Impact of elevated C-reactive protein levels on erythropoiesis-stimulating agent (ESA) dose and responsiveness in hemodialysis patients

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Abstract

Background. Inflammation in an ESRD patient may impact responsiveness to erythropoiesis-stimulating agent (ESA) therapy. We sought to investigate the association between C-reactive protein (CRP) levels and average per-administration epoetin alfa (EPO) dose over 3 months following a CRP measurement.

Methods. The study is a retrospective cohort study of hemodialysis patients ≥18 years of age receiving care at a Fresenius Medical Care-North America facility between 1 July 2000 and 30 June 2002 who had no history of peritoneal dialysis. All patients had ≥1 CRP measurement and ≥3 months of recorded information before the CRP measurement (entry period). We evaluated the association between CRP levels and average hemoglobin (Hb) and per-administration EPO dose over the 3 months following the CRP measurement.

Results. We identified 1754 patients with a CRP measurement; mean age was 62.6 years (SD 14.1), 51.5% were male, 56.2% were white and the median CRP value was 2.04 mg/dL (20.4 mg/L). Patients in the upper CRP quartiles were more likely to be older, recently hospitalized; have a catheter vascular access; have lower albumin, Hb and transferrin saturation levels and greater EPO doses. In the subsequent 3 months, EPO doses but not Hb levels were significantly higher for patients in the highest CRP quartile [3.21 mg/dL (32.1 mg/L)] (P = 0.01).

Conclusions. Inflammation as measured by an elevated CRP level appears to be an independent predictor of greater ESA dose requirements. Patients with the highest CRP levels required significantly higher ESA doses to achieve comparable Hb levels even after controlling for potential confounding variables.

Keywords: anemia; C-reactive protein; end-stage renal disease; epoetin alfa; erythropoiesis

Introduction

The importance of inflammation as a prognostic indicator in hemodialysis patients is receiving more attention [1]. Elevations in inflammatory markers including C-reactive protein (CRP), interleukin-6 (IL-6) and fetuin-A have been associated with increased risk of cardiovascular disease and mortality [2–8], and these findings were independent of other well-known mortality risk factors. Estimates from two cross-sectional studies suggest that the prevalence of elevated CRP levels in hemodialysis patients is between 32% [9] and 46% [10], though studies in small samples of patients with multiple CRP measurements have reported considerable within-patient variability [11–13]. This variability may be attributable to transient factors that are likely to cause inflammation [14,15], such as hospitalization events, which occur at an average rate of two times per year in hemodialysis patients [16], catheter access insertion and sub-clinical infections.

In addition to being a prognostic indicator, a patient’s inflammatory state may also impact responsiveness to erythropoiesis-stimulating agent (ESA) therapy. Previous studies in small samples have shown a correlation between elevated levels of inflammation and reduced responsiveness to ESAs [17–19], as measured by total ESA dose requirements. Considering the large inter-patient variability of administered ESA doses required to maintain patients at specific hemoglobin (Hb) levels [20,21], evaluating the influence of inflammation on Hb response to ESA dose is important for guiding anemia management. Yet few studies have had sufficient sample size and collection of factors that may impact ESA dosing to evaluate the independent role of inflammation, as measured by inflammatory markers (e.g., CRP, IL-6, etc.), on ESA dose requirements.

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The objective of the current analysis was to evaluate the effect of a single CRP measurement on ESA dose requirements over a 3-month time window in a population of US hemodialysis patients.

**Subjects and methods**

This study was exempt from human subjects review, as the research utilized existing anonymous data derived from dialysis medical records.

**Data source**

Data were obtained from Fresenius Medical Care-North America (FMC-NA), a large dialysis organization that provides dialysis services to over 120,000 patients in the USA. The FMC-NA database captures patient-level information across numerous domains including demographics, dialysis care, laboratory parameters, medical history, concomitant medications and clinical outcomes. Demographic data are collected at the first hemodialysis session. Dialysis care information, including urea reduction ratio (URR) and vascular access (VA) type in use, are reported as needed. Laboratory parameters including Hb, albumin, calcium and phosphorus are obtained at bi-weekly or monthly intervals. Medication use including dose information and date of administration is routinely collected, including epoetin alfa (EPO), intravenous (IV) iron and IV vitamin D. Clinical outcomes, including hospitalizations and deaths, are collected on an ongoing basis. Causes of hospitalization are identified based on International Classification of Disease—9th Revision (ICD-9) codes.

