ORIGINAL RESEARCH

Associations Among Epoetin Therapy, Inflammation, Nutritional Status, and Mortality in Patients on Hemodialysis

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Objective: Inflammation contributes to hemopoiesis by lowering responses to epoetin (EPO) and to an increase in the mortality of patients on hemodialysis. However, nutritional status might alter associations among inflammation, EPO responsiveness, and the risk of mortality. We assessed the effect of inflammation on mortality according to nutritional status among EPO responses in a cohort of prevalent hemodialysis patients.

Design and Methods: The observational cohort study analyzed data from the Japanese Dialysis Registry (2005-2006; n = 36,956; mean follow-up 11.5 months). Patients were categorized into tertiles of the EPO responsiveness index (ERI; the weekly weight-adjusted EPO dose [IU/kg/week] divided by hemoglobin [g/dL]) and an EPO-free group. Body mass index (BMI) and C-reactive protein (CRP) levels were measured.

Results: Bimodal peaks indicated associations between CRP and BMI in each group. Hazard ratio (HR) curves of CRP for mortality according to BMI in the upper ERI tertile, particularly among those with diabetes mellitus (DM), were reverse J-shaped. However, HR curves in the other groups were increased below a threshold BMI of 21 kg/m^2. These associations were confirmed in propensity score-matched populations.

Conclusion: Risk of CRP for death is apparently changed by BMI in hemodialysis patients with a lower EPO response, especially in those with DM.

Introduction

RECENT META-ANALYSES OF studies have identified a beneficial effect of erythropoiesis-stimulating agents (ESAs) on hospitalization for heart failure and some signs of symptomatic improvement with no increase in mortality or other adverse events in patients with chronic kidney disease.[1-4] However, large prospective trials of anemia correction in patients who have end-stage kidney disease (ESKD) treated with and without hemodialysis (HD) therapy have found either no benefit or detrimental outcomes of higher hemoglobin (Hb) targets,[5-9] and analyses of the results of these trials have confirmed that high-dose ESA therapy confers an increased risk of cardiovascular disease (CVD)-related events and mortality in patients who respond poorly to these drugs.[9-11] However, the prognosis is significantly better for good responders to ESA.[12]

Wang and colleagues used a marginal structural model to analyze ESA hyporesponsiveness and high ESA doses in a cohort on HD. They identified appreciable confounding at a higher epoetin (EPO) dose and did not associate the EPO dose with increased mortality.[13] That is, confounders influence the mortality of patients who respond poorly to ESA and can be independent predictors of mortality in patients on dialysis.[14] Although several confounders influence ESA responsiveness,[15,16] nutritional status and inflammation are closely associated with ESA responsiveness. Locatelli and colleagues reported that a low body mass index (BMI) can serve as a marker of nutritional status and ESA hyporesponsiveness in patients on HD.[17] The Trial to Reduce Cardiovascular Events with Aranesp Therapy found that high-dose ESA therapy with concomitant inflammation and high C-reactive protein (CRP) levels is closely

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associated with a high rate of composite CVD events in ESKD patients with concomitant diabetes mellitus (DM).[18] Thus, inflammation and nutritional status are key factors for increased mortality associated with high-dose ESA therapy in patients with ESKD, particularly those who also have DM.

On another front, the association between inflammation and body composition is quite complex in patients on HD because inflammation develops in those who are malnourished and overweight. However, the association between a high or a low BMI, especially when accompanied by inflammation and better or worse survival, respectively, is paradoxical in such patients.[19] This association is interpreted to mean that a higher BMI afforded via mechanisms other than better nutrition confers a survival advantage that might partially offset the toxic effects of uremia among obese patients on dialysis,[19] although the status of such patients is that of extreme inflammation.[20] On the other hand, a high BMI with a low lean body mass is a risk for mortality among those who frequently experience extreme inflammation.[20] Thus, inflammation as a risk for mortality is associated with nutritional status resulting in a poor response to ESA.

