

High circulating levels of the IL-1 type II decoy receptor in critically ill patients with sepsis: association of high decoy receptor levels with glucocorticoid administration

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Abstract: The objective of this study was to evaluate whether the interleukin (IL)-1 decoy receptor (R), a negative pathway of regulation of IL-1, is correlated with severity of infection in critically ill patients and reflects the activation of anti-inflammatory pathways by glucocorticoid hormones. Plasma samples were obtained from 101 consecutive, critically ill patients admitted to the intensive care unit with different severities of microbial infection, as defined by standardized criteria. Here, we report that the IL-1 type II decoy R(II) is elevated in critically ill patients, especially in severe, systemic infection and culture-positive infections. In patients with a marked systemic inflammatory response syndrome 4, a pronounced, sepsis-induced further increase of circulating IL-1 decoy RII levels was evident. Thirty-six patients treated with glucocorticoid hormones had significantly higher levels of IL-1 decoy RII, but lower IL-6 and C-reactive protein, than 67 untreated subjects. The usefulness of IL-1RII, in particular as a potential marker for the activation of anti-inflammatory pathways or for responsiveness to anti-inflammatory agents such as glucocorticoid hormones, deserves further analysis. *J. Leukoc. Biol.* 72: 643–649; 2002.

Key Words: microbial infection · severe sepsis · glucocorticoid hormones · cytokines

INTRODUCTION

Interleukin (IL)-1 is a prototypic, primary inflammatory cytokine, which affects virtually all cells and tissues in the body [1]. Evidence has accumulated that IL-1 plays an important role in local and systemic inflammation [1]. In particular, preclinical models suggest that IL-1 is an important mediator involved in the pathogenesis of sepsis and septic shock [1]. However, clinical trials aimed at assessing the therapeutic value of the IL-1 blockade using the IL-1 receptor antagonist (IL-1ra) have failed to give unequivocal, positive results, although a subset of patients may have benefited from treatment [2].

IL-1 activates cellular responses by interacting with a signaling receptor complex formed by type I IL-1 receptor (IL-1RI) and the accessing protein (IL-1 RacP) [3]. The IL-1 type II decoy receptor (IL-1 decoy RII) acts as a negative pathway of regulation of IL-1 [4–6]. The IL-1 decoy RII binds IL-1 β (but not IL-1ra) with high affinity, does not signal, and prevents the agonist from interacting with the signaling receptor complex. In addition, by forming a nonsignaling receptor complex with IL-1 β and the IL-1 RacP, it acts as a dominant negative for IL-1 signaling [6–9]. The decoy IL-1RII is released from neutrophils and monocytes by a matrix metalloproteinase similar or identical to tumor necrosis factor α (TNF- α)-converting enzyme [10–12]. Expression and release of the decoy IL-1RII are controlled by pro- and anti-inflammatory signals [6]. Glucocorticoid hormones, IL-4 and IL-13, induce augmented expression and release of the IL-1 decoy RII [4, 13, 14], whereas bacterial lipopolysaccharides (LPS) cause rapid shedding, followed by inhibition of transcript expression [6, 15–17].

There is a pressing need for new serum markers, which may help the diagnosis of infection and sepsis in critically ill patients as well as the stratification of patients in clinical trials. The IL-1RII was reported to be elevated in relatively small case lists of patients with sepsis or experimental endotoxemia [18–20]. The present study was designed to investigate the plasma levels of the IL-1 decoy RII in a series of 101 critically ill patients with different severities of infection and sepsis and to compare them with other inflammatory markers. In particular, we wanted to test the possibility that the IL-1 decoy RII may reflect the activation of anti-inflammatory pathways.

MATERIALS AND METHODS

Over a 9-month period, 101 consecutive patients admitted to the Medical Intensive Care Unit (ICU) at the University Hospital, Basel, Switzerland, were eligible, including neutropenic and immunosuppressed patients. When feasible, consent was obtained prior to enrollment in conscious patients; otherwise,

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the consent was obtained from the patients' next of kin. The study protocol had prior approval by the hospital Institute Ethical Review Board. The characteristics of this population, diagnostic criteria, and the levels of different markers of inflammation and infection [including IL-6, C-reactive protein (CRP), and calcitonin precursors (CTpr) including procalcitonin] have been reported in detail [21, 22].

Study design

The data were collected on admission (i.e., during the first 24 h), on day 2, and on the day of discharge from the ICU or on the day of death, as previously described [23]. At these time points (total n=276), the patients were very sick or in a stable condition and were ready for discharge to a medical ward, respectively. In patients who died within 24 h after admission, only data from admission were collected (n=5).

The severity of disease was estimated by the Acute Physiology and Chronic Health Evaluation (APACHE II) [24, 25]. It was calculated by means of deviation of 12 physiological variables from normality plus correction for age and different chronic illnesses [26]. Vital signs, clinical status, and severity of disease parameters (APACHE II) were assessed daily. APACHE II score was calculated by means of maximal daily deviations of 12 physiological variables from normality plus correction for age and different chronic illnesses [26].

Infection was diagnosed according to textbook standard criteria [27] or, in case of uncertainty, by an infectious disease specialist. This ascertainment was done retrospectively on the basis of the review of the complete patient charts, results of microbiological cultures, chest radiographs, and when available, postmortem examination reports. The distribution of the site of infection and the microbiology were described previously [22]. The principal site of infection was the lung. The etiological microorganism was identified, and 14 patients had bacteremia (culture positive). Colonizations with bacteria (e.g., in patients with bladder catheter without leucocyturia) were disregarded. Microbiological tests and antibiotic therapy were prescribed by physicians on duty, according to the usual practice, without interference by the research team. Because the clinical spectrum of systemic inflammatory response syndrome (SIRS) to septic shock is a fluid continuum that can progress very rapidly, the patients were classified at the time of blood collection.

