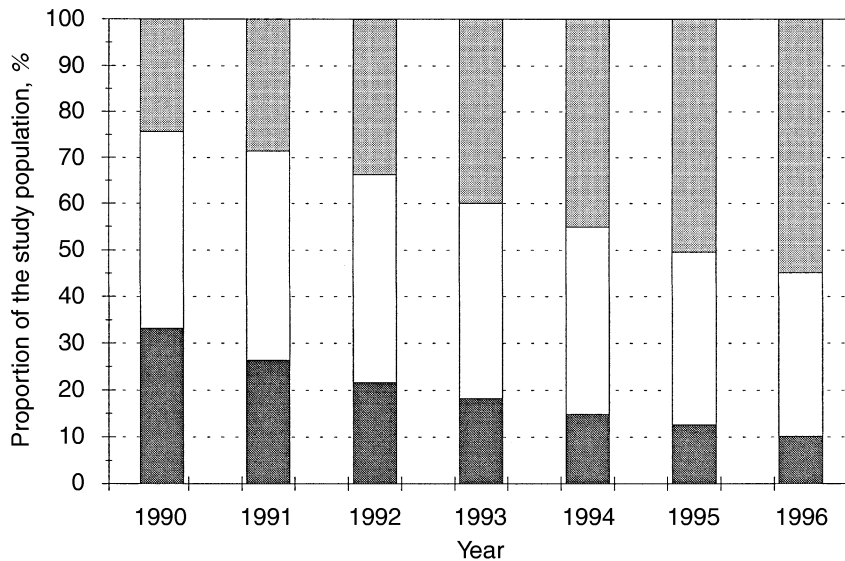
Fig. 1. Proportion of the study population disaggregated by initial hematocrit incident to recombinant human erythropoietin (rHuEPO) therapy reimbursed by Medicare. Symbols are: (■) <0.25; (□) 0.25 to 0.29; (▨) >0.30.

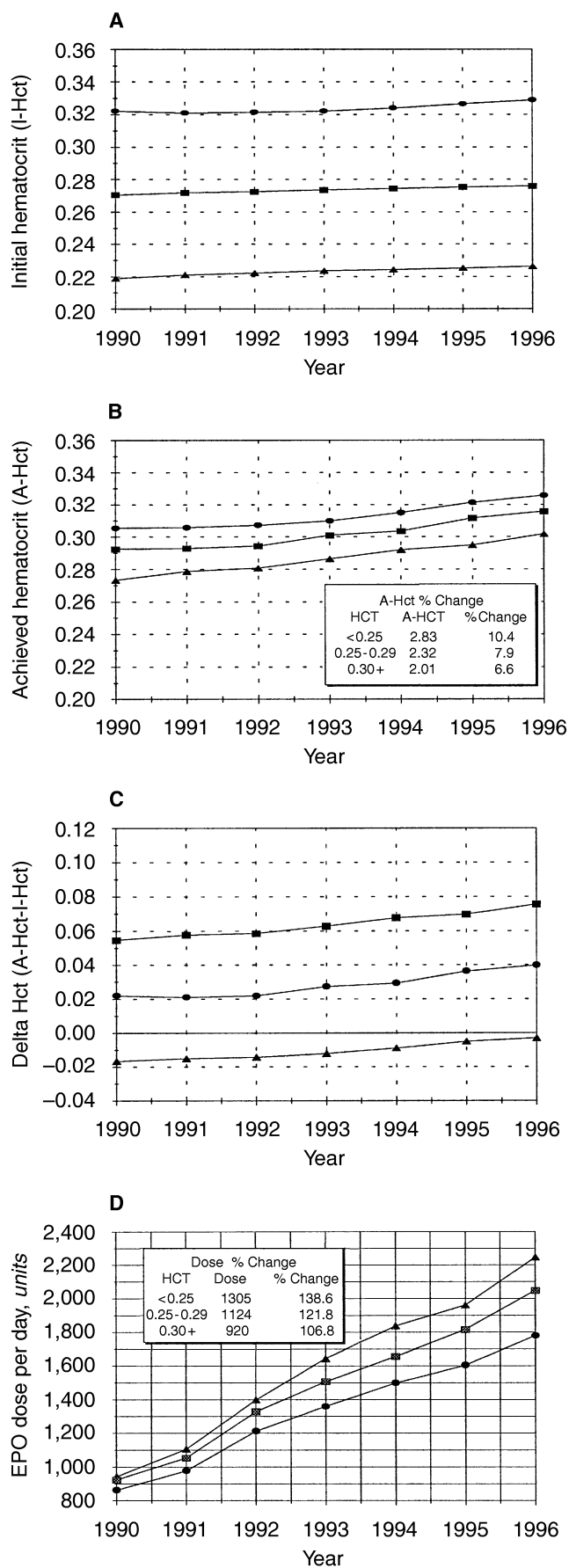there was no significant difference in rHuEPO dosing based on facility profit status.