**Study population**

The study population for this analysis was limited to hemodialysis patients at least 18 years of age receiving dialysis in an FMC-NA facility between 1 July 2000 and 30 June 2002 with no history of peritoneal dialysis. All subjects had at least one CRP measurement recorded in the database (the index month) and at least 3 months of recorded information in the database before the index month of CRP measurement (the entry period). The entry period was necessary to enable characterization of subjects with respect to baseline demographic, laboratory and comorbidity factors. We further restricted the study population to subjects with non-missing Hb and EPO dose information in the 3 months following the index month. CRP is not a routinely collected laboratory parameter in the hemodialysis population, particularly during the study time period. Consequently, it is reasonable to assume that this population of subjects with a CRP measurement were targeted for assessment, possibly due to coexistent disease or acute or chronic inflammation, and may represent a sub-population with greater disease burden.

**C-reactive protein**

Serum CRP values in the subset of FMC-NA subjects with CRP measurements recorded were assayed at a single central laboratory (Spectra Labs, Memphis, TN) using the Olympus CRP kit (Olympus, Memphis, TN), a low-sensitivity assay with a lower limit of detection of 5 µg/mL. We categorized CRP levels based on the quartile distribution [≤1.3, >1.3 to 2.04, >2.04 to 3.21 and >3.21 mg/dL (≤13, >13 to 20.4, >20.4 to 32.1 and >32.1 mg/L)]. Subjects in the lowest quartile were considered the reference group for all analyses. CRP values were not normally distributed, thus log-transformed CRP values were also evaluated in the regression analyses.

**Outcomes**

We assessed Hb levels and EPO doses in each of the 3 months following the index month. We used the average value for months with multiple Hb measurements, and we assessed EPO dose as the average dose per administration. EPO dose was not normally distributed, so log-transformed EPO dose was evaluated.

**Covariates**

Information on baseline patient characteristics including demographics, dialysis care, medical history and laboratory parameters was assessed during the entry period. Demographic characteristics included age, gender, race (white, non-white), diabetes status (yes, no) and length of time on dialysis (vintage). Dialysis care information included type of VA [catheter, arteriovenous fistulae (AVF), arteriovenous graft (AVG), and other] and urea reduction ratio (URR). Medical history was assessed as the number of hospitalizations during the entry period (0, ≥1). The available laboratory parameters included albumin, calcium, ferritin, Hb phosphorus, parathyroid hormone and transferrin saturation (TSAT). For each parameter we calculated the mean of the measurements captured during the entry period. Baseline EPO dose was assessed as the average per-administration dose in the index month.

**Statistical analysis**

Since CRP is not a routinely collected laboratory parameter in hemodialysis patients, we had concerns that these patients were targeted due to coexistent disease or acute inflammation. To evaluate any potential selection bias, we compared all subjects who had a CRP measurement with a cohort of subjects without a CRP measurement, frequency matched on length of time on dialysis (±1 year) and date of the CRP measurement (±3 months). We then used bivariate statistics [analysis of variance (ANOVA) and Mantel–Haenszel chi-square analysis] to compare the two cohorts with respect to important demographic characteristics and other patient factors.

We used descriptive statistics for continuous variables (mean ± SD) and categorical variables (N, %) to characterize the study population overall and according to the CRP quartile distribution. We used the Cochran–Mantel–Haenszel test to compare each of the CRP quartiles according to the baseline categorical covariates, and the Kruskal–Wallis test to compare each of the CRP quartiles according to the baseline continuous covariates. We then used a
Results

A total of 1754 hemodialysis patients with a CRP measurement were available for this analysis. We compared this population with a matched cohort of patients who did not have a CRP measurement and found that the two populations did differ significantly with respect to age and race, but not gender (Table 1). Patients with a CRP measurement did have lower baseline albumin levels, but higher Hb levels and average per administration EPO doses, and were more likely to have been hospitalized in the entry period (previous 3 months). We were unable to find suitable matches for 97 patients (5.5%); compared with the CRP patients we were able to match, these patients tended to be younger and healthier, as measured by higher Hb and TSAT levels and lower EPO dose requirements.

The mean CRP value in the population was 2.89 mg/dL [SD 1.55; 28.9 mg/L (SD 15.5)] and the median CRP value was 2.04 mg/dL (20.4 mg/L). The mean age of patients with CRP measurements was 62.6 years (SD 14.1), 51.5% were male and 56.2% were white. Patients with CRP values in the upper quartiles were more likely to be older, to have been hospitalized in the entry period, to have a catheter VA, to have lower albumin, Hb and TSAT levels and to have lower EPO dose requirements.