The clinical investigation and classification were carried out without knowledge of the test results for CTpr, peptaxin (PTX3), IL-1 decoy RII, or IL-6, which were analyzed in batch analyses after the end of the study. Results of the routine blood analyses (i.e., complete blood count, serum chemistry including CRP, blood gas analyses) were known and recorded. Blood was obtained from an in-dwelling arterial or venous catheter. The blood was separated into plasma at the time of blood draw and was frozen at -70°C until assay. The 36 patients on glucocorticoid therapy received 20–1500 mg per day of prednisolone parenterally.

Definitions

The following terms were used in this study:

SIRS

SIRS shows no signs of infection. It is characterized by the presence of at least two of the four following clinical criteria: fever or hypothermia [temperature, $>100.4^{\circ}\text{F}$ ($>38^{\circ}\text{C}$) or $<96.8^{\circ}\text{F}$ ($<36^{\circ}\text{C}$)], tachycardia (>90 beats per min), tachypnea [>20 breaths per min, PaCO_2 , <4.3 kPa (32 mmHg)], or the need for mechanical ventilation], and an altered white blood cell count of $>12,000$ cells/ μl , <4000 cells/ μl , or the presence of $>10\%$ band forms, respectively.

The severity of infection was categorized into the following groups, as previously described [21]:

No infection

These critically ill patients showed no signs of infection, but showed one to four signs of SIRS.

Concomitant infection

In some of the polymorbid patients, their critical illness was primarily a result of a noninfectious process, but they coincidentally suffered from an infection. As an example, a patient admitted to the ICU for acute pulmonary embolism who coexistently suffered from a urinary tract infection was classified in this

category. Patients with clinical evidence of infection do not necessarily score positive on culture.

Sepsis

Patients with sepsis had a SIRS caused by infection. Thus, these patients suffered from infections, which were severe and life-threatening. Patients with sepsis were further classified into two groups, severe sepsis and septic shock.

Severe sepsis. Severe sepsis is defined as the presence of sepsis and at least one of the following manifestations of inadequate organ perfusion or function: hypoxemia [PaO_2 , <10 kPa (<75 mmHg)], metabolic acidosis (pH <7.30), oliguria (output, <30 ml/h), lactic acidosis (serum lactate level, >2 mmol/l), or an acute alteration in mental status without sedation (i.e., a reduction by at least three points from baseline value in the Glasgow coma score).

Septic shock. Septic shock is defined as the presence of sepsis accompanied by a sustained decrease in systolic blood pressure (<90 mmHg or a drop of 40 mmHg from baseline systolic blood pressure) despite fluid resuscitation and the need for vasoactive amines to maintain adequate blood pressure.

Culture result

An isolated microorganism was considered to be pathogenic if recovered within a 24-h period before or after the onset of the systemic response. Postmortem positive blood cultures were disregarded.

Laboratory measurements

Plasma concentrations of the IL-1 decoy RII were measured by solid-phase, enzyme-linked immunosorbent assay based on the sandwich principle using monoclonal antibody 8.5 and a polyclonal rabbit generated by us (Hycul Biotechnology, The Netherlands) with a sensitivity of 20 ng/l.

CRP was determined by an enzyme immunoassay (EMIT, Merck Diagnostica, Zurich, Switzerland). A serum level greater than 5 ng/l was considered abnormally elevated. Serum IL-6 concentrations were measured with a commercially available quantitative sandwich enzyme immunoassay (CLB, Pelikine CompactTM, Amsterdam, Netherlands) with a limit of detection at 0.6 ng/l.

For rapidity of determination in the present study, we chose a commercially available immunoluminometric assay to measure CTpr (LUMitest PCT, BRAHMS Diagnostica, Berlin, Germany). This assay has the disadvantage of insensitivity and a detection limit of 0.3–0.5 ng/ml. A sensitive radioimmunoassay for calcitonin precursors has been developed. This assay, which was not available at the time the current study began, has the advantage of a sensitivity of 0.004 ng/ml and detects values in nearly all normal persons. Recent literature refers to measurement of "procalcitonin." This is incorrect, however, as none of the presently available assays measure exclusively the procalcitonin molecule. For exactness of terminology, we have therefore chosen the term "calcitonin precursors" to indicate, globally, the immunoreactive material detected by these assays [22, 23].

Statistical analysis

Data in the text are shown as mean \pm SD and in the figures, as SEM. Logarithmic transformation was applied to reduce skewness and normalize the distribution of data if indicated by Shapiro-Wilk's W test. Two-group comparison of normally distributed data was performed by Student's *t*-test. For multigroup comparisons, one-way ANOVA was applied, with least-square difference for post-hoc comparison. For data that were not normally distributed, the Mann-Whitney U test was used if only two groups were being compared; the Kruskal-Wallis one-way ANOVA was used if more than two groups were being compared. Levels that were nondetectable were assigned a value equal to the lower limit of detection for the assay. All testing was two-tailed, and *P* values less than 0.05 were considered to indicate statistical significance.

RESULTS

Characteristics of the study population

The relevant diagnoses on 101 patients admitted to a medical ICU are summarized in **Table 1** and have been published in detail elsewhere [21, 22, 28]. On admission, 48% of the

TABLE 1. Principal Diagnoses and Etiologies on Admission

Clinical Diagnoses	%
Sepsis (including severe sepsis and septic shock)	33
—Pneumonia	22
—Urinary tract infection	4
—Abdominal infection	4
—Others	3
Systemic inflammatory response syndrome (SIRS) (including concomitant infections*)	67
—Respiratory	21
—Cardiovascular	17
—Cerebral	16
—Others	13

* In some of the polymorbid patients, their critical illness was primarily a result of a noninfectious process, but they coincidentally suffered from an infection. As an example, a patient admitted to the Intensive Care Unit for acute pulmonary embolism who coexistently suffered from a urinary tract infection was classified in this category.

critically ill patients showed no signs of infection (**Table 2**). Another 20% of the critically ill patients suffered from a concomitant infection; i.e., their critical illness was primarily a result of a noninfectious process, but they coincidentally suffered from an infection (e.g., urinary tract infection). The remaining 33% suffered from sepsis, severe sepsis, or septic shock; thus, their critical illness was primarily a result of the infectious process. On admission, the patients in the different groups were similar in regards to APACHE II score, gender distribution, and age. Thirty-six patients (36%) were on immunosuppressive steroid therapy ranging from 20 to 1500 mg prednisone per day. Thereby, in all but one patient, the maximal dose was 120 mg prednisone per day. One patient with Wegener's Granulomatosis and hemorrhagic pneumonitis was treated with exorbitant doses of 1500 mg prednisone per day.