The response to rHuEPO (the difference between the I-Hct in month one and the A-Hct at least 12 weeks later) is presented by year in Table 2. The aggregate change in Hct for the study years 1991 through 1996 is similar. For illustrative purposes, response to rHuEPO therapy was categorized by a Hct change as follows: >0.02 points; between 0.02 and −0.02; and < −0.02 points. The proportion of patients that comprised each of the three response categories was similar for every study year, suggesting that the response to rHuEPO, measured by improvement in Hct levels, did not change markedly over the seven year period. The mean Hct change in 1990 was significantly larger than in subsequent years (mean change of 0.023 Hct points vs. a high of 0.021 to a low of 0.018, depending on the year; $P < 0.0001$), reflecting the large cohort of severely anemic patients present in 1990. Among the potential confounders that may be associated with the level of response to rHuEPO [12, 13], African-Americans, the elderly, non-diabetics and persons receiving dialysis in a non-profit facility had a significantly larger change in Hct compared to their counterparts ($P < 0.0001$). Unadjusted, the most significant predictor of rHuEPO response, however, was I-Hct: the lower the I-Hct, the larger the change in Hct.

Results of the multivariate analysis concur with the findings reported in Table 2. In addition, the multivariate model indicates that the I-Hct is the most important predictor of both A-Hct and change in Hct after a minimum 12-week rHuEPO therapy, adjusting for patient demographics, underlying cause of ESRD, type of dialysis facility, year in which rHuEPO therapy was initiated, and rHuEPO dose per day-at-risk. Because of the caveats associated with the regression model discussed earlier in the statistical methods section, these results are not presented separately.

Notably, for persons with an I-Hct greater than 0.30, there was a failure to achieve an increase in Hct levels, shown by a negative change of 0.009 Hct points between the I-Hct and A-Hct. For simplicity, a failure to achieve an increase in patient hematocrit levels is subsequently referred to in the text and attached tables as a 'negative change.' To further investigate this phenomena, we combined all three anemia cohorts and disaggregated them into two groups: those who had a positive A-Hct change and those who had a negative A-Hct change (Table 3). Overall, we observed that 68.7% of all the patients had an improved A-Hct with a mean increase of +0.0449 Hct points and 31.7% of the patients had an A-Hct with a mean decrease of −0.0337 Hct points lower than their I-Hct. We subdivided these groups by age, gender, race, and primary cause of renal failure and found a response similar to the overall group (data not shown). We also subdivided these groups by the three I-Hct categories and found severely anemic patients with a 91.9% positive response (with a mean increase of +0.0684 Hct points) and 8.1% with a negative response (with a mean decrease of −0.022 Hct points). Moderately anemic patients had a 78.7% positive response (+0.0433 Hct points) and 21.3% with a negative response (with a mean decrease of −0.0269 Hct points). Mildly anemic patients had a 47.0% positive response (with a mean increase of +0.0229 Hct points) and 53.0% with a negative response (with a mean decrease of −0.0374 Hct points). We also subdivided these groups by age, gender, race, and primary cause of renal failure and found a response similar to the overall group as stated above.