Of the 1754 patients with a CRP measurement, 502 did not have EPO dose or Hb data available in all 3 months following the index date and an additional 26 did not have complete covariate information, leaving 1226 (70%) for inclusion in the multiple variable analyses. Excluded patients did not differ from included patients with respect to demographic characteristics, baseline hemoglobin levels or number of previous hospitalizations, but they did have slightly higher average per administration baseline EPO doses (9523 versus 8504, \(P = 0.05\)). In the first month following the CRP measurement, the mean adjusted Hb level was 11.5 g/dL (115 g/L) for patients in the highest CRP and 11.7 g/dL (117 g/L) for patients in the lowest CRP quartile; in the third month, Hb levels were similar, 11.7 g/dL (117 g/L) across CRP quartiles (Figure 1). Overall, mean Hb levels over the 3-month follow-up period did not differ for patients based on CRP level. In the first month following the CRP measurement, patients in the upper CRP quartile had significantly higher average EPO doses (9759 units/administration) compared with patients in each of the other quartiles [8179 units/administration \((P = 0.01)\), 8476 units/administration \((P = 0.04)\) and 8243 units/administration \((P = 0.01)\) for Q1, Q2 and Q3, respectively] (Figure 2). This trend persisted and in the third month following the CRP measurement, mean per-administration epoetin alfa doses remained significantly elevated for patients in the upper CRP quartile, though the average units per administration dose for patients in each CRP quartile did decrease. Similar results were obtained when data were analyzed using log-transformed CRP values and EPO doses (data not shown).

Discussion

In this analysis of 1754 hemodialysis patients with at least one CRP measurement, we observed a strong correlation between elevated CRP levels and EPO dose requirements over the subsequent 3-month period. Patients with a single CRP measurement > 3.2 mg/dL (32 mg/L) were more likely to require significantly higher EPO doses to achieve comparable Hb levels compared to patients with lower CRP levels, suggesting a potentially important role for inflammation in Hb response to EPO dosing. This relationship persisted even after adjustment for many potential correlates of inflammation suggesting that elevated inflammatory levels are independently predictive of greater EPO dose requirements for up to 3 months.

Recent studies have demonstrated the considerable variability in ESA dose requirements [21,22] among hemodialysis patients. A limited number of investigations have attempted to identify factors predictive of greater dose requirements [18,19,23–25] though only a few have assessed the influence of inflammatory markers. Two small

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CRP* ((N = 1657))</th>
<th>Non-CRP* ((N = 1657))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, N (%)</td>
<td>Male</td>
<td>854 (51.5)</td>
<td>890 (53.7)</td>
</tr>
<tr>
<td>Racc, N (%)</td>
<td>White</td>
<td>932 (56.2)</td>
<td>811 (48.9)</td>
</tr>
<tr>
<td>Age</td>
<td>Mean (SD)</td>
<td>62.6 (14.1)</td>
<td>59.0 (15.5)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>Mean (SD)</td>
<td>3.7 (0.4)</td>
<td>3.8 (1.7)</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>Mean (SD)</td>
<td>11.3 (1.4)</td>
<td>11.0 (1.6)</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>Mean (SD)</td>
<td>26.4 (11.7)</td>
<td>27.0 (13.8)</td>
</tr>
</tbody>
</table>

*CRP and EPO dose. All analyses were conducted using SAS 9.13 (Cary, NC).

**Table 1. Comparison of CRP and matched non-CRP patients**
Table 2. Baseline patient characteristics according to CRP quartiles