Characteristics of IL-1 decoy RII in critically ill patients

Table 2 summarizes demographic and laboratory data on admission in patients with different severities of infection. In critically ill patients, circulating levels of IL-1 decoy RII were markedly elevated as compared with normal, healthy controls (38.1 ± 53.9 vs. 6.46 ± 2.0 $\mu\text{g/l}$, $P < 0.001$). IL-1 decoy RII increases in critically ill patients with sepsis, similar to other inflammatory markers such as PTX3, IL-6, or CTpr. However, IL-1 decoy RII levels tend to be only slightly increased in patients with concomitant (mild) infection, in contrast to the sensitive CRP levels. The increase of IL-1 decoy RII levels is further evaluated in **Figure 1**. The observed increase of IL-1 decoy RII in infected patients (Fig. 1A) is mainly a result of markedly elevated levels in patients with severe infections, i.e., sepsis. Interestingly, culture positive infections resulted in significantly higher levels as compared with culture negative infections ($P < 0.001$, Fig. 1B). Neither in the presence nor absence of an infection was the IL-1 decoy RII significantly higher in patients who died as compared with patients who survived (Fig. 1C). When patients with Gram+ and Gram- infections were compared, IL-1RII levels were higher in Gram- infection (90.6 ± 17.1 $\mu\text{g/l}$ vs. 43.1 ± 7.6 $\mu\text{g/l}$, $P < 0.0001$). The two populations did not differ in terms of CRP (not shown). To analyze the inflammation-related increase of the different markers, we plotted the circulating levels of IL-1 decoy RII in relation to the SIRS criteria in patients with different severities of infection (Fig. 1D). In the absence of an infection, IL-1 decoy RII was not significantly elevated with increasing severity of SIRS. In contrast, in critically ill patients with a marked inflammatory response (SIRS 4), a pronounced, sepsis-induced, further increase of circulating IL-1 decoy RII levels was evident. Milder, concomitant infection did not increase circulating levels of IL-1 decoy RII. Finally, to compare the infection related with other

TABLE 2. Demographic and Laboratory Data in Patients with Different Severities of Infection

Parameter	No infection	Concomitant infection	Sepsis	<i>P</i>
Number (<i>n</i> = 101)	48	20	33	
Age (years)	59 \pm 15 [23–81]	57 \pm 12 [36–80]	55 \pm 16 [28–68]	n.s.
APACHE II (score points)	20 \pm 7 [3–33]	23 \pm 6 [14–38]	24 \pm 9 [9–49]	n.s.
IL-1 decoy R II (<10 $\mu\text{g/l}$)	25.5 \pm 29.4 [6.6–201.6]	27.2 \pm 24.5 [7.53–99.5]	78.7 \pm 90.4 ^{a,b} [7.1–421.6]	<0.001
PTX3 (<2 $\mu\text{g/l}$)	26.5 \pm 90.1 [0.6–844.2]	31.4 \pm 40.25 [1.7–144.3]	187.1 \pm 444.3 ^{a,c} [0.9–2407]	<0.001
Interleukin-6 (<36 ng/l)	84 \pm 160 [0.6–787]	214 \pm 520 [0.6–2371]	1351 \pm 2371 ^{a,c} [9.3–9085]	<0.001
CRP (<5 mg/l)	44 \pm 47 [4.9–309]	152 \pm 127 ^c [6–590]	243 \pm 141 ^{a,c} [21–500]	<0.001
CTpr (<0.3 $\mu\text{g/l}$)	0.4 \pm 0.3 [0.08–7.4]	2.0 \pm 1.3 [0.14–5.88]	38.1 \pm 54.2 ^{a,d} [1.10–248]	<0.001

Infection was diagnosed according to textbook standard criteria, and the three different categories are described in Materials and Methods. Data from admission are shown as mean \pm SD. Values in parentheses denote normal values and units. Values in brackets denote range. *P* values were calculated by nonparametric Kruskal-Wallis ANOVA. Post-hoc comparisons were done by least-square difference test: ^a $P < 0.001$ (for comparisons vs. "no infection"); ^b $P < 0.05$; ^c $P < 0.01$; ^d $P < 0.001$ (for comparisons vs. "concomitant infection"); n.s.: not significant.