DISCUSSION

In interpreting the findings of this research, several areas warrant discussion: the transition from controlled trials to broader clinical use (and the associated policy and financial

A

B

A-Hct % Change		
HCT	A-HCT	%Change
<0.25	2.83	10.4
0.25-0.29	2.32	7.9
0.30+	2.01	6.6

C

D

Dose % Change		
HCT	Dose	% Change
<0.25	1305	138.6
0.25-0.29	1124	121.8
0.30+	920	106.8

Fig. 2. Initial (*A*), achieved (*B*) and Δ hematocrit (*C*; achieved hematocrit − initial hematocrit) and the rHuEPO (*D*) dosing patterns among the study population disaggregated by initial hematocrit during the years 1990 to 1996. Symbols in panels A, B, and D are: (▲) <0.25; (■) 0.25 to 0.29; (●) >0.30. Symbols in panel C are: (■) <0.25; (●) 0.25 to 0.29; (▲) >0.30.

incentives); resistance to rHuEPO therapy; inadequate supplementation of iron among iron deficient patients; and the impact of reimbursement policies and financial incentives. Finally, the role of adequacy of dialysis and membrane clearance in relation to rHuEPO therapy are currently undetermined and warrant further research.

Transition from clinical trials to the broader clinical arena

Based on clinical trial results, rHuEPO was determined to be highly effective in ameliorating anemia among persons with ESRD receiving hemodialysis therapy [1, 2]. Unlike the dramatic results observed in the clinical trials where the mean rHuEPO dose was 225 U/kg/week, a Phase IV study of the effectiveness of rHuEPO used in broader clinical practice concluded that "patients do not seem to be realizing the full potential beneficial effects of this remarkable agent" presumably because low doses of rHuEPO, with a mean rHuEPO dose of 100 U/kg/week were being used, resulting in a low mean A-Hct level [6]. In contrast to our study, Nissenson et al did not disaggregate their analysis, findings and conclusions by patients' I-Hct. The authors were told by participating centers that HCFA's initial reimbursement regulations were the primary reason why physicians administered rHuEPO in doses lower than those used in the clinical trials (for example, dosing at 100 U/kg/week vs. 150 to 300 U/kg/week used in the Phases I and II clinical trials was required to achieve a Hct >0.30). Others argued that it was a new drug, and therefore, physicians were initially very conservative in its use. The dosing regimen in Phase IV, based on an average dose of 100 U/kg/week for incident rHuEPO patients, resulted in a mean A-Hct level of 0.31, lower than that achieved in the earlier clinical trials. Furthermore, only 58% of all patients achieved a Hct level greater than 0.30. Another variation in clinical practice reported by the Prospective Payment Assessment Commission was that rHuEPO dosages were not necessarily increased for patients with lower Hct values during the period from 1989 to 1990 [14]. Previously, Sisk, Gianfrancesco and Coster showed that fewer than 45% of patients who had been treated for six months or more prior to August 1990 had ever attained the target Hct of 0.30 to 0.33 set by HCFA [9].

