IL-1β Receptor Antagonist Reduces Inflammation in Hemodialysis Patients

Adriana M. Hung,*† Charles D. Ellis,† Ayumi Shintani,† Cindy Booker,† and T. Alp Ikizler*†

*Veterans Administration Tennessee Valley Healthcare System, Nashville, Tennessee; and †Vanderbilt University Medical Center, Nashville, Tennessee

ABSTRACT

Chronic inflammation is highly prevalent in maintenance hemodialysis (MHD) patients and associates with increased mortality. IL-1β, a pro-inflammatory cytokine, is elevated in MHD patients. A balance between IL-1β and its naturally occurring antagonist may determine the inflammatory response and its consequences in this population. We performed a pilot randomized placebo-controlled trial to evaluate the efficacy of the administration of recombinant human IL-1 receptor antagonist (IL-1ra) on biomarkers of inflammation and nutrition in MHD patients with three consecutive high sensitivity C-reactive protein (hsCRP) measurements >5 mg/L. We randomly assigned 22 patients to placebo or IL-1ra (1:1) for 4 weeks; 14 completed the trial. Patients in the IL-1ra arm had a 53% reduction in mean hsCRP compared with 1% in the placebo arm (P = 0.008), a 40% reduction in mean IL-6 levels compared with a 20% increase in the placebo arm (P = 0.03), and a 23% increase in mean prealbumin compared with 6% in the placebo arm (P = NS). In conclusion, the administration of IL-1ra in MHD patients can lower biomarkers of inflammation. Whether IL-1ra administration improves survival in this population requires additional long-term studies.


Despite all of the technical advances in dialysis therapy over the last several decades, there has been minimal improvement in the death rate of maintenance hemodialysis (MHD) patients in the United States. A significant portion of the MHD patients die because of cardiovascular events. Randomized controlled trials targeting traditional and nontraditional cardiovascular risk factors have had no significant impact in improving survival in this patient population. Systemic chronic inflammation is highly prevalent in MHD patients, and it has been shown to be a strong predictor of morbidity and mortality. Chronic inflammation in ESRD is highly prevalent and multifactorial. Some of the most commonly postulated etiologies include dialysis-related factors such as the extracorporeal circulation, the quality of the dialysate, the biocompatibility of the hemodialysis membranes, acute and chronic access thrombosis, and dialysis catheters. Non–dialysis-related factors include decreased clearance and increased production of cytokines, retention of uremic solutes, increased oxidative stress burden, genetic factors, and high prevalence of comorbidities associated with inflammation. Nevertheless, a significant percent of the patients have no identifiable preventable or treatable cause of persistent inflammation. It has been suggested that these patients are at increased risk for cardiovascular mortality and morbidity and that ameliorating inflammatory response could potentially improve their survival.

Copyright © 2011 by the American Society of Nephrology

BRIEF COMMUNICATION www.jasn.org
Figure 1. Patient enrollments, randomization, and completion flow diagram.

Table 1. Inflammation and nutritional biomarkers at baseline by randomization group

<table>
<thead>
<tr>
<th>Variables</th>
<th>All (n = 14)</th>
<th>IL-1ra (n = 7)</th>
<th>Placebo (n = 7)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>49 ± 13</td>
<td>48 ± 12</td>
<td>51 ± 14</td>
<td>0.8</td>
</tr>
<tr>
<td>Race, % (n) African Americans</td>
<td>71.4% (10)</td>
<td>86% (6)</td>
<td>57% (4)</td>
<td>0.3</td>
</tr>
<tr>
<td>Gender, % (n) males</td>
<td>71.4% (10)</td>
<td>71.4% (5)</td>
<td>71.4% (5)</td>
<td>0.99</td>
</tr>
<tr>
<td>Body mass index (mean ± SD)</td>
<td>31 ± 8</td>
<td>34 ± 6</td>
<td>31 ± 10</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes, % (n)</td>
<td>21.4% (3)</td>
<td>0% (0)</td>
<td>42.9% (3)</td>
<td>0.03*</td>
</tr>
<tr>
<td>KTV (mean ± SD)</td>
<td>1.61 ± 0.33</td>
<td>1.55 ± 0.19</td>
<td>1.66 ± 0.44</td>
<td>0.9</td>
</tr>
<tr>
<td>Vintage, months (median, IQR)</td>
<td>35 (8 to 90)</td>
<td>43 (15 to 104)</td>
<td>27 (5 to 88)</td>
<td>0.3</td>
</tr>
<tr>
<td>Arteriovenous fistula, (%) (n)</td>
<td>50% (7)</td>
<td>28.6% (2)</td>
<td>71.4% (5)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*Significant at α < 0.05.

