

Henry Ford Health

## Henry Ford Health Scholarly Commons

---

Nephrology Articles

Nephrology

---

1-1-2011

### De novo once-monthly darbepoetin $\alpha$ treatment for the anemia of chronic kidney disease using a computerized algorithmic approach

E. Chalhoub  
*Henry Ford Health*

Stanley Frinak  
*Henry Ford Health, Sfrinak1@hfhs.org*

Gerald Zasuwa  
*Henry Ford Health, gzasuwa1@hfhs.org*

Mark D. Faber  
*Henry Ford Health, Mfaber1@hfhs.org*

Edward Peterson  
*Henry Ford Health, epeters1@hfhs.org*

*See next page for additional authors*

Follow this and additional works at: [https://scholarlycommons.henryford.com/nephrology\\_articles](https://scholarlycommons.henryford.com/nephrology_articles)

---

#### Recommended Citation

Chalhoub E, Frinak S, Zasuwa G, Faber MD, Peterson E, Besarab A, Yee J. De novo once-monthly darbepoetin  $\alpha$  treatment for the anemia of chronic kidney disease using a computerized algorithmic approach. *Clinical Nephrology* 2011; 76(1):1-8.

This Article is brought to you for free and open access by the Nephrology at Henry Ford Health Scholarly Commons. It has been accepted for inclusion in Nephrology Articles by an authorized administrator of Henry Ford Health Scholarly Commons.

---

**Authors**

E. Chalhoub, Stanley Frinak, Gerald Zasuwa, Mark D. Faber, Edward Peterson, A. Besarab, and Jerry Yee



©2011 Dusterl-Verglag Dr. K. Feistle  
ISSN 0301-0430

DOI 10.5414/CN106807

# De novo once-monthly darbepoetin $\alpha$ treatment for the anemia of chronic kidney disease using a computerized algorithmic approach

E. Chalhoub, S. Frinak, G. Zasuwa, M.D. Faber, E. Peterson, A. Besarab and J. Yee

Henry Ford Hospital, Division of Nephrology and Hypertension, Detroit, MI, USA

## Key words

chronic kidney disease (CKD) – darbepoetin  $\alpha$  (DA) – erythropoiesis-stimulating agent (ESA)

**Abstract.** **Background:** Anemia of chronic kidney disease (CKD) has been traditionally treated by erythropoiesis-stimulating agents (ESAs) and/or iron following manual determination of dose. We hypothesized that once-monthly (QM) algorithmically dosed darbepoetin  $\alpha$  (DA) and iron administration would successfully treat anemia of CKD in ESA-naïve CKD subjects. **Methods:** QM DA and iron doses were determined via a computerized program targeting a hemoglobin (Hb) of 10.5 – 12.5 g/dl in anemic, ESA-naïve, CKD Stages 3 – 5 subjects. Six consecutive QM doses were administered. Hb, ferritin, and transferrin saturation were recorded. Data are presented as means  $\pm$  standard deviation. **Results:** Anemia was identified in 133 subjects, with a mean follow-up of 188 days. DA doses and Hb were significantly greater at Months 3 and 6 compared to baseline ( $p < 0.05$ ); DA doses were  $109 \pm 68 \mu\text{g}$  and  $118 \pm 91$ , respectively, at Months 3 and 6. Hemoglobin levels were correspondingly  $11.3 \pm 1.1 \text{ g/dl}$  and  $11.3 \pm 1.0$ . 78% of patients achieved the target Hb by 6 months of therapy. The elevation of Hb was greater in non-proteinuric than proteinuric subjects at 6 months of treatment ( $11.6 \pm 0.8 \text{ g/dl}$  vs.  $11.0 \pm 1.1$ ;  $p < 0.05$ ), despite lower DA dose ( $96 \pm 76 \mu\text{g}$  vs.  $139 \pm 98$ ;  $p < 0.05$ ). **Conclusion:** Successful treatment of the anemia of CKD by QM DA based upon a computerized dosing program was achieved by 6 months in 78% of ESA-naïve, CKD subjects.

implementation and outcomes standpoints [5, 6, 7]. Only one-third of CKD patients were reported as receiving ESA therapy at the onset of ESRD with a mean hemoglobin (Hb) of 10.2 g/dl [8]. In non-dialysis CKD patients, progressive lengthening of the ESA dosing interval has occurred during the past decade. Erythropoietin  $\alpha$  dosing increased from several weekly doses to weekly doses [9], and darbepoetin  $\alpha$  (DA) has been administered weekly or bi-weekly. More recently, clinical trials have demonstrated the efficacy of even longer ESA dosing intervals, i.e., every 4 weeks [10, 11, 12, 13, 14, 15, 16, 17, 18, 19].