The Medicare payment policy for rHuEPO treatment for dialysis patients changed in January 1991 from a relatively fixed payment per treatment based on an allowed charge of $40 per dose under 10,000 units injected to variable payment based on an allowed charge of $11 for each 1,000 units injected. The change in insurance payment policy in
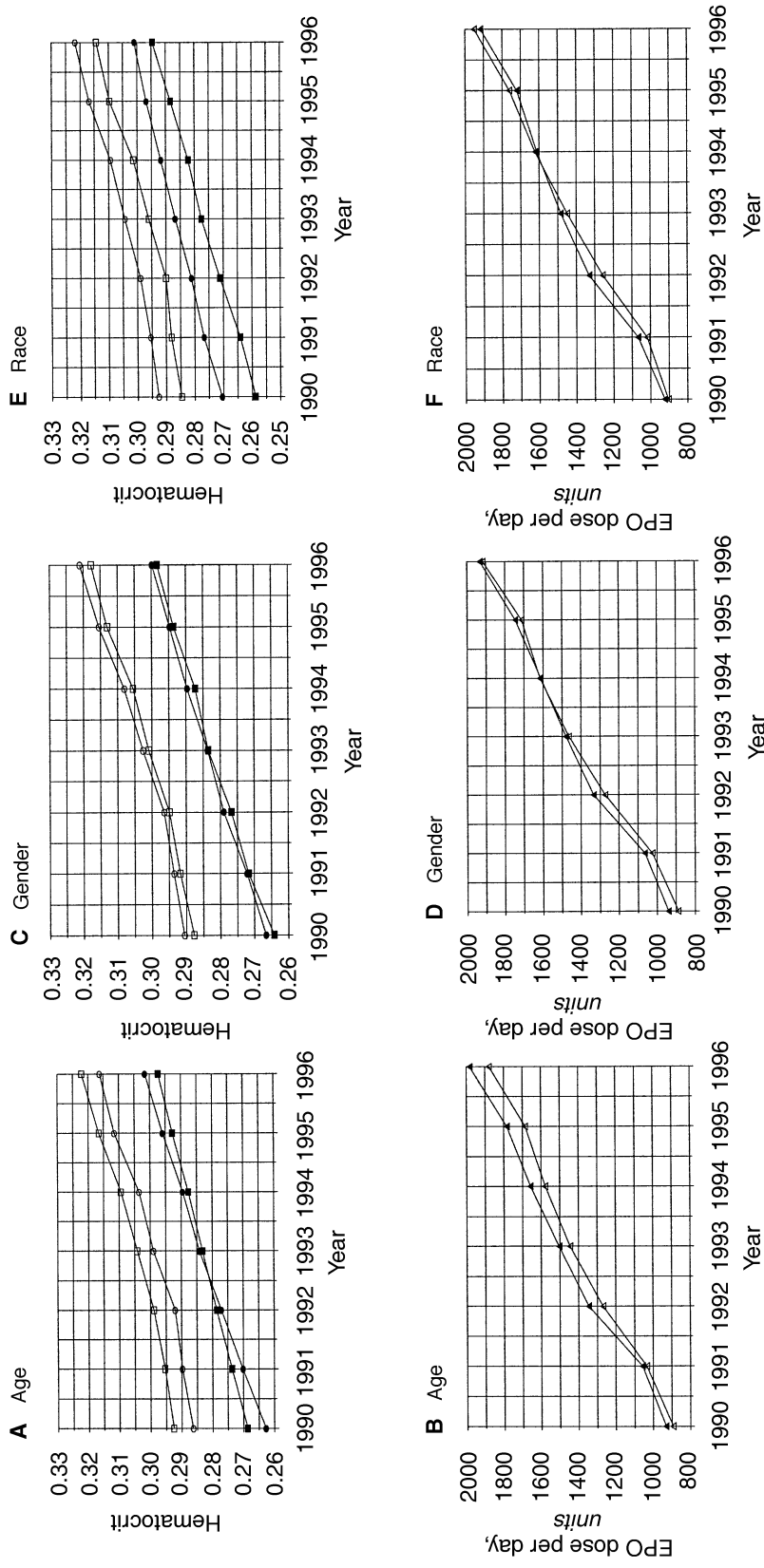
Fig. 3. Hematocrit values and rHuEPO dosing based on selected patient characteristics for the years 1990 to 1996. (*A*) Hematocrit by age (<65 and ≥65). (*B*) EPO dose by age (> 65 and ≤65). (*C*) Hematocrit by gender. (*D*) EPO dose by gender. (*E*) Hematocrit by race. (*F*) EPO dose by race. Symbols in panels A and B are: (□) A-Hct ≥ 65; (○) A-Hct < 65; (■) I-Hct ≥ 65; (●) I-Hct < 65; (▲) EPO dose <65; (△) EPO dose ≥ 65. Symbols in panels C and D are: (□) A-Hct female; (○) A-Hct male; (■) I-Hct female; (●) I-Hct male; (▲) EPO dose male; (△) EPO dose female. Symbols in panels E and F are: (□) A-Hct black; (○) A-Hct white; (■) I-Hct black; (●) I-Hct white; (▲) EPO dose white; (△) EPO dose black. Abbreviations are: I-HCT, initial hematocrit; A-HCT, achieved hematocrit.

combination with increasing experience with use of rHuEPO appeared to influence dosing practices of dialysis providers, particularly at for-profit dialysis centers [15].

There was a trend toward increasing average charges for rHuEPO per treatment during the observation period after the change in payment policy [16].