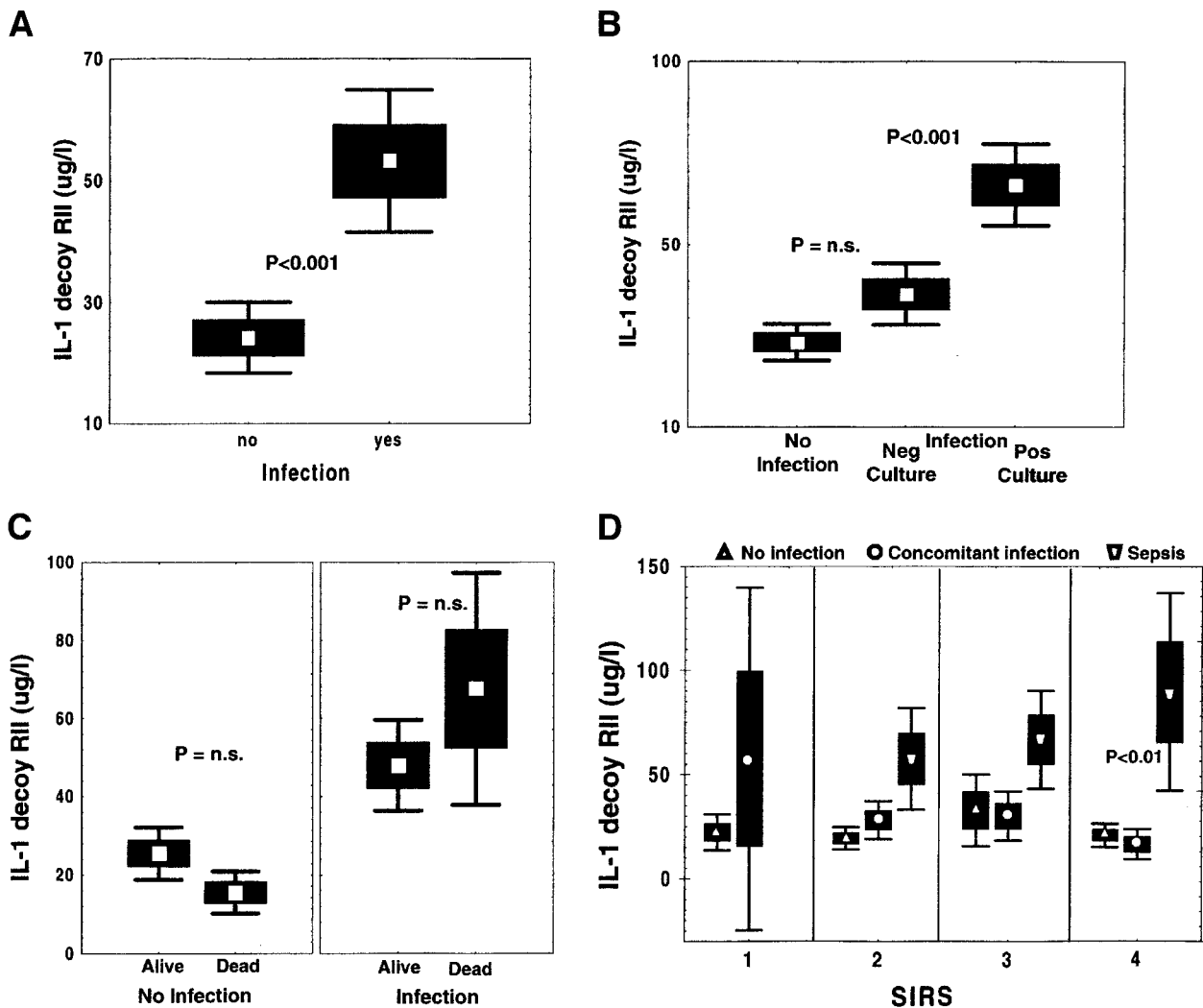


Fig. 1. Circulating IL-1 decoy RII levels of critically ill patients with different severities of SIRS and infection. Fifty-three patients with concomitant infection ($n=20$) or sepsis ($n=33$) were classified as infected. The serum concentrations of IL-1 decoy RII is shown according to the presence of infection (A), the culture result (B), and the survival in patients with or without infection, respectively (C). To analyze the inflammation-related increase of the different markers, we plotted the circulating IL-1 decoy RII levels in relation to the number of SIRS criteria fulfilled (1–4) in patients with different severities of infection (D). Boxes represent SEM and whiskers, $1.96 \pm \text{SEM}$. (D) Patients without infection are represented by triangles; patients with concomitant infection, by circles; and patients with sepsis, by trapezoids.

markers of inflammation and infection, we compared the increase of circulating IL-1 decoy RII levels with PTX3 [28], CRP, and CTpr [22] (Fig. 2). In critically ill patients, the maximal mean increase of circulating levels induced by microbial infection is 4-fold for IL-1 decoy RII, 13-fold for PTX3, 5-fold for CRP, and 103-fold for CTpr. IL-1 decoy RII plasma levels are highest in patients with severe sepsis and septic shock, similar to circulating PTX3 levels. They increased moderately but significantly in septic patients without organ dysfunction or shock ($P=0.048$ for the comparison of SIRS and sepsis). IL-1 decoy RII levels were not correlated to survival, unlike PTX3 and other markers in this same case list [28]. This in contrast to more sensitive markers such as CRP or CTpr, which are significantly increased in septic patients without organ dysfunction or shock.

Glucocorticoid hormones are potent inducers of IL-1 decoy RII expression and release in mononuclear phagocytes and

polymorphonuclear leukocytes [6]. It was therefore of interest to investigate IL-1 decoy RII levels in steroid-treated versus untreated patients. As shown in Figure 3, administration of glucocorticoid hormones was associated with significantly higher levels of the IL-1 decoy RII ($55.9 \pm 71.7 \mu\text{g/l}$ vs. $30.8 \pm 42.8 \mu\text{g/l}$, $P < 0.001$). In contrast, the same patients had significantly lower CRP ($P < 0.01$) and IL-6 ($P < 0.001$) levels with glucocorticoid therapy. Circulating CTpr levels were not influenced by glucocorticoid therapy ($P = \text{n.s.}$). There was no significant dose-response effect, implying a maximum glucocorticoid effect already at relatively low doses of 20 mg prednisone. Results presented in Figure 3 refer to the entire population. When subgroup analysis was performed in relation to steroid administration (data not shown), patients with sepsis showed high levels of IL-1R_{II} ($57.6 \pm 8.4 \mu\text{g/l}$), but these were significantly lower ($P < 0.0002$) than those in sepsis patients treated with glucocorticoid hormones ($106.7 \pm 24.4 \mu\text{g/l}$). No such difference was evident for CRP and IL-6 (not shown).