Although QM DA dosing trials have documented efficacy at maintaining Hb levels between 10 and 13 g/dl in patients previously treated with more frequent dosing regimens, the issue of patient selection for “responsiveness” to ESA is notable [17, 18, 19]. First, subjects were required to have a stable Hb within the target range during the pre-existing regimen and often, an iron replete state was required. Therefore, the selection of ESA-responsive patients is not immediately generalizable and transferable to real world practice where there is heterogeneity of iron sufficiency, ESA dosing practice and/or ESA dosing intervals. Moreover, published clinical trials have generally imposed a fixed dosing schedule with predefined parameters for conversion from EA to DA, without the benefit of automation or a clinical decision support system. Often, a bodyweight-based system of ESA dosing was employed. In addition, the erythropoietic environment was usually optimized in advance of conversion to DA from EA by excluding individuals with iron deficiency and/or significant inflammatory or hematological illness.

## Introduction

Anemia is common feature in chronic kidney disease (CKD) and progresses with deterioration of kidney function [1]. Effective treatment for anemia in CKD is available and consists of iron supplementation and erythropoiesis-stimulating agents (ESA) [2, 3, 4]. Despite the availability of these agents, treatment of anemia is often suboptimal from

Received  
May 10, 2010;  
accepted in revised form  
December 6, 2010

Correspondence to  
E. Chalhoub, MD  
Division of Nephrology  
and Hypertension,  
2799 West Grand Blvd.,  
CFP-517, Detroit, MI  
48202, USA  
echalho1@hfhs.org

We hypothesized that management of the anemia of CKD in ESA-naïve patients could be achieved with an automated algorithm that employed the longer-acting ESA, darbepoetin. As the primary objective of this study, we determined the proportion of ESA-naïve subjects who could attain a target Hb of 10.5 – 12.5 g/dl by Month 6 of DA treatment, in a broadly based outpatient clinic population, using such an algorithm. A secondary objective of this study was determination of the effects of diabetes and proteinuria on anemia treatment outcomes.

## Methods

**Study design:** A retrospective analysis was conducted on all patients being initiated on treatment for anemia of CKD at the Nephrology and Hypertension clinic at Henry Ford Health System, Detroit MI between 5/2005 and 7/2007. The Nephrology and Hypertension clinic is multidisciplinary and affiliated with the Henry Ford Hospital, a 903-bed urban medical center, located in Detroit, MI. In addition to regular follow-up by a nephrologist, the patients were seen on-site by dietitians, social workers and mid-level providers in order to provide comprehensive CKD management.

We implemented an automated, web-based algorithm specifically designed for the nephrology clinic. The algorithm uses trend analysis of Hb and DA dose as well iron parameters to determine QM DA and iron supplementation if indicated. Approval for retrospective analysis of data was granted by our local research review committee. In addition to the primary objective, fraction of patients achieving target Hb between 10.5 and 12.5 g/dl by 6 months of therapy, we also determined the effect of proteinuria and diabetes on DA dose, Hb, transferrin saturation (TSAT) and ferritin responses with QM DA and iron therapy.

The study population consisted of all CKD 3 – 5 patients that initiated de novo QM DA for treatment for anemia of CKD, and received 6 consecutive doses between 05/2005 and 07/2007. Exclusionary criteria included organ transplantation recipient status, ongoing immunosuppressive therapy or the

need for hemodialysis or peritoneal dialysis within 6 months of first DA dose. Overall, 133 patients met the inclusion criteria. Time elapsed between two consecutive DA doses was no less than 20 days and no longer than 45 days. We did not exclude iron deplete patients, or patients with comorbid conditions that might affect ESA response.

Anemia was defined as Hb of < 10.5 g/dl on two or more separate readings at least 1 month apart. CKD Stages were defined by the Modification of Diet in Renal Disease GFR Equation 4 based on the serum creatinine level at the time of the visit preceding initiation of ESA treatment [20, 21]. The following data for all patients meeting inclusion/exclusion criteria was retrieved for analysis at the time of the CKD clinic visit preceding initiation of ESA therapy: ethnicity, gender, diabetic status, CKD stage and the presence or absence of proteinuria on routine urinalysis. Blood pressure (BP), Hb, serum iron, transferrin saturation (TSAT), serum ferritin, and DA dose were determined monthly. Etiology of CKD, age, body weight (kg), and use of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) were specified. The etiology of CKD was determined by the evaluating nephrologist and included primarily hypertensive angiosclerosis (43.7%), Type 2 diabetic nephropathy (22.6%) or a combination of both (12.9%). Other diagnoses included a pre-renal state (4.7%), chronic glomerulonephritis (2.4%), incomplete recovery from ATN (1.6%), HIV-associated nephropathy (1.6%), and unknown diagnoses (5.3%).