Table 2. Response to rHuEPO therapy by year and by selected patient and provider characteristics

		% of Patients by change in hematocrit points			Mean change in Hct	P value[a]
	N	<−0.02	−0.02 to 0.02	>0.02		
Total	64,957	17.8	35.6	46.6	0.0195	
Year						
1990	11,715	16.3	33.4	50.3	0.0234	0.0001[b]
1991	7,346	16.7	36.0	47.3	0.0206	
1992	7,934	18.3	36.9	44.8	0.0179	
1993	8,772	18.5	36.4	45.1	0.0182	
1994	9,074	18.4	37.5	44.2	0.0181	
1995	9,780	18.2	35.4	46.3	0.0198	
1996	10,336	18.3	34.9	46.8	0.0201	
Initial Hct						
<0.25	12,786	3.07	17.3	79.6	0.0611	0.0001
0.25–0.29	26,363	10.29	33.0	56.8	0.0283	
0.30+	25,808	32.72	47.5	19.8	−0.0090	
Facility						
For-profit	40,676	17.8	36.6	45.6	0.0192	0.0001
Non-profit	21,362	17.8	34.2	48.1	0.0209	
Cause of ESRD						
Diabetic	23,694	18.1	36.1	45.8	0.0189	0.0001
Non-diabetic	41,263	17.6	35.4	47.0	0.0205	
Race						
White	37,804	17.8	36.3	45.9	0.0194	0.0001
Black	22,367	17.7	34.4	47.9	0.0210	
Age *years*						
<65	30,994	19.2	37.7	43.2	0.0168	0.0001
≥65	33,958	16.5	33.8	49.7	0.0227	
Gender						
Male	33,732	17.3	35.9	46.8	0.0204	0.0171
Female	31,225	18.3	35.4	46.3	0.0194	

[a] Difference in means between each characteristic level
[b] Mean change in hematocrit in 1990 is significantly greater than the mean of each subsequent year

Following the change in the payment method from a fixed amount to one based on the dose administered, dosing increased markedly. However, Hct levels still remained below the optimal level of 0.30 [7]. Several explanations are plausible, including the possibility that the clinical symptoms of anemia in this range may not be fully appreciated by physicians for this patient population; the principles of rHuEPO therapy may not be adequately followed; there may be concern about potential "side effects" of administering rHuEPO; there may be a bias that moderate anemia is acceptable for dialysis patients, although not for "healthy" subjects; and the relative lack of published physiological studies designed to determine the optimal target Hct [17]. Other explanations include inadequate iron supplementation (discussed in the next section), inadequate nutrition, and less than complete blood recovery during the dialysis procedure. Finally, HCFA's reimbursement policy itself, that is, an upper limit of 0.36 on the hematocrit that would normally be reimbursed without accompanying documentation provided by a physician, may

also have contributed to the suboptimal response to rHuEPO seen in this article.

Since the end of our study, two new policy initiatives regarding Medicare's coverage of erythropoietin have been enacted by HCFA. The first policy, dated May 1997, instructed that no payment was to be made during a month if the 90-day average hematocrit exceeded 0.365. This was subsequently rescinded in March 1998, re-establishing the policy that was in place during the majority of this study. The motivation behind these policy initiatives is unclear as are the potential effects they have on rHuEPO dosing and patient hematocrit. The unexpected reversal of the original "three months rolling average" policy indicates the continued involvement of Congress and HCFA in regulating EPO use and pricing.

We speculate that the vast majority of patients in the study with initial mild anemia may have received rHuEPO therapy prior to this service being reimbursed by Medicare and are therefore being maintained in this hematocrit range. This occurrence is due to the HCFA required three-month waiting period after the onset of ESRD that must lapse before Medicare pays for this service. Based on the Medicare secondary payer (MSP) indicator found in the enrollment records, an average of 1.0% of severely anemic, 1.4% of moderately anemic, and 2.4% of mildly anemic patients in the study may have received EPO therapy prior to reimbursement by Medicare. This occurrence is due to MSP rules that require other payers to reimburse for rHuEPO therapy if the patient is covered by an employer group health plan. Since the Medicare database used in this study does not contain records for other carriers, this MSP rule offers no access to their prior rHuEPO history.

A portion of the mildly anemic cohort may have received rHuEPO therapy at a Hct level slightly below 0.30, and that by the end of the first month of rHuEPO treatment their Hct rose above 0.30 to a value that we observed and reported as their I-Hct. Also, some of the patients contained in this cohort may have initiated rHuEPO therapy at Hct levels higher than 0.30 if there was medical documentation showing the need for rHuEPO. For example, HCFA also allows payment for these patients if they have angina, pulmonary distress, or hypotension and may require rHuEPO to prevent adverse symptoms even if they have higher Hct or hemoglobin levels. For the mildly anemic cohort, the change in Hct over a minimum observed 12-week study period was slightly negative. This negative change could be associated with the difficulty in maintaining a stable Hct above 0.30 and below the target Hct levels imposed by HCFA.