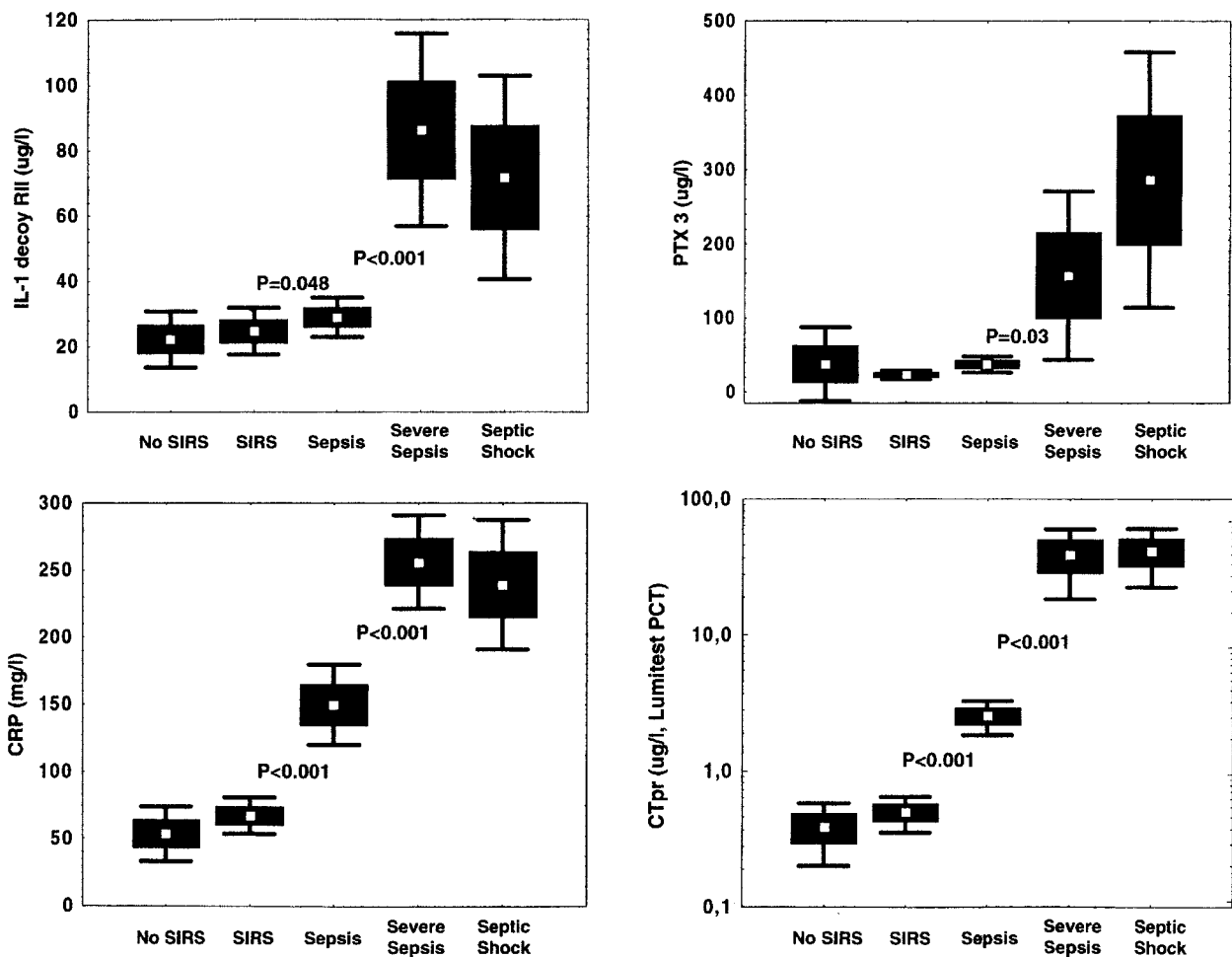


Fig. 2. Comparison of different markers of infection and inflammation. Squares (□) represent means; boxes, SEM; and whiskers, 1.96 ± SEM. Terms and statistical analysis are used as defined in Materials and Methods.

DISCUSSION

The results presented here show that patients admitted to an ICU with systemic infection have elevated levels of circulating decoy IL-1RII. This increase is especially marked in patients with severe sepsis or septic shock. The IL-1RII is a negative pathway of regulation of IL-1 [6]. In membrane bound or in soluble form, it captures IL-1 β and prevents it from interacting with signaling receptor complexes. Moreover, it acts as a dominant negative by forming a nonsignaling receptor complex with IL-1 β and the IL-1 RacP. Subsequent to the identification of the IL-1 decoy RII, decoy receptors, i.e., receptors structurally incapable of signaling, have been identified in the IL-1, TNF, and IL-10 receptor families, and possibly among chemokine receptors as well [6, 29–36]. In addition to soluble decoy receptors, signaling cytokine receptors can be released and measured in biological fluids [37, 38]. Different strategies are used to release cytokine receptors, including generation of differentially spliced mRNA and proteolytic shedding. Elevated plasma levels of cytokine receptors (e.g., TNF receptor and IL-6 receptor) have been detected in diverse pathological conditions including septic shock [37, 38].

Presumably because of lack of appropriate reagents, only a few studies have investigated circulating IL-1RII in patholog-

ical conditions. These include hairy cell leukemia, where the leukemic cells express the IL-1RII, and patients undergoing major surgery and hospitalized patients with chronic obstructive pulmonary disease [17, 19, 20, 39–41]. Here, we report that the IL-1 decoy RII is elevated in critically ill patients, especially in severe systemic infection. The pronounced increase in culture positive sepsis could indicate a role of microbial products or viable bacteria as a trigger for IL-1 decoy RII production and/or release. Alternatively, host-response mediators might be involved. Expression and release of the IL-1 decoy RII are regulated by pro- and anti-inflammatory signals in a unique way, distinct from that of other released cytokine receptors. LPS causes rapid shedding of the IL-1RII, followed by inhibition of transcript expression. Diverse anti-inflammatory agents, including glucocorticoid hormones, IL-4, IL-13, and IL-10, cause augmented expression and release of the decoy IL-1RII in myelomonocytic cells [4, 13, 16, 17, 42–44]. Aspirin also increases the circulating levels of IL-1RII [45]. Therefore, circulating levels of IL-1RII may in part reflect the activation of negative circuits of regulation of the cytokine action. Consistent with this view, it was recently observed that IL-1RII increased, and other markers of inflammation decrease in COPS patients hospitalized and treated with steroids to control exacerbation of disease [46]. In the present study, we