The Computerized Anemia Management Program (CAMP<sup>®</sup>) is a pair of proprietary, network-distributed DA and iron treatment algorithms. The same iron and DA dosing algorithms were applied in all patients. CAMP<sup>®</sup> is designed to treat the anemia of CKD by querying a database that includes continuous quality initiatives. After initial data input, CAMP<sup>®</sup> calculates an iron dosing strategy based upon ferritin, TSAT and Hb levels and prescribes either no iron, oral iron (Nephron FA<sup>®</sup> or ferrous sulfate) or intravenous iron (Figure 1). CAMP<sup>®</sup> employs separate protocols for the first, second and maintenance (dose 3 and afterward) monthly DA doses. The first DA dose is based on entry Hb: a) Hb < 9 g/dl, 200 µg, b) Hb 9.0 and

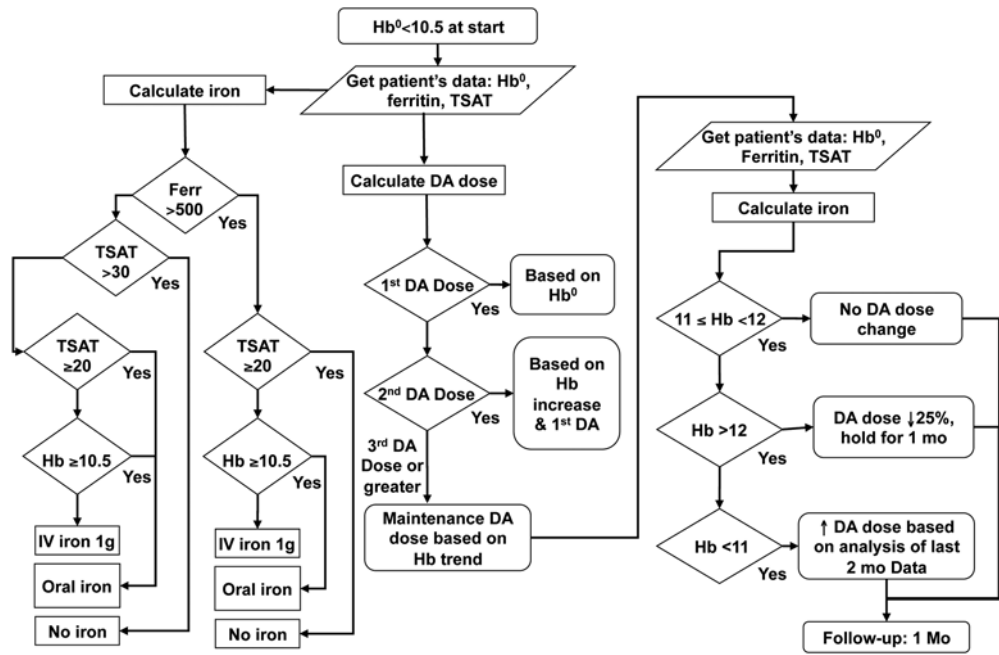


Figure 1 Darbepoetin  $\alpha$  and iron treatment protocols. DA = darbepoetin  $\alpha$ ,  $\mu\text{g}$ ; Hb = hemoglobin, g/dl; Hb<sup>0</sup> = hemoglobin prior to initiation of darbepoetin  $\alpha$  therapy, g/dl; TSAT = transferrin saturation, percent; ferritin, ng/ml.

< 10.5 g/dl, 100  $\mu\text{g}$  and c) Hb 10.5 g/dl, 60  $\mu\text{g}$ . The second DA dose is based on the initial DA dose and the change in Hb from the initial Hb. Maintenance DA doses (dose 3 and thereafter) are based on trend analysis of the most recent Hb, the last two DA doses and any increase or decrease in the last two doses with a target Hb in the range of 10.5 – 12.5 g/dl. Using NKF KDOQI-based parameters, CAMP<sup>®</sup> analyzes monthly parameters of iron saturation, ferritin and hemoglobin and recommends a form of iron therapy (no iron, oral or i.v. iron). Simultaneously, CAMP<sup>®</sup> analyzes DA dose and Hb trends and generates a DA dose recommendation. Dose escalations proceed in an algorithmic fashion also. DA doses are increased if Hb declines or is stable but below goal for 2 consecutive months.

CAMP<sup>®</sup>-recommended DA doses were allocated only as total syringe (Aranesp Singleject<sup>™</sup>) – or unit vial-sized doses: 25, 40, 60, 100, 150, 200 and 300  $\mu\text{g}$ . Supervising nephrologists were electronically notified by CAMP<sup>®</sup> if there was an abrupt elevation or decline of Hb of  $\geq 1.5$  g/dl in a single month, an elevation of Hb to  $\geq 13$  g/dl or a decrease to  $\leq 9$  g/dl. Following ascertainment of DA and iron dose(s), CAMP<sup>®</sup> generates real-time procedural documentation that is forwarded electronically to the healthcare provider for attestation.

Table 1. Demographics of the patient population studied.