Our results have important clinical and research implications. It has been consistently shown that MHD patients...
have an unacceptably high morbidity and mortality and that biomarkers of inflammation are robust predictors of these outcomes. Accordingly, a number of different potential anti-inflammatory interventions have been proposed in this patient population with only mild to moderate effect. These include but are not limited to resistance training, pentoxifylline (TNF-α blocker), angiotensin converting enzyme inhibition, hydroxy-methyl-glutaryl-CoA reductase inhibitors, and vitamin E. In terms of anti-cytokine therapies, a recent randomized controlled trial of a TNF-α blocker in 10 MHD patients showed no effect on biomarkers of inflammation (hsCRP or IL-6). Although the reasons for the lack of response to the TNF-α blocker are not clear, this particular study was limited by number of patients because of drop-outs, and the effects were examined over 44 weeks rather than 1 month as performed in our study. It is also possible that inflammation of CKD could be mainly IL-1β and IL-6 driven, as observed in other chronic conditions.

### Table 2. Inflammation and nutritional biomarkers at baseline and after intervention by randomization group

<table>
<thead>
<tr>
<th>Variable</th>
<th>IL-1ra</th>
<th>Placebo</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Mean ± SD</td>
<td>Mean Percent Change</td>
</tr>
<tr>
<td>Baseline CRP, mg/dl</td>
<td>9.50 (6.80, 12.60)</td>
<td>9.57 ± 3.95</td>
<td>-53%</td>
</tr>
<tr>
<td>Post-CRP, mg/dl</td>
<td>4.50 (2.50, 6.80)</td>
<td>4.67 ± 2.87</td>
<td></td>
</tr>
<tr>
<td>Baseline IL-6, pg/ml</td>
<td>4.62 (4.35, 8.40)</td>
<td>7.77 ± 7.48</td>
<td>-40%</td>
</tr>
<tr>
<td>Post-IL-6, pg/ml</td>
<td>2.15 (0.77, 5.77)</td>
<td>3.34 ± 3.09</td>
<td></td>
</tr>
<tr>
<td>Baseline albumin, g/dl</td>
<td>4.05 (3.73, 4.30)</td>
<td>4.03 ± 0.37</td>
<td>3%</td>
</tr>
<tr>
<td>Post-albumin, g/dl</td>
<td>4.20 (4.00, 4.80)</td>
<td>4.26 ± 0.40</td>
<td></td>
</tr>
<tr>
<td>Baseline prealbumin, mg/dl</td>
<td>40.0 (31.0, 47.0)</td>
<td>38.2 ± 8.8</td>
<td>23%</td>
</tr>
<tr>
<td>Post-prealbumin, mg/dl</td>
<td>49.0 (40.0, 54.0)</td>
<td>46.4 ± 11.3</td>
<td></td>
</tr>
<tr>
<td>Baseline LBM, g</td>
<td>54.00 (47.1, 65.5)</td>
<td>55.73 ± 9.9</td>
<td>1.70%</td>
</tr>
<tr>
<td>Post-LBM, g</td>
<td>59.00 (50.6, 67.6)</td>
<td>59.1 ± 8.7</td>
<td></td>
</tr>
<tr>
<td>Baseline % body fat</td>
<td>40.0 (35.9, 50.7)</td>
<td>39.8 ± 9.3</td>
<td>-1%</td>
</tr>
<tr>
<td>Post % body fat</td>
<td>37.6 (33.3, 42.7)</td>
<td>37.6 ± 8.0</td>
<td></td>
</tr>
</tbody>
</table>

CRP and IL-6 were log-transformed to achieve normality for the analysis. Comparison of baseline characteristics was done using nonparametric methods. None of the comparisons between groups for baseline CRP, IL-6, albumin, prealbumin, LBM, or % body fat were significant at α < 0.05.

*pComparison for the percent change from baseline to 4 weeks for each marker between groups was done using ANCOVA.

Figure 2. Pre- and poststudy levels of hsCRP (mg/dl) and IL-6 (pg/ml) in individual study subjects. hsCRP decreased in all but one individual in the IL-1ra arm, whereas all placebo subjects were either stable or increased their hsCRP. A similar trend was observed for IL-6 levels. *Comparison for the percent change from baseline to 4 weeks for each marker between groups was done using ANCOVA.
and, by selectively targeting myosin,35 activate the ubiquitin proteosome system advanced CKD. IL-6 has been shown to activate the effects of IL-1ra blockade on nutritional parameters in MHD patients with protein energy wasting over a longer period of time. Although this is the first study using an IL-1ra blocker in chronically inflamed MHD patients, it has certain limitations. Most importantly, the sample size is small, and the intervention is of short duration. Nevertheless, the response in improving inflammation was seen in all subjects, supporting that the effect is real. Indeed, the study was terminated at the first interim analysis by the data safety and monitoring board (DSMB) because of reaching efficacy boundaries (vide infra). On the other hand, our inclusion criteria were stringent, resulting in a high drop-out rate. For example, patients with catheters and history of recent infection were excluded because of the potential risk of predisposing to a new or recurrent infection. This approach resulted in a selected patient population, and the results cannot be generalized to all MHD patients.