Resistance to rHuEPO therapy

In addition to the change in reimbursement policy, the more aggressive use of rHuEPO among an increasing number of rHuEPO resistant patients has been postulated

Table 3. Overall response to rHuEPO therapy based on the change between the initial hematocrit and the achieved hematocrit by selected patient characteristics

Subgroups	Response (+ positive, − negative)	Mean subgroup change in Hct *points*	*P* value	Number of patients *N*	Percent of subgroup %
All	(+)	0.0449	0.0001	44,624	68.7%
All	(−)	−0.0337		20,333	31.3%
Initial Hct.					
<0.25	(+)	0.0684	0.0001	11,754	91.9%
<0.25	(−)	−0.0220		1,032	8.1%
0.25–0.29	(+)	0.0433		20,742	78.7%
0.25–0.29	(−)	−0.0269		5,621	21.3%
0.30+	(+)	0.0229		12,128	47.0%
0.30+	(−)	−0.0374		13,680	53.0%
Age *years*					
65+	(+)	0.0459	0.0001	24,059	70.8%
65+	(−)	−0.0335		9,899	29.2%
<65	(+)	0.0426		20,561	66.3%
<65	(−)	−0.0339		10,433	33.7%
Race					
White	(+)	0.0435	0.0001	25,853	68.4%
White	(−)	−0.0328		11,951	31.6%
Black	(+)	0.0460		15,491	69.3%
Black	(−)	−0.0352		6,876	30.7%
Other	(+)	0.0435		2,801	68.3%
Other	(−)	−0.0348		1,301	31.7%
Gender					
Male	(+)	0.0443	0.0001	23,303	69.1%
Male	(−)	−0.0331		10,429	30.9%
Female	(+)	0.0444		21,321	68.3%
Female	(−)	−0.0344		9,904	31.7%
Cause of ESRD					
Diabetes	(+)	0.0434	0.0322	16,163	68.2%
Diabetes	(−)	−0.0337		7,531	31.8%
Hypertension	(+)	0.0455		13,250	69.9%
Hypertension	(−)	−0.0337		5,699	30.1%
Glomerulonephritis[a]	(+)	0.0447		6,776	69.1%
Glomerulonephritis[a]	(−)	−0.0343		3,026	30.9%
Other[b]	(+)	0.0454		3,974	67.3%
Other[b]	(−)	−0.0328		1,929	32.7%

[a] Includes other interstitial kidney diseases such as kidney infections and polycystic disease
[b] Other includes systemic lupus erythematosus, multiple myeloma, congenital, metabolic disorders and sickle cell anemia

as an important reason to explain the significantly increasing dose over the past seven years, without a concomitantly large increase in A-Hct. For example, pathologic conditions of the bone marrow, such as myelofibrosis or hypoplasia, or inadequate stores of required nutrients such as iron, folic acid, and vitamin B_{12} can dampen the Hct response, producing "resistance" to rHuEPO [18–21]. In the Phase III trial, 17% of all patients required greater than 150 U/kg in order to maintain a stable Hct. Nonresponders to rHuEPO, who comprised less than 2% of the Phase III study population, had the following causes of anemia: myelofibrosis, osteitis fibrosa, osteomyelitis and acute or chronic blood loss [1].

To investigate whether there was a fundamental shift toward greater resistance over time, we compared the change in Hct over a minimum of 12 weeks as a proxy for characterizing the dose response of these patients from 1990 through 1996. In profiling the difference between their I-Hct and A-Hct, we did not find a shift in the distribution of patients based on Hct response to rHuEPO therapy across the study period, as shown in Table 2. The proportion of nonresponders as indicated by the percentage of patients with less than a 2% point change in hematocrit was stable across the study period comprising approximately 18% of all patients in each year.