Characteristic	% of patients (n = 133)	
<b>Gender</b>		
Male	45.9	
Female	54.1	
<b>CKD Stage</b>		
Stage 3	41.4	
Stage 4	37.6	
Stage 5	21.1	
<b>Race</b>		
African-American	62.4	
Caucasian	33.1	
Other	4.5	
<b>Disease status</b>		
Diabetic:	Yes	54.2
	No	45.8
Proteinuric:	Yes	45.7
	No	54.3
<b>Diabetic and proteinuric</b>		
Yes/Yes	31.0	
Yes/No	22.5	
No/Yes	14.7	
No/No	31.8	

### Statistical methods

Data on hemoglobin, DA dose, ferritin and TSAT were collected at baseline, 3 months and 6 months into this study. Analysis of variance (ANOVA) for repeated measures was used for analysis as implemented

Table 2. Temporal trends of hemoglobin and iron parameters during darbepoetin  $\alpha$  therapy.

Variable	Time 0		Month 3		Month 6	
	Mean	SD	Mean	SD	Mean	SD
Hb	10.02	0.70	11.28 <sup>a</sup>	1.09	11.31 <sup>a</sup>	1.03
DA dose	96.39	40.21	109.06 <sup>a</sup>	67.58	118.20 <sup>a</sup>	90.95
TSAT (%)	23.10	9.64	26.04 <sup>a</sup>	9.22	29.78 <sup>a,b</sup>	10.99
Ferritin (Ln)	4.93	1.08	4.93	0.94	5.15	0.89
Ferritin Geometric mean	138.12		138.36		171.92 <sup>a</sup>	

Hb = Hemoglobin, g/dl; TSAT = transferrin saturation, SD = standard deviation; DA = darbepoetin  $\alpha$ ,  $\mu$ g; ferritin, ng/ml. <sup>a</sup> $p < 0.05$  vs. baseline parameter; <sup>b</sup> $p < 0.05$  3 month parameter vs. 6 month parameter.

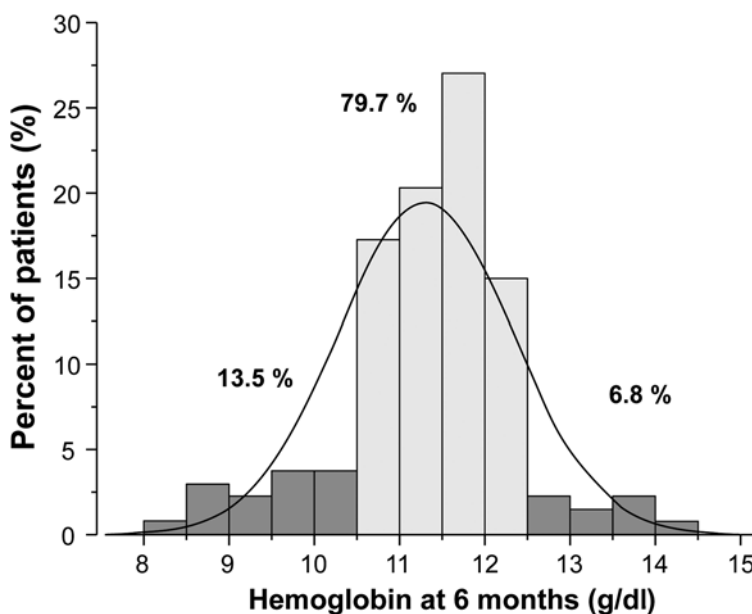


Figure 2. Hemoglobin (Hb) distribution after 6 months of darbepoetin  $\alpha$  treatment (N = 133). ■ = Hemoglobin < 10.5 or > 12.5 g/dl. □ = Hemoglobin > 10.5 and < 12.5 g/dl.

by PROC MIXED in SAS version 9.2 (SAS Institute, Cary, NC, USA). This procedure allows for incomplete data points to be used in the analysis. Ferritin distribution was highly skewed and log-transformed to provide a more normal distribution (Tables 2, 3, 4). Pairwise comparisons for all variables were carried out with Hochberg's method applied to adjust for multiple testing. Additional parameters of diabetes and proteinuria were added into repeated measures ANOVA to assess for additional potential influences. In these designs, the two main effects of time and diabetic status (or proteinuria status) were tested for two-way interaction.

## Results

Following application of exclusion criteria, data from 133 patients were analyzed, and demographics are displayed in Table 1. The average time from enrollment to administration of the sixth QM DA dose was  $188 \pm 14$  days.

The analysis of Hb (Table 2) revealed a significant overall effect ( $p = 0.001$ ), and pairwise comparisons revealed a significant difference between baseline and 3-month Hb levels that increased from 10.02 g/dl to 11.28 g/dl,  $p < 0.001$ . A similar relationship was noted at 6 months, with Hb increasing to 11.31 g/dl ( $p < 0.001$ ). Comparisons of Hb between Months 3 and 6 were not significant.