In summary, our results suggest that the administration of IL-1ra over a period of 4 weeks successfully controls the inflammatory response in MHD patients as reflected by significant decreases in hsCRP and IL-6 levels. The treatment is generally well tolerated and safe. It should also be noted that the study sample size is small, and the follow-up was relatively short. Future long-term studies with larger and more heterogeneous patient populations are needed to examine the effects of administration of IL-1ra on cardiovascular and other outcomes in chronically inflamed MHD patients.

### CONCISE METHODS

#### Study Participants

This study was conducted at the Vanderbilt University Medical Center and Nashville Veterans Affairs Outpatient Dialysis units between January 2008 and May 2010. Prevalent MHD patients 18 to 75 years old on MHD three times a week were eligible to participate. Inclusion criteria included the average of three consecutive serum CRP levels >5 mg/L and adequate dialysis delivery Kt/V ≥1.2. Patients were excluded if they had hemodialysis catheters, had any active or chronic infection (HIV, hepatitis B or C, or tuberculosis/tuberculin test positive), had a history of malignancy in the previous 5 years, were hospitalized within 1 month needed any immune suppression therapy, or had received any investigational study drug within 1 month before the study. The study was approved by the Institutional Review Boards from Vanderbilt University Medical Center and from the Nashville Veterans Affairs hospital, and signed informed consent was obtained from all patients.

#### Study Design

This was a placebo-controlled, double-blinded study (ClinicalTrials.gov number, NCT00420290). Of 239 screened patients from two centers, 22 prevalent MHD patients were randomized in a 1:1 ratio to receive recombinant 100 mg of human recombinant IL-1ra or placebo by subcutaneous injection at each dialysis session for 4 weeks. The medication was administered by the study coordinator or the principal investigator in all subjects.

#### Procedures

Blood samples were drawn at baseline and at the end of the study (4 weeks). Vacutainer (Becton Dickinson, Franklin Lakes, NJ) tubes containing EDTA were used for plasma separation. Samples were transported on ice and centrifuged at 20°C at 3000 rpm for 15 minutes. Supernatants were stored in aliquots at −80°C until further use. Dual energy x-ray absorptiometry scans were performed 1 to 2
hours after dialysis (at dry weight) at baseline and at 4 weeks to evaluate changes in body composition.

**Study Endpoints**
The primary endpoint was the percent change in serum hsCRP from baseline to 4 weeks. Secondary outcomes were the percent changes in IL-6, serum prealbumin, serum albumin, and LBm from baseline to 4 weeks. Covariates included demographics, vintage, access type, KT/V, body mass index, CVD, and diabetes.

**Statistical Analysis**
Data are presented as mean ± SD or as median with interquartile range depending on their distribution. Baseline characteristics were compared using Mann-Whitney U or χ² tests when appropriate. Analysis of covariance (ANCOVA) was used to compare percent change from baseline to 4 weeks for the primary and secondary outcomes between the groups. Outcome variables were log-transformed to improve normality in residuals, and the log-transformed baseline value of the outcome variable was adjusted as a covariate. Regression coefficients from the ANCOVA model were exponentiated, which indicates the ratio of percent change from baseline to 4 weeks. ANCOVA assesses change by adjusting baseline as a regression coefficient rather than using change directly as an outcome variable.37–39 Because of the small number of participants, no adjustment of other variables was performed. The study was overseen by a DSMB, which reviewed the interim analyses of efficacy. A sequential determination for termination by DSMB was based on the prespecified stopping rule for efficacy of the intervention on reduction of hsCRP with \( P < 0.031 \).

**ACKNOWLEDGMENTS**
This study was supported in part by Grants R21 DK077373 and K24 DK 062849 from the National Institute of Diabetes and Digestive and Kidney Diseases, Clinical Translational Science Award 1UL-1RR024975 from the National Center for Research Resources, and a National Kidney Foundation Young Investigator Award. A.H. is supported by VA Career Development Award 2-031-09S. Study drug and matching placebo were kindly provided by Amgen (Thousand Oaks, CA).

**DISCLOSURES**
The sponsors had no influence on the design, execution, and analysis of the results of the study.

**REFERENCES**

Supplemental information for this article is available online at http://www.jasn.org/.