Role of supplemental iron

The most common cause of decreased responsiveness to rHuEPO among patients with chronic renal failure is insufficient iron stores [22, 23]. Untreated iron deficiency reduces the effectiveness of rHuEPO and adds unnecessary cost to the treatment as well as delays to patient rehabilitation [24]. The necessity of administering oral and/or intravenous iron concomitantly with rHuEPO has been well established and widely disseminated [25, 26], including by the Anemia Cooperative Project [27], whose goal is to advance the treatment of anemia among dialysis patients in the U.S. While oral iron supplementation was available throughout the study period, intravenous supplementation was only available during the years 1991 to 1994, although some providers may have stockpiled it and used their supply during the time when intravenous iron was unavailable. Such supplementation is often less than optimal in clinical practice [16] and oral iron supplementation is often inadequate to replete iron stores [28]. Such iron deficiency may result in a less than expected effect of rHuEPO on Hct. This study did not include information on iron supplementation among persons receiving rHuEPO, although it is anticipated that iron deficiency existed among members of the study population.

In another example, in a USRDS special study, the Dialysis Morbidity and Mortality Study (DMMS wave 1), iron deficiency among the dialysis population included in this study was evaluated [29]. The DMMS found that more than 50% of the 2,613 dialysis patients examined in 1993 had transferrin saturation levels of <20%, 36% had serum ferritin levels of <100 ng/ml, and 56% had serum ferritin levels of <200 ng/ml. Furthermore, only 11.2% of these patients had received i.v. iron, while 25% had received neither i.v. nor oral iron. HCFA's 1997 ESRD Core Indicators Project also reported data on the treatment of iron deficiency among the ESRD population [30]. The Core Project found that the national average percent transferrin saturation for patients in their sample (October to December 1996 survey period) was 27.4% and ranged from 24.7% to 29.4%. Nationally 63% of the patients (ranging from 49% to 75%) had transferrin saturation values ≥ 20%. They also reported that the national average ferritin level was 377 ng/ml and ranged from 320 to 426

ng/ml. Nationally 73% of the patients (ranging from 60% to 80%) had ferritin levels ≥ 100 ng/ml.

The results of this study lend credence to the salient clinical need to ascertain the appropriate target hematocrit levels for patients based on their medical condition. The initial clinical trials and physiologic and quality of life studies of anemic dialysis patients treated in the U.S. and in Europe had target hematocrit levels >0.36. Virtually all of these studies showed that the increased Hct levels were concomitant with improvements in various physiologic measures [31–37]. However, since the FDA initially approved a target Hct level of 0.30 to 0.33 in June 1989 (and later widened it to 0.36 in June 1994) and HCFA imposed a policy under which it limited reimbursement to hematocrit values under 0.36, there have been no new studies in the U.S. to examine the potential beneficial effects of an achieved hematocrit value >0.36. In their analysis of this issue, based on a medical literature review, the Anemia Work Group concluded that hematocrit values <0.33 were associated with increased morbidity and mortality compared to those >0.36 [38]. A widely noted exception to this conclusion is the preliminary results of a study that examined 1,200 hemodialysis patients with heart disease that was discontinued when patients with a target hematocrit in the normal range (0.39 to 0.45) began to experience a greater incidence of non-fatal myocardial infarctions or death than did the control group with a target hematocrit in the range of 0.27 to 0.33 [38]. No conclusions, however, can be drawn from this study regarding ESRD patients with anemia who do not have heart disease. This study combined with additional concerns regarding other possible side effects of rHuEPO therapy, led the Anemia Work Group to recommend that Hct levels be maintained between 0.33 and 0.36, pending new studies [39].

Future studies to clarify the relationship between rHuEPO dose and Hct and patient outcomes are clearly warranted, including the empirical determination of the purported non-linear dose-response relationship. In addition, the cost implications of achieving higher target Hct levels, especially among mildly anemic patients, need to be examined. Finally, quality-of-life studies have been published based on severely anemic patients included in the clinical trial patient population [39] and elsewhere on the moderately anemic ESRD population [40]. Studies are therefore needed to determine quality-of-life improvements as well as the cost-effectiveness resulting from rHuEPO therapy for patients who are maintained at a mildly anemic level, who represent the majority of ESRD hemodialysis patients currently receiving rHuEPO therapy.

In conclusion, our results concur with USRDS findings that after an almost doubling of the dose of rHuEPO per patient between 1990 and 1996 (from 2,700 to 4,900 units/administration), the mean Hct for the ESRD medicare hemodialysis patient population increased by only 3 percentage points during the same period (from 0.0285 to 0.314) [5]. Overall, our research findings also suggest that substantial increases in rHuEPO dose provided to anemic patients over the seven year study have resulted in only modest increases in Hct.

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