The primary objective of the study was to determine the proportion of patients that achieved the target Hb range following 6 months of QM DA. At study end-point, 79.7% of subjects attained the target Hb range ( $p = 0.001$ ). The remainder of subjects attained a Hb lower than the target in 13.5% of cases and a Hb exceeding 12.5 g/dl in 6.8% of cases (Figure 2). Significant differences were detected between baseline and 6-month values for DA dose ( $p = 0.002$ ), TSAT ( $p = 0.001$ ) and ferritin ( $p = 0.012$ ). The DA dose was not significantly different at 3 and 6 months. TSAT was different in pairwise comparisons, with a steady increase from 23.1% to 26.0% to 29.8% at 6 months ( $p = 0.0019$  for 3 months versus baseline;  $p = 0.001$  for 6 months versus 3 months). Ferritin levels were highly skewed (Table 2) and showed no statistically significant change from baseline to 3 months. However, the 6-month geometric mean ferritin (171.92 ng/ml) was significantly higher than at 3 months (138.36 ng/ml).

The secondary objective of this trial was to determine the effects of diabetes and proteinuria on achieved Hb. An analysis of diabetic status demonstrated no significant impact of diabetes for any variable (Table 3). The analysis of Hb over time followed the pattern discussed previously, with no significant interactions between time and diabetic status. A parallel analysis by proteinuric status was also completed (Table 4), and a significant effect of proteinuria on Hb and DA dose was found. Hemoglobin levels were lower in patients with proteinuria and DA doses were higher. An analysis of temporal

Table 3. Effect of diabetes on anemia and iron parameters during darbepoetin  $\alpha$  treatment.

Parameter	Time	Non-Diabetics; n = 60		Diabetics; n = 71	
		Mean	SD	Mean	SD
Hemoglobin (g/dl)	Time 0	10.12	0.69	9.94	0.71
	Month 3	11.28 <sup>a</sup>	0.97	11.32 <sup>a</sup>	1.18
	Month 6	11.55 <sup>a</sup>	0.96	11.15 <sup>a</sup>	1.02
Darbepoetin $\alpha$ dose ( $\mu$ g)	Time 0	92.00	41.04	100.00	40.00
	Month 3	109.50 <sup>a</sup>	71.76	107.54 <sup>a</sup>	64.97
	Month 6	109.33 <sup>a</sup>	84.94	120.56 <sup>a</sup>	92.19
TSAT (%)	Time 0	24.32	10.81	22.27	8.70
	Month 3	26.42	10.69	26.00	7.78
	Month 6	31.03 <sup>a</sup>	12.68	28.90 <sup>a</sup>	9.25
Ferritin (Ln)	Time 0	4.90	1.12	5.02	1.01
	Month 3	5.01	1.05	4.91	0.82
	Month 6	5.16	0.90	5.18	0.87

TSAT = transferrin saturation; SD = standard deviation; DA = darbepoetin  $\alpha$ . <sup>a</sup>p < 0.05 vs. Month 0.

Table 4. Effect of proteinuria on hemoglobin, erythropoiesis stimulating agent dose and iron parameters.

Parameter	Time	Non-Proteinuric; n = 70		Proteinuric; n = 59	
		Mean	SD	Mean	SD
Hemoglobin (g/dl)	Baseline	10.16	0.60	9.83	0.79
	3 months	11.44 <sup>a</sup>	0.89	11.14 <sup>ab</sup>	1.28
	6 months	11.62 <sup>a</sup>	0.82	10.97 <sup>ab</sup>	1.10
DA Dose ( $\mu$ g))	Baseline	89.14	33.65	105.42	46.51
	3 months	100.29	64.80	119.07 <sup>ab</sup>	71.43
	6 months	96.36	75.89	139.41 <sup>ab</sup>	97.68
TSAT (%)	Baseline	23.60	9.90	22.78	9.65
	3 months	25.88 <sup>a</sup>	9.26	26.32 <sup>a</sup>	9.19
	6 months	30.47 <sup>a</sup>	11.10	29.13 <sup>a</sup>	11.00
Ferritin (Ln)	Initial	4.97	1.03	4.94	1.11
	3 months	4.86	1.02	5.03	0.81
	6 months	5.17	0.92	5.15	0.84

TSAT = transferrin saturation; SD = standard deviation; DA = darbepoetin  $\alpha$ . <sup>a</sup>p < 0.05 vs. baseline, <sup>b</sup>p < 0.05 vs. non-proteinuric.

changes in Hb in both subgroups reflects that reported above, and no significant interactions appeared. Lastly, the absolute values and temporal changes in TSAT and serum ferritin were not different between proteinuric and non-proteinuric patients.

## Discussion

This study represents a single-center analysis of a computerized program, CAMP<sup>®</sup>, that “treats” ESA-naïve patients with anemia of CKD in a real world setting. With this automated clinical decision support system, we evaluated the hypothesis that CKD Stage 3 – 5 patients could be successfully targeted by QM DA therapy to the Hb range of 10.5 – 12.5 g/dl. The extension of the ESA dosing

interval provides several advantages. Aside from patient convenience and choice, with a reduction of “out-of-pocket” expenses, extended dosing intervals improve resource utilization and reduce administrative paperwork and medicolegal documentation. The expansion of healthcare provider time garnered by reducing injections from once-weekly to once-monthly additionally provided greater opportunities for other medical activities.