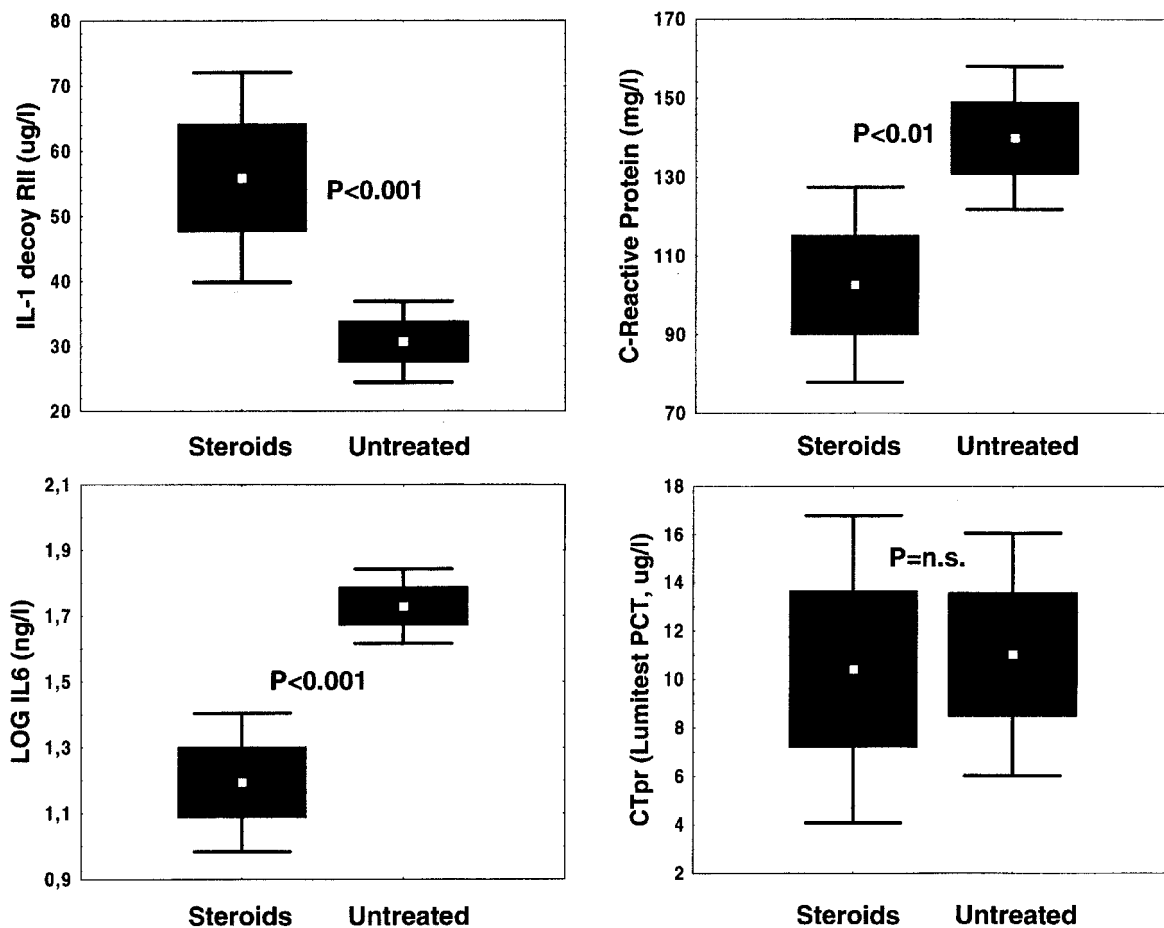


Fig. 3. Circulating marker levels in patients treated with glucocorticoid hormones. Squares (□) represent means; boxes, SEM; and whiskers, $1.96 \pm \text{SEM}$. Results refer to 36 steroid-treated and 65 untreated patients. LOG means logarithmic transformed data.

found significantly higher levels of the IL-1 decoy RII in patients treated with glucocorticoid hormones. In contrast, the same steroid-treated subjects showed significantly lower circulating CRP and IL-6 levels. The dissociation between IL-1 decoy RII and CRP/IL-6 in steroid-treated versus untreated patients strongly suggests, although does not prove, that these differences are treatment-related. IL-1 is an important mediator of septic shock, yet IL-1ra trials have been disappointing, though a subset of patients may have benefited from treatment [1]. Patient heterogeneity is a major stumbling block in the development of novel therapeutic strategies in septic shock. In view of our data, the usefulness of IL-1RII measurement in monitoring and stratifying critically ill patients with septic shock deserves further analysis. In particular, the IL-1 decoy RII may represent a useful indicator of the activation of anti-inflammatory pathways during systemic inflammation and sepsis and/or in response to pharmacological agents such as glucocorticoid hormones.

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REFERENCES

- Dinarello, C. A. (1996) Biological basis for IL-1 in disease. *Blood* 87, 2095–2147.
- Mantovani, A., Dinarello, C., Ghezzi, P. (2000) *Pharmacology of Cytokines*, Oxford, UK, Oxford University Press.
- O'Neill, L. A., Dinarello, C. A. (2000) The IL-1 receptor/toll-like receptor superfamily: crucial receptors for inflammation and host defense. *Immunol. Today* 21, 206–209.
- Colotta, F., Re, F., Muzio, M., Bertini, R., Polentarutti, N., Sironi, M., Giri, J. G., Dower, S. K., Sims, J. E., Mantovani, A. (1993) Interleukin-1 type II receptor: a decoy target for IL-1 that is regulated by IL-4. *Science* 261, 472–475.
- Colotta, F., Dower, S. K., Sims, J. E., Mantovani, A. (1994) The type II ‘decoy’ receptor: novel regulatory pathway for interleukin-1. *Immunol. Today* 15, 562–566.
- Mantovani, A., Locati, M., Vecchi, A., Sozzani, S., Allavena, P. (2001) Decoy receptors: a strategy to regulate inflammatory cytokines and chemokines. *Trends Immunol.* 22, 328–336.
- Re, F., Sironi, M., Muzio, M., Matteucci, C., Introna, M., Orlando, S., Penton-Rol, G., Dower, S. K., Sims, J. E., Colotta, F., Mantovani, A. (1996)