We speculated that the effect of inflammation on mortality according to BMI might differ among ESA responses. That is, risk of inflammation for mortality might be increased not only in patients with a low BMI but also in those who are overweight and hyporesponsive to ESA. In this setting, the results of a comparison of patients with naturally higher levels of Hb (concomitant endogenous erythropoietin) and various responses were remarkable because the survival rates were quite similar between such patients and patients who responded well to ESA.[21] Therefore, the study presented here aimed to clarify differences in risk of inflammation, increased CRP levels, and mortality according to BMI among patients on HD with a low (hypo) ESA response, a good ESA response, and those who were not treated with ESA.

Materials and Methods

Data Source

The Japanese Society for Dialysis Therapy (JSDT) has been conducting an annual survey of dialysis facilities throughout Japan since 1968, and several publications have been based on the outcomes of these surveys.[16,22,23] JSDT also started compiling a computer-based registry in 1983. Details about the origins, limitations, validity, variables, and questionnaires used in the study are available online at www.jsdt.or.jp. In brief, questionnaires requesting information about patients are sent to all Japanese dialysis facilities at the end of each year. Volunteers selected from among the doctors and staff of the facilities, the principal investigators in each prefecture, and JSDT committee members anonymously administer the questionnaires. We analyzed data extracted from standard analysis files in the JSDT 2005 to 2006 dialysis registry (JRDR-08005; $n = 221{,}917$) with the approval of the JSDT. The database contains demographic information (age, sex, dialysis vintage, primary cause of end-stage renal disease, diabetes, history of CVD, systolic and diastolic blood pressure at predialysis, body weight at postdialysis, and weekly dose of EPO α or β) and clinical data (Hb, serum albumin, creatinine, urea nitrogen, CRP, transferrin saturation, ferritin, calculated values for single-pool Kt/V, normalized protein catabolic rate, rate [%] of creatinine generation, and BMI).

This cohort study included patients older than 20 years of age who had been under at least 3 months of HD therapy and with the nutritional index and clinical data described previously. However, we excluded patients who had been treated with peritoneal dialysis, hemofiltration, hemodiafiltration, HD with hemoadsorption, and HD other than 3 sessions per week. Outliers defined as having a BMI less than 12 or more than 60 kg/m^2 as well as patients with polycystic kidney disease, multiple myeloma, or acute CVD at baseline were excluded.

Baseline demographic and clinical data were collected once in December 2005. Doses of EPO in December 2005 are described as categorical values (IU/week; <1,500, 1,500-2,999, 3,000-4,499, 4,500-5,999, 6,000-8,999 and 9,000). Mortality data (time and cause) were collected from the database between December 2005 and December 2006 (mean follow-up 11.5 months).

Categories of Patients

Patients were grouped into tertiles of ESA responsiveness (the weekly weight-adjusted EPO dose [IU/kg/week] divided by Hb [g/dL] and no EPO therapy [EPO-free]).

Outcomes

The primary and secondary outcomes were all-cause and cardiovascular mortality rates, respectively. Cardiovascular mortality included death from heart failure, myocardial infarction, or stroke, and death from other vascular diseases.

Statistical Analysis

Data are presented as means ± standard deviation or medians (range) unless otherwise noted, and P values less than .05 were considered to indicate statistical significance. Normally distributed variables between 2 groups were compared using Student's t-test, and non-normally distributed variables were compared using the Wilcoxon rank-sum test. Each variable in the model was checked and log-transformed or categorical variables were constructed when appropriate. Nominal variables between 2 and among more than 2 groups were compared using Fisher's exact test and the χ^2 test, respectively.

Association Between Inflammation and BMI in Patients With Different ESA Responses

The continuous variables, log-transformed CRP and BMI, were fit using Lowess curves according to EPO responsiveness index (ERI) tertiles and EPO-free groups.