In terms of efficacy, CAMP<sup>®</sup> achieved the target Hb of 10.5 – 12.5 g/dl after 3 – 6 doses in nearly 80% of all patients treated (coefficient of variation, 9.7% at 3 months and 9.1% at 6 months). This result occurred irrespective of the prior Hb and the degree of pre-CAMP<sup>®</sup> iron repletion status and Hb

stability. This observation is in contradistinction to published QM DA trials. In fact, the mean entry Hb of 10.0 g/dl was comparable to that of other individuals initiated on RRT [20]. Notably, the Hb versus time curve of the study population essentially flattened by 90 – 150 days of therapy. The salutary nature of prophylactic iron monitoring and delivery by CAMP<sup>®</sup> produced a significant steady elevation of TSAT in treated subjects. In addition, the initial TSAT of 23.2% was lower than the 28 – 32% levels cited in prior trials in which ESAs were administered at two-weekly intervals [13, 14, 15, 16].

CAMP<sup>®</sup> was conceived of as a secure, web-deployable, HIPAA-compliant decision support system for the anemia management. This program facilitated medicolegal documentation and “notified” healthcare providers regarding DA dosing, Hb levels and ferrokinetic status. The CAMP<sup>®</sup>-based DA prescription based on entry Hb rather than bodyweight was selected because this practice is more akin to real world-based practice. In typical real world practice without automated decision support, healthcare practitioners gauge the Hb response to ESA therapy after the first 2 or 3 ESA doses.

Programmatic instillation of trend analysis into the CAMP<sup>®</sup> logic tree safeguarded against “instinctive” reactions to alter the DA dose solely predicated on the prevailing Hb level. Furthermore, the application of synergistic, dually applied algorithms for iron management and ESA dosing prevented the development of iron insufficiency/depletion during ESA-driven augmentation of erythropoiesis. This “iron forward” approach was facile enough to identify patients in whom oral iron failed to improve the ferrokinetic profile. Oral iron was discontinued in lieu of i.v. iron treatment with 500 – 1,000 mg of low molecular weight iron dextran. Finally, because all data input was incorporated into a “back end” database, metrics at the individual provider level could be readily ascertained for continuous quality improvement. The institutional use of CAMP<sup>®</sup> generated a favorable response from patients, improvements in resource allocation and reduced prescribing variability by providers. In our experience, the monthly injection and documentation time per patient decreased by nearly 84% from 60 to 7 minutes per patient

per month. In addition, there were no significant differences among monitored variables at any CKD stage throughout the observation period.

In general, the diabetic condition is associated with enhanced expression of inflammatory biomolecules [22], and several of these markers have been correlated with hyporesponsiveness to ESA therapy [23]. In this study, we were unable to show statistically significant differences in Hb between diabetics and non-diabetics. By contrast, proteinuria was associated with decreased ESA responsiveness [24, 25, 26, 27] and may have reflected ongoing inflammation [28]. Proteinuric individuals manifested the worst Hb outcomes, despite significantly higher DA doses.

One limitation of this analysis is its observational nature. CAMP<sup>®</sup> was not directly compared to traditional, non-automated physician-driven, anemia management practices in a randomized clinical trial. Such a prospective, randomized controlled trial, would require the control of any iron replacement strategies. Therefore, the benefits of CAMP<sup>®</sup> as a clinical decision support system include its prescription homogeneity, Hb and iron parameter trend analysis, medicolegal documentation and time savings [29, 30].

In summary, automated QM DA administration to ESA-naïve patients successfully treats the anemia of CKD in a real world clinical setting and reduces the heterogeneity of treatment practice and responses. Concurrent algorithmic dosing of DA and iron, orally or intravenously, prevents absolute or functional iron deficiency and optimally balances the treatment of anemia of CKD [29], even in a population where ferrokinetic parameter interpretation may be insensitive, nonspecific or misleading [31, 32]. Other advantages of computerized, programmatic therapy include substantial reductions in ESA delivery time, timely procedural documentation and improved patient satisfaction. Lastly, CAMP<sup>®</sup> with its real-time database collection and trend analysis of clinical data facilitates continuous quality improvement at individual and group provider levels. We postulate that CAMP<sup>®</sup> will demonstrate similar efficacy with ESAs that possess longer durations of action than darbepoetin  $\alpha$  [33, 34, 35, 36, 37, 38].



## Disclosures and conflict of interest

Elias Chalhoub, and Edward Peterson have nothing to disclose.

Stanley Frinak, Gerard Zasuwa, Mark D. Faber, Anatole Besarab, and Jerry Yee are inventors of CAMP<sup>®</sup>, Computerized Algorithm Management Protocol.

Anatole Besarab has received research funds, grants or contracts from Abbott Laboratories, Advanced Magnetics, Affymax, American Regent Laboratories Inc., Amgen Inc., Baxter, Hoffman-La Roche Ltd., Rockwell International, Takeda Pharmaceuticals, Transonic Systems Inc., VascAlert<sup>™</sup>, and Watson Pharmaceuticals.