- Inhibition of interleukin-1 responsiveness by type II receptor gene transfer: a surface "receptor" with anti-interleukin-1 function. *J. Exp. Med.* 183, 1841–1850.
8. Lang, D., Knop, J., Wesche, H., Raffetseder, U., Kurrle, R., Boraschi, D., Martin, M. U. (1998) The type II IL-1 receptor interacts with the IL-1 receptor accessory protein: a novel mechanism of regulation of IL-1 responsiveness. *J. Immunol.* 161, 6871–6877.
 9. Malinowsky, D., Lundkvist, J., Layé, S., Bartfai, T. (1998) Interleukin-1 receptor accessory protein interacts with the type II interleukin-1 receptor. *FEBS Lett.* 429, 299–302.
 10. Orlando, S., Sironi, M., Bianchi, G., Drummond, A. H., Boraschi, D., Yabes, D., Colotta, F., Mantovani, A. (1997) Role of the metalloproteases in the release of the IL-1 type II decoy receptor. *J. Biol. Chem.* 272, 31764–31769.
 11. Orlando, S., Polentarutti, N., Mantovani, A. (2000) Selectivity release of the type II decoy IL-1 receptor. *Cytokine* 12, 1001–1006.
 12. Colotta, F., Orlando, S., Fadlon, E. J., Sozzani, S., Matteucci, C., Mantovani, A. (1995) Chemoattractants induce rapid release of the interleukin 1 type II decoy receptor in human polymorphonuclear cells. *J. Exp. Med.* 181, 2181–2188.
 13. Re, F., Muzio, M., De Rossi, M., Polentarutti, N., Giri, J. G., Mantovani, A., Colotta, F. (1994) The type II "receptor" as a decoy target for IL-1 in polymorphonuclear leukocytes: characterization of induction by dexamethasone and ligand binding properties of the released decoy receptor. *J. Exp. Med.* 179, 739–743.
 14. Colotta, F., Saccani, S., Giri, J. G., Dower, S. K., Sims, J. E., Introna, M., Mantovani, A. (1996) Regulated expression and release of the interleukin-1 decoy receptor in human mononuclear phagocytes. *J. Immunol.* 156, 2534–2541.
 15. Penton-Rol, G., Orlando, S., Polentarutti, N., Bernasconi, S., Muzio, M., Introna, M., Mantovani, A. (1999) Bacterial lipopolysaccharide causes rapid shedding, followed by inhibition of mRNA expression, of the IL-1 type II receptor, with concomitant up-regulation of the type I receptor and induction of incompletely spliced transcripts. *J. Immunol.* 162, 2931–2938.
 16. Brown, E. A., Dare, H. A., Marsh, C. B., Wewers, M. D. (1996) The combination of endotoxin and dexamethasone induces type II interleukin 1 receptor (IL-1r II) in monocytes: a comparison to interleukin 1 beta (IL-1 beta) and interleukin 1 receptor antagonist (IL-1ra). *Cytokine* 8, 828–836.
 17. Yu, P. W., Schuler, L. A., Kehrl, M., Mattocks, L., Nonnecke, B. J., Czuprynski, C. J. (1997) Effects of dexamethasone treatment on IL-1 receptor mRNA levels in vivo. *J. Leukoc. Biol.* 62, 401–404.
 18. Giri, J. G., Wells, J., Dower, S. K., McCall, C. E., Guzman, R. N., Slack, J., Bird, T. A., Shanebeck, K., Grabstein, K. H., Sims, J. E., Alderson, M. R. (1994) Elevated levels of shed type II IL-1 receptor in sepsis. Potential role for type II receptor in regulation of IL-1 responses. *J. Immunol.* 153, 5802–5809.
 19. Pruijt, J. H., Welborn, M. B., Edwards, P. D., Harward, T. R., Seeger, J. W., Martin, T. D., Smith, C., Kenney, J. A., Wesdorf, R. I., Meijer, S., Cuesta, M. A., Abouhanza, A., Copeland III, E. M., Giri, J. G., Moldawer, L. L., Oldenburg, H. S. (1996) Increased soluble interleukin-1 type II receptor concentrations in postoperative patients and in patients with sepsis syndrome. *Blood* 87, 3282–3288.
 20. van Deuren, M., van der Ven-Jongekrijg, J., Vannier, E., van Dalen, R., Pesman, G., Bartelink, A. K. M., Dinarello, C. A., van der Meer, J. W. M. (1997) The pattern of interleukin-1b (IL-1b) and its modulating agents IL-1 receptor antagonist and IL-1 soluble receptor type II in acute meningococcal infections. *Blood* 90, 1101–1108.
 21. Muller, B., Becker, K. L., Kranzlin, M., Schachinger, H., Huber, P. R., Nysten, E. S., Snider, R. H., White, J. C., Schmidt-Gayk, H., Zimmerli, W., Ritz, R. (2000) Disordered calcium homeostasis of sepsis: association with calcitonin precursors. *Eur. J. Clin. Invest.* 30, 823–831.
 22. Muller, B., Becker, K. L., Schachinger, H., Rickenbacher, P. R., Huber, P. R., Zimmerli, W., Ritz, R. (2000) Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit. Care Med.* 28, 977–983.
 23. Muller, B., White, J. C., Nysten, E. S., Snider, R. H., Becker, K. L., Habener, J. F. (2001) Ubiquitous expression of the calcitonin-1 gene in multiple tissues in response to sepsis. *J. Clin. Endocrinol. Metab.* 86, 396–404.
 24. Knaus, W. A., Draper, E. A., Wagner, D. P., Zimmerman, J. E. (1985) APACHE II: a severity of disease classification system. *Crit. Care Med.* 13, 818–829.
 25. Wagner, D. P., Knaus, W. A., Harrell, F. E., Zimmerman, J. E., Watts, C. (1994) Daily prognostic estimates for critically ill adults in intensive care units: results from a prospective, multicenter, inception cohort analysis. *Crit. Care Med.* 22, 1359–1372.