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CRP Q1</th>
<th>CRP Q2</th>
<th>CRP Q3</th>
<th>CRP Q4</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1.3 g/dL (N = 453)</td>
<td>&gt;1.3 to 2.04 g/dL (N = 425)</td>
<td>&gt;2.04 to 3.21 g/dL (N = 441)</td>
<td>&gt;3.21 g/dL (N = 435)</td>
<td></td>
</tr>
<tr>
<td>Categorical variables, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>227 (50.1)</td>
<td>223 (52.5)</td>
<td>260 (59.0)</td>
<td>270 (62.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Male</td>
<td>251 (55.4)</td>
<td>207 (48.7)</td>
<td>225 (51.0)</td>
<td>213 (49.0)</td>
<td>0.16</td>
</tr>
<tr>
<td>Diabetes</td>
<td>160 (35.3)</td>
<td>143 (33.6)</td>
<td>181 (41.0)</td>
<td>179 (41.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>≥1 hospitalization</td>
<td>153 (33.8)</td>
<td>137 (32.2)</td>
<td>185 (42.0)</td>
<td>235 (54.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vascular access</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter</td>
<td>111 (24.5)</td>
<td>105 (24.7)</td>
<td>132 (29.9)</td>
<td>148 (34.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fistula</td>
<td>137 (30.2)</td>
<td>98 (23.1)</td>
<td>92 (20.9)</td>
<td>86 (19.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Graft</td>
<td>182 (40.2)</td>
<td>201 (47.3)</td>
<td>191 (43.3)</td>
<td>184 (42.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>23 (5.1)</td>
<td>21 (4.9)</td>
<td>26 (5.9)</td>
<td>17 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Continuous variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>59.7 (15.1)</td>
<td>62.6 (14.2)</td>
<td>63.4 (13.2)</td>
<td>64.4 (13.5)</td>
</tr>
<tr>
<td>Vintage (years)</td>
<td>Mean (SD)</td>
<td>2.9 (3.2)</td>
<td>3.3 (3.5)</td>
<td>2.6 (2.7)</td>
<td>2.8 (3.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Mean (SD)</td>
<td>27.4 (8.0)</td>
<td>28.1 (8.4)</td>
<td>28.7 (9.4)</td>
<td>28.6 (9.6)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>Mean (SD)</td>
<td>3.8 (0.4)</td>
<td>3.8 (0.4)</td>
<td>3.7 (0.4)</td>
<td>3.5 (0.5)</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>Mean (SD)</td>
<td>29.6 (13.7)</td>
<td>28.5 (12.9)</td>
<td>25.4 (11.4)</td>
<td>22.7 (10.6)</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>Mean (SD)</td>
<td>11.6 (1.4)</td>
<td>11.6 (1.3)</td>
<td>11.3 (1.4)</td>
<td>10.8 (1.4)</td>
</tr>
<tr>
<td>Epoetin alfa (units/admin) Mean (SD)</td>
<td>7271.9 (7138.4)</td>
<td>7386.5 (7005.5)</td>
<td>8404.5 (6507.2)</td>
<td>11 253.5 (9602.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Phosphorus (mg/dL) Mean (SD)</td>
<td>5.8 (1.9)</td>
<td>5.8 (1.8)</td>
<td>5.8 (1.9)</td>
<td>5.6 (1.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>PTH (pg/mL) Mean (SD)</td>
<td>310.4 (329.4)</td>
<td>288.5 (279.6)</td>
<td>298.0 (346.4)</td>
<td>277.7 (316.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Ferritin (ng/mL) Mean (SD)</td>
<td>650.9 (493.6)</td>
<td>693.3 (470.4)</td>
<td>684.3 (543.8)</td>
<td>753.1 (716.7)</td>
<td>0.11</td>
</tr>
<tr>
<td>Calcium (mg/dL) Mean (SD)</td>
<td>9.2 (0.8)</td>
<td>9.3 (0.9)</td>
<td>9.2 (0.8)</td>
<td>9.1 (0.8)</td>
<td>0.30</td>
</tr>
<tr>
<td>URR (%)</td>
<td>Mean (SD)</td>
<td>71.7 (7.3)</td>
<td>72.1 (7.7)</td>
<td>71.0 (8.0)</td>
<td>71.2 (7.9)</td>
</tr>
</tbody>
</table>

*P-values for categorical variables were obtained from the Cochran–Mantel–Haenszel test; P-values from continuous variables were obtained from the Kruskal–Wallis test.

BMI, body mass index; CRP, C-reactive protein; Hb, hemoglobin; PTH, parathyroid hormone; TSAT, transferrin saturation; URR, urea reduction ratio.

cross-sectional studies, one in 30 hemodialysis patients [23] and the other in 92 patients [24], found higher CRP levels associated with greater ESA dose requirements for any given Hb level. Locatelli et al. [25] studied 677 Italian hemodialysis patients, and found a strong association between CRP levels and both absolute EPO dose and the erythropoietin response index, even after adjustment for many potential confounding factors. However, Singh et al., using clinical trial data from 134 subjects enrolled in the Dialysis Patients’ Response to IV Iron with Elevated Ferritin (DRIVE) study, did not find a statistically significant correlation between CRP levels and ESA dose requirements [19]. The relatively healthy study population included in the DRIVE study (as evidenced by lower average CRP levels compared with other studies in hemodialysis patients) may partially explain the lack of association in that study. In our study, we found that, in addition to the association between elevated CRP levels and higher EPO dose requirements, elevated CRP levels were also correlated with low albumin, Hb, and TSAT levels; catheter VA and hospitalization in the three preceding months, consistent with previous research [14,15], and investigations demonstrating associations between these patient comorbidities and greater EPO requirements, lower Hb levels and EPO responsiveness [18,26,27]. The mechanism by which inflammation may impair ESA response may be multifactorial. Inflammation may slow the progression of erythroid progenitor cell maturation and affect red blood cell survival [28–30]. Additionally, inflammation may induce functional iron deficiency. Inflammatory cytokines have been known to increase hepcidin levels, which in turn regulates absorption of dietary iron, the release of recycled iron by macrophages and the transfer of stored iron from hepatocytes [31,32].