Jerry Yee has received research funds, grants or contracts from Abbott Laboratories, Affymax, Amgen Inc., Fresenius Medical Care, North America, Otsuka, Genzyme Corp., Merck and Company, Takeda Pharmaceuticals, VascAlert<sup>™</sup>, and Watson Pharmaceuticals.

## Acknowledgment

The authors express their gratitude toward Robert Toto, MD, for his critical reading of the manuscript.

## References

- [1] *El-Achkar TM, Ohmit SE, McCullough PA, Crook ED, Brown WW, Grimm R, Bakris GL, Keane WF, Flack JM.* Higher prevalence of anemia with diabetes mellitus in moderate kidney insufficiency: The Kidney Early Evaluation Program. *Kidney Int.* 2005; *67*: 1483-1488.
- [2] *Jauréguy M, Choukroun G.* Factors affecting the response to erythropoiesis-stimulating agents. *Nephrol Ther.* 2006; *2 (Suppl 4)*: 274-282.
- [3] *Hörl WH, Cavill I, MacDougall IC, Schaefer RM, Sunder-Plassmann G.* How to diagnose and correct iron deficiency during rHuEpo therapy – a consensus report. *Nephrol Dial Transplant.* 1996; *11*: 246-250.
- [4] *Arndt U, Kaltwasser JP, Gottschalk R, Hoelzer D, Möller B.* Correction of iron-deficient erythropoiesis in the treatment of anemia of chronic disease with recombinant human erythropoietin. *Ann Hematol.* 2005; *84*: 159-166.
- [5] *Andrews NC.* Disorders of iron metabolism. *N Engl J Med.* 1999; *341*: 1986-1995.
- [6] *Weiss G, Goodnough LT.* Anemia of chronic disease. *N Engl J Med.* 2005; *352*: 1011-1023.
- [7] *Vyoral D, Petrak J.* Hepcidin: a direct link between iron metabolism and immunity. *Int J Biochem Cell Biol.* 2005; *37*: 1768-1773.
- [8] *USRDS 2006.* Annual Data Report, Chapter 3; Patient Characteristics, [http://www.usrds.org/2006/pdf/03\\_pt\\_char\\_06.pdf](http://www.usrds.org/2006/pdf/03_pt_char_06.pdf). Accessed July 01, 2009.
- [9] *Provenzano R, Garcia-Mayol L, Suchinda P, Von Hartitzsch B, Woollen SB, Zabaneh R, Fink JC for the POWER Study Group.* Once-weekly epoetin alfa for treating anemia of chronic kidney disease. *Clin Nephrol.* 2004; *61*: 392-405.
- [10] *Locatelli F, Canaud B, Giacardy F, Martin-Malo A, Baker N, Wilson J.* Treatment of anaemia in dialysis patient with unit dosing of darbepoetin alfa at a reduced dose frequency relative to recombinant human erythropoietin (rHuEpo). *Nephrol Dial Transplant.* 2003; *18*: 362-369.
- [11] *Vanrenterghem Y, Bárány P, Mann JFE, Kerr PG, Wilson J, Baker NF, Gray SJ.* European/Australian NESP 970200 Study Group: Randomized trial of darbepoetin alfa for treatment of renal anaemia at a reduced dosing frequency compared with rHuEpo in dialysis patients. *Kidney Int.* 2002; *62*: 2167-2175.
- [12] *Germain M, Ram CV, Bhaduri S, Tang KL, Klausner M, Curzi M.* Extended epoetin alfa dosing in chronic kidney disease patients: a retrospective review. *Nephrol Dial Transplant.* 2005; *20*: 2146-2152.
- [13] *Provenzano R, Bhaduri S, Singh AK.* Extended epoetin alfa dosing as maintenance treatment for the anemia of chronic kidney disease: the PROMPT study. *Clin Nephrol.* 2005; *64*: 113-123.
- [14] *Joy MS, Candiani C, Vaillancourt BA, Chin H, Hogan SL, Falk RJ.* Reengineering clinical operations in a medical practice to optimize the management of anemia of chronic kidney disease. *Pharmacotherapy.* 2007; *27*: 734-744.
- [15] *Toto RD, Pichette V, Navarro J, Brenner R, Carroll W, Liu W, Roger S.* Darbepoetin alfa effectively treats anemia in patients with chronic kidney disease with de novo every-other-week administration. *Am J Nephrol.* 2004; *24*: 453-460.
- [16] *Suranyi MG, Lindberg JS, Navarro J, Elias C, Brenner RM, Walker R.* Treatment of anemia with darbepoetin alfa administered de novo once every other week in chronic kidney disease. *Am J Nephrol.* 2003; *23*: 106-111.
- [17] *Ling B, Walczyk M, Agarwal A, Carroll W, Liu W, Brenner R.* Darbepoetin alfa administered once monthly maintains hemoglobin concentrations in patients with chronic kidney disease. *Clin Nephrol.* 2005; *63*: 327-334.
- [18] *Agarwal AK, Silver MR, Reed JE, Dhingra RK, Liu W, Varma N, Stehman-Breen C.* An open-label study of darbepoetin alfa administered once monthly for the maintenance of haemoglobin concentrations in patients with chronic kidney disease not receiving dialysis. *J Intern Med.* 2006; *260*: 577-585.
- [19] *Agarwal A, Silver MR, Walczyk M, Liu W, Audhya P.* Once-monthly darbepoetin alfa for maintaining hemoglobin levels in older patients with chronic kidney disease. *J Am Med Dir Assoc.* 2007; *8*: 83-90.
- [20] *Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration.* Using standardized serum creatinine values in the

- modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006; *145*: 247–254.
- [21] Poggio ED, Wang X, Greene T, Van Lente F, Hall PM. Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. *J Am Soc Nephrol.* 2005; *16*: 459–466.
- [22] Wellen KE, Hotamisligil GS. Inflammation, stress and diabetes. *J Clin Invest.* 2005; *115*: 1111–1117.
- [23] Rusten L, Jacobsen SEW. Tumor necrosis factor (TNF)- $\alpha$  directly inhibits human erythropoiesis in vitro: role of p55 and p75 TNF receptors. *Blood.* 1995; *86*: 989–996.
- [24] Li Vecchi M, Fuiano G, Francesco M, Mancuso D, Faga T, Sponton A, Provenzano R, Andreucci M, Tozzo C. Prevalence and severity of anaemia in patients with type 2 diabetic nephropathy and different degrees of chronic renal insufficiency. *Nephron Clin Pract.* 2007; *105*: 62–67.
- [25] Lorber DL, Provenzano R, McClellan W. Prevalence and treatment of anemia with once-weekly epoetin alfa in patients with diabetes and chronic kidney disease. *Endocr Pract.* 2006; *12*: 506–513.
- [26] McFarlane SI, Salifu MO, Makaryus J, Sowers JR. Anemia and cardiovascular disease in diabetic nephropathy. *Curr Diab Rep.* 2006; *6*: 213–218.
- [27] Thomas MC. Anemia in diabetes: marker or mediator of microvascular disease? *Nat Clin Pract Nephrol.* 2007; *3*: 20–30.
- [28] Tu X, Chen X, Xie Y, Shi S, Wang J, Chen Y, Li Y. Anti-inflammatory renoprotective effect of clopidogrel and irbesartan in chronic renal injury. *Am Soc Nephrol.* 2008; *19*: 77–83.
- [29] <http://www.iom.edu/Object.File/Master/27/184/Chasm-8pager.pdf>. Last accessed, July 1, 2009.
- [30] Ramnarayan P, Tomlinson A, Kulkarni G, Rao A, Britto J. A novel diagnostic aid (ISABEL): development and preliminary evaluation of clinical performance. *Medinfo.* 2004; *11*: 1091–1095.
- [31] Besarab A, Frinak S, Yee J. An indistinct balance: the safety and efficacy of parenteral iron therapy. *J Am Soc Nephrol.* 1999; *10*: 2029–2043.
- [32] Singh AK, Coyne DW, Shapiro W, Rizkala AR. Predictors of the response to treatment in anemic hemodialysis patients with high serum ferritin and low transferrin saturation. *Kidney Int.* 2007; *71*: 1163–1171.
- [33] Stead RB, Lambert J, Wessels D, Iwashita JS, Leuther KK, Woodburn KW, Schatz PJ, Okamoto DM, Naso R, Duliege AM. Evaluation of the safety and pharmacodynamics of Hematide, a novel erythropoietic agent, in a phase 1, double-blind, placebo-controlled, dose-escalation study in healthy volunteers. *Blood.* 2006; *108*: 1830–1834.
- [34] Fan Q, Leuther KK, Holmes CP, Fong KL, Zhang J, Velkovska S, Chen MJ, Mortensen RB, Leu K, Green JM, Schatz PJ. Preclinical evaluation of Hematide, a novel erythropoiesis stimulating agent, for the treatment of anemia. *Exp Hematol.* 2006; *34*: 1303–1311.
- [35] Bunn HF. New agents that stimulate erythropoiesis. *Blood.* 2007; *109*: 868–873.
- [36] Osterborg A. New erythropoietic proteins: rationale and clinical data. *Semin Oncol.* 2004; *31*: 12–18.
- [37] Provenzano R, Besarab A, Macdougall IC, Ellison DH, Maxwell AP, Sulowicz W, Klinger M, Rutkowski B, Correa-Rotter R, Dougherty FC; BA 16528 Study Investigators. The continuous erythropoietin receptor activator (C.E.R.A.) corrects anemia at extended administration intervals in patients with chronic kidney disease not on dialysis: results of a phase II study. *Clin Nephrol.* 2007; *67*: 306–317.
- [38] Remy I, Wilson IA, Michnick SW. Erythropoietin receptor activation by a ligand-induced conformation change. *Science.* 1999; *283*: 990–993.