 26. Castella, X., Artigas, A., Bion, J., Kari, A. (1995) A comparison of severity of illness scoring systems for intensive care unit patients: results of a multicenter, multinational study. *The European/North American Severity Study Group. Crit. Care Med.* 23, 1327–1335.
 27. Young, L. S. (1995) Sepsis syndrome. In *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases* (G. L. Mandell, J. E. Bennett, R. Dolin, eds.), Philadelphia, PA, Churchill Livingstone, 690–705.
 28. Muller, B., Peri, G., Doni, A., Torri, V., Landmann, R., Bottazzi, B., Mantovani, A. (2001) Circulating levels of the long pentraxin PTX3 correlate with severity of infection in critically ill patients. *Crit. Care Med.* 29, 1404–1407.
 29. Novick, D., Kim, S. H., Fantuzzi, G., Reznikov, L. L., Dinarello, C. A., Rubinstein, M. (1999) Interleukin-18 binding protein: a novel modulator of the Th1 cytokine response. *Immunity* 10, 127–136.
 30. Kong, Y. Y., Boyle, W. J., Penninger, J. M. (2000) Osteoprotegerin ligand: a regulator of immune responses and bone physiology. *Immunol. Today* 21, 495–502.
 31. Lacey, D. L., Timms, E., Tan, H. L., Kelley, M. J., Dunstan, C. R., Elliott, R., Colombero, A., Elliott, G., Scully, S., Hsu, H., Sullivan, J., Hawkins, N., Davy, E., Capparelli, C., Eli, A., Qian, Y. X., Kaufman, S., Sarosi, I., Shalhoub, V., Senaldi, G., Guo, J., Delaney, J., Boyle, W. J. (1998) Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell* 93, 165–176.
 32. Yasuda, H., Shima, N., Nakagawa, N., Mochizuki, S. I., Yanai, K., Sato, Y., Goto, M., Yamaguchi, K., Kuriyama, M., Kanno, T., Murakami, A. T., Morinaga, T., Higashio, K. (1998) Identity of osteoclastogenesis inhibitory factor (OCIF) and osteoprotegerin (OPG): a mechanism by which OPG/OCIF inhibits osteoclastogenesis in vitro. *Endocrinology* 139, 1329–1337.
 33. Ashkenazi, A., Dixit, V. M. (1998) Death receptors: signaling and modulation. *Science* 281, 1305–1308.
 34. Sheridan, J. P., Marsters, S. A., Pitti, R. M., Gurney, A., Skubatch, M., Baldwin, D., Ramakrishnan, L., Gray, C. L., Baker, K., Wood, W. I., Goddard, A. D., Godowski, P., Ashkenazi, A. (1997) Control of TRAIL-induced apoptosis by a family of signaling and decoy receptors. *Science* 277, 818–821.
 35. Jenkins, M., Keir, M., McCune, J. M. (2000) A membrane-bound Fas decoy receptor expressed by human thymocytes. *J. Biol. Chem.* 275, 7988–7993.
 36. D'Amico, G., Frascaroli, G., Bianchi, G., Transidico, P., Doni, A., Vecchi, A., Sozzani, S., Allavena, P., Mantovani, A. (2000) Uncoupling of inflammatory chemokine receptors by IL-10: generation of functional decoys. *Nat. Immunol.* 1, 387–391.
 37. Fernandez-Botran, R., Chilton, P. M., Ma, Y. (1996) Soluble cytokine receptors: their roles in immunoregulation, disease, and therapy. In *Advances in Immunology* (F. J. Dixon, ed.), San Diego, CA, Academic, 269–336.
 38. Heaney, M. L., Golde, D. V. (1996) Soluble cytokine receptors. *Blood* 87, 847–857.
 39. Barak, V., Nisman, B., Polliack, A., Vannier, E., Dinarello, C. A. (1998) Correlation of serum levels of interleukin-1 family members with disease activity and response to treatment in hairy cell leukemia. *Eur. Cytokine Netw.* 9, 33–39.
 40. van der Poll, T., de Waal Malefyt, R., Coyle, S. M., Lowry, S. F. (1997) Antiinflammatory cytokine responses during clinical sepsis and experimental endotoxemia: sequential measurements of plasma soluble interleukin (IL)-1 receptor type II, IL-10, and IL-13. *J. Infect. Dis.* 175, 118–122.
 41. Vannier, E., Kaser, A., Atkins, M. B., Fantuzzi, G., Dinarello, C. A., Mier, J. W., Tilg, H. (1999) Elevated circulating levels of soluble interleukin-1 receptor type II during interleukin-2 immunotherapy. *Eur. Cytokine Netw.* 10, 37–42.
 42. Colotta, F., Re, F., Muzio, M., Polentarutti, N., Minty, A., Caput, D., Ferrara, P., Mantovani, A. (1994) IL-13 induces expression and release of the IL-1 decoy receptor in human polymorphonuclear cells. *J. Biol. Chem.* 269, 12403–12406.
 43. Tam, F. W., Smith, J., Karkar, A. M., Pusey, C. D., Rees, A. J. (1997) Interleukin-4 ameliorates experimental glomerulonephritis and up-regulates glomerular gene expression of IL-1 decoy receptor. *Kidney Int.* 52, 1224–1231.
 44. Dickensheets, H. L., Donnelly, R. P. (1997) IFN-gamma and IL-10 inhibit induction of IL-1 receptor type I and type II gene expression by IL-4 and IL-13 in human monocytes. *J. Immunol.* 159, 6226–6233.
 45. Daun, J. M., Ball, R. W., Burger, H. R., Cannon, J. G. (1999) Aspirin-induced increases in soluble IL-1 receptor type II concentrations in vitro and in vivo. *J. Leukoc. Biol.* 65, 863–866.
 46. Dentener, M. A., Creutzberg, E. C., Schols, A. M., Mantovani, A., van't Veer, C., Buurman, W. A., Wouters, E. F. (2001) Systemic anti-inflammatory mediators in COPD: increase in soluble interleukin 1 receptor II during treatment of exacerbations. *Thorax* 56, 721–726.