These findings should be evaluated in light of the following limitations. CRP is not a routinely collected laboratory parameter in the hemodialysis patient population. Patients evaluated in this study should therefore not be considered a random sample of hemodialysis patients; in contrast, these patients represent a sicker subset of the population as highlighted in Table 1. This study was meant to examine the association between elevations in CRP levels and future ESA dose requirements. Importantly, because...
Association of CRP with epoetin alfa dose

Fig. 1. Adjusted mean monthly hemoglobin (g/dL) level by CRP quartile in each of the 3 months following the CRP measurement. Error bars represent the standard error of the mean. Variables adjusted for include age, gender, race, BMI, albumin (g/dL), ferritin (ng/mL), TSAT%, hospitalization events and vascular access type.

Fig. 2. Adjusted mean per administration EPO dose (units/administration) by CRP quartile in each of the 3 months following the CRP measurement. Error bars represent the standard error of the mean. Variables adjusted for include age, gender, race, BMI, albumin (g/dL), ferritin (ng/mL), TSAT%, hospitalization events and vascular access type.

this patient population is enriched with sicker patients and likely over-represents patients with elevated CRP levels [as evidenced by a mean CRP near 3 mg/dL (30 mg/L) compared with 0.3 to 0.6 mg/dL (3 to 6 mg/L) from previous studies [2,3]], patients with lower CRP levels are largely under-represented. Consequently, the reference group for all of these analyses consists of generally sicker patients, which likely contributes to an underestimation of the true association between elevated CRP levels and other markers of disease severity and future EPO dose requirements. The greater disease burden of the reference group in this study may also partially explain the lack of association
observed for the comparisons with subjects in the second and third CRP quartiles. In this study, the mean Hb level and per administration EPO dose requirements for subjects in the lowest three quartiles were similar, ~11.3 g/dL and 8000 units, respectively. In comparison, in the larger US hemodialysis population in 2001, the mean Hb level and per administration EPO dose were ~11.5 g/dL and 5000 units, respectively [16]. The markedly higher dose requirements to achieve a similar Hb level observed in our population support the following: (i) even patients in the lowest CRP quartiles in this population have a greater disease burden and (ii) the magnitude of the association between elevated CRP levels and EPO dose requirements, even for patients with CRP values between 13–30 mg/L, would be more pronounced were the reference population more reflective of the general hemodialysis population.

We limited our assessment of baseline patient characteristics available from the database to the 3 months immediately preceding the CRP measurement. Additional comorbidity information, such as history of cardiovascular disease, HIV/AIDS, gastrointestinal bleeding and other conditions, were not captured, which limited our ability to evaluate their impact. For the purposes of our study, CRP was hypothesized to be reflective of acute cross-sectional inflammatory episodes. This is supported by the correlation we found between the percentage of patients with a hospitalization in the 3 months before the CRP measurement was considerably higher for patients in the upper CRP quartiles ($P < 0.0001$).

Conclusions

Inflammation as measured by an elevated single point in time CRP level appears to be predictive of ESA dose requirements for up to 3 months in the future, and this relationship persisted, even after accounting for severity of illness, and other important correlates of elevated inflammatory levels. These data suggest that monitoring of CRP levels may guide clinicians in their diagnosis and treatment of patients with impaired response to ESAs. Obtaining these laboratory values may be a part of the workup for hyporesponsive patients as suggested by the 8th November 2007 ESA label revisions. However, prospective studies are required to evaluate the utility of repeated measures of inflammatory markers in guiding ESA treatment in patients with end-stage renal disease.

Acknowledgements. The authors thank Mandy Suggitt for her assistance with manuscript preparation and editing.

Conflict of interest statement. This research was supported by Amgen, Inc. Brian Bradbury, Cathy Critchlow, Ron Stewart and Mahesh Krishnan work in the Departments of Epidemiology and Global Health Economics at Amgen, Inc. Matthew Weir is consultant to Amgen, Inc., and Raymond Hakim is an employee of Fresenius Medical Care.

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Association of CRP with epoetin alfa dose


Received for publication: 17.3.08
Accepted in revised form: 